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Confinia Cephalalgica è la prima rivista interdisciplinare italiana che si occupa delle cefalee e delle algie facciali. Nata come rivista interdisciplinare in posizione intermedia tra le riviste formative-informative per l'aggiornamento di una vasta platea di medici e quelle iperpecialistiche, rivolte a selezionati esperti di determinate patologie, Confinia ha mantenuto le premesse, suscitando vasto interesse in vari settori della medicina, anche non specialistica.
Nel '98 la rivista ha rinnovato il suo organigramma editoriale, con cambiamenti nella redazione scientifica e l'istituzione di un comitato editoriale, composto dai responsabili di diversi Centri Cefalee e dal Presidente in carica della SISC.
Questa novità è in sintonia con il nuovo orientamento generale della rivista, il cui obiettivo è di rivolgersi non solo agli specialisti direttamente coinvolti nello studio e nella cura delle cefalee e delle algie facciali, ma anche ai medici di base e alle istituzioni. Accanto alla pubblicazione di rassegne, articoli originali, casi clinici e rubriche informative, Confinia dà spazio ad argomenti di interesse più generale e di grande attualità, come la ricerca sanitaria o la valutazione della qualità dell'assistenza.

I VECCHI LIBRI ITALIANI SULLE CEFALEE

Un'analisi dell'evoluzione che ha avuto, dall'ultimo dopoguerra ad oggi in Italia, il settore dell'editoria sulle cefalee si presta ad alcune interessanti considerazioni. Prenderò in considerazione solo i libri riguardanti specificamente le cefalee scritti da autori italiani, escludendo sia le traduzioni in lingua italiana di libri stranieri che gli atti di congressi. Pure esclusi da questa analisi saranno i capitoli sulle cefalee di volumi o manuali di neurologia o di medicina interna. Fino ai primi anni '80 i libri sull'argomento erano pochissimi. Infatti, nell'arco temporale di oltre un trentennio, ne ritroviamo solamente quattro.

Seguendo uno stretto ordine cronologico, il primo è quello edito nel 1950 da La Settimana Medica di Firenze, ad opera di Enrico Greppi, all'epoca Direttore della Clinica Medica Generale dell'Università di Firenze, dal titolo "L'emicrania. Aspetti neurologici, vascolari, metabolici. Terapia". Si tratta di 134 pagine che accolgono, in apertura, il testo della conferenza tenuta dallo stesso Greppi all'Accademia Medica di Napoli nel marzo 1949, dal titolo "Ai margini dell'emicrania. Collegamenti con la patologia nervosa, digestiva, vascolare". Nihil novi sub tegmine soli! Margini dell'emicrania e, a distanza di mezzo secolo, Confinia Cephalalgica. Seguono quindi quattro capitoli, rispettivamente di Filippo Cardona, Direttore della Clinica delle Malattie Nervose e Mentali dell'Università di Siena, "Il problema dell'emicrania dal punto di vista neurologico-psichiatrico", e di due assistenti e dell'aiuto di Greppi, Oreste Bongini "Mutamenti biochimici dell'emicrania", Mario Rosselli "L'arterite temporale - malattia di Horton", Renato Martinetti "Orientamenti terapeutici per l'emicrania".

Nel 1959 compare, per i tipi della Casa Editrice Vallardi di Milano, un volume di grande importanza e diffusione, molto esteso e dettagliato, che riesce a mantenere, a distanza di oltre quaranta anni, un interesse non solo storico ed un'indiscutibile validità grazie, soprattutto, ai suoi pregi clinico-descrittivi. Si tratta delle "Sindromi nevralgiche del capo. Fisiopatologia, clinica e terapia", noto come il Martinetti e Ficini, dagli autori, allievi di Greppi, di questa opera che si compone di 620 pagine e 116 figure. La prefazione è di Gianbattista Belloni, Direttore della Clinica delle Malattie Nervose e Mentali dell'Università di Padova. E' strutturato in due parti: una parte generale, "Il dolore", che comprende 6 capitoli per complessive 102 pagine, ed una parte speciale suddivisa in 3 sezioni. La prima sezione, dal titolo "Sindromi nevralgiche pure", occupa circa 280 pagine ed è costituita da 5 capitoli che trattano rispettivamente di nevralgia del trigemino, di nevralgia del glossofaringeo, di nevralgia del nervo facciale, di nevralgie cervicali e di nevralgia del nervo laringeo superiore. La seconda sezione, tratta di "nevralgie cefaliche da herpes zoster". La terza sezione, "sindromi dolorose cefaliche da patimento neurovegetativo vascolare", si estende per circa 200 pagine e comprende 6 capitoli che riguardano rispettivamente la nevralgia del ganglio

sfenopalatino di Sluder, la nevralgia del nervo nasale di Charlin, la sindrome di Neri Barrè, la cefalalgia istaminica di Horton, la sindrome di Costen e le nevralgie cefaliche ectopiche (atypical neuralgia). Come è possibile rilevare dall'analisi dei temi trattati, così come dal titolo stesso dell'opera, in questo volume non vengono prese in considerazione le cefalee primarie, ad eccezione però della cefalea a grappolo che Martinetti e Ficini curiosamente inseriscono, con la denominazione di cefalalgia istaminica di Horton, nell'ambito delle sindromi nevralgiche del capo.

Ancora Greppi, questa volta insieme a Sicuteri, danno alle stampe, nel 1964 "L'emicrania. Motivi di fisiopatogenesi e di terapia", scritto insieme a tutti i collaboratori di quegli anni del Centro Cefalee di Firenze, Anselmi, Del Bianco, Fanciullacci, Franchi e Michelacci. Il libro, ristampato nella veste originaria nel 1985 per iniziativa di Sicuteri, comprende, in circa 290 pagine complessive, oltre al testo della relazione di Greppi al 65° Congresso della Società Italiana di Medicina Interna, capitoli dello stesso Greppi e di Sicuteri sulla clinica, fisiopatologia e terapia dell'emicrania, di Michelacci sull'analisi di una casistica di 800 pazienti, di Franchi e Fanciullacci sulla cefalalgia istaminica di Horton. La lettura di questo ultimo capitolo sorprende positivamente per il taglio ancora moderno ed attuale con cui viene trattata la cefalea a grappolo.

L'ultimo, in ordine cronologico, dei "vecchi" libri italiani sulle cefalee (mi riservo di trattare in prossimi editoriali i libri "recenti" e quelli "nuovi") è "Le cefalee" dei neurologi Vincenzo Bonavita, attuale presidente della Società Italiana di Neurologia, ed Ettore Savagnone, edito per i tipi della Edizioni Idelson di Napoli nel 1969. Consiste, per la prima volta in Italia, di una monografia che tratta in modo sistematico e completo tutto il capitolo delle cefalee, quelle primarie e quelle secondarie secondo uno schema classico-tradizionale con rigorose basi metodologiche. Dopo una prefazione di Vincenzo Rubino, allora Direttore della Clinica delle Malattie Nervose e Mentali dell'Università di Palermo, vengono esposti, per complessive 180 pagine circa, concetti di anatomia e semeiotica (i primi due capitoli) e quindi le diverse forme di cefalea (i successivi cinque capitoli) sistematizzate secondo un ordine e denominate secondo una terminologia che risentono ampiamente della classificazione internazionale delle cefalee in vigore all'epoca, quella della Ad hoc Committee on Classification of Headache comparsa nel 1962. Troviamo così un capitolo sulle cefalee da dilatazione delle arterie esocraniche che riguarda fondamentalmente l'emicrania, un capitolo sulle cefalee da dilatazione delle arterie endocraniche che comprende le cefalee da ipertensione, da hang-over, quella post-convulsiva, da ipossia, da carenza di caffeina e da ipoglicemia, un capitolo sulle cefalee da trazione o compressione, un capitolo sulla cefalea muscolo-tensiva ed infine un capitolo sulle cefalee da propagazione di stimoli algogeni localizzati (occhio, naso, denti, orecchio).

Gian Camillo Manzoni

RASSEGNA

Emicrania senza aura e cefalea di tipo tensivo: problematiche diagnostico-terapeutiche nella gestione delle forme miste episodiche e croniche

Migraine without aura and tension-type headache: diagnostic and therapeutic issues in the management of mixed forms

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PAROLE CHIAVE: cefalea di tipo tensivo, diagnosi, emicrania, farmaci, linee guida, terapia

KEY WORDS: diagnosis, drugs, guidelines, migraine, tension-type headache, therapy

Introduzione

La coesistenza di emicrania senza aura e cefalea di tipo tensivo in uno stesso paziente e' un'evenienza tutt'altro che remota, rappresentando un fenomeno di frequente riscontro nella pratica clinica. Vari studi epidemiologici sono stati condotti nel corso degli anni, anche su ampie casistiche, alla ricerca di evidenze a supporto o a sfavore di un possibile legame eziopatogenetico fra le due forme di cefalea idiopatica. A tutt'oggi non e' possibile trarre conclusioni assolutistiche per una serie di motivazioni che saranno di seguito valutate; ciononostante, appare rilevante cercare di analizzare, sulla base dei dati clinici e pre-clinici finora disponibili, un fenomeno che, oltre alle ovvie implicazioni diagnostiche, pone serie problematiche sia di tipo fisiopatologico che terapeutico.

Rapporti tra emicrania senza aura e cefalea di tipo tensivo nella classificazione della Società Internazionale delle Cefalee (IHS)

La classificazione dell'IHS promulgata nel 1988 (1) si basa sull'identificazione diagnostica delle varie forme di cefalee, idiopatiche e non, in funzione di alcune caratteristiche cliniche e temporali definite da rigidi criteri operativi. Un paziente viene cioe' diagnosticato come emicranico nel caso in cui abbia manifestato almeno 5 attacchi di cefalea che soddisfino gli altrettanti criteri operativi previsti dall'IHS per l'emicrania senza aura (tabella 1), mentre sara' classificato come affetto da cefalea di tipo tensivo nel caso in cui abbia presentato almeno 10 attacchi con le caratteristiche identificate dai corrispondenti 5 criteri diagnostici (tabella 2). La classificazione dell'IHS non prevede in

nessun caso una diagnosi di cefalea mista quando il paziente manifesti attacchi di diverso tipo che soddisfino alternativamente i criteri diagnostici per l'emicrania e la cefalea di tipo tensivo. Pertanto il soggetto che presenti l'associazione delle due forme di cefalea andra' identificato dalla doppia diagnosi di *emicrania senza aura* e *cefalea di tipo tensivo*.

TABELLA 1 - Criteri diagnostici classificativi della Societa' Internazionale delle Cefalee (IHS) per l'emicrania senza aura

1. Almeno 5 attacchi che soddisfano i punti successivi
2. Durata compresa fra 4 e 72 ore (in assenza di trattamento)
3. Il dolore presenta almeno due delle seguenti caratteristiche
    - unilaterale
    - pulsante
    - intensita' media o severa
    - peggiora con l'attivita' fisica
4. Almeno uno delle seguenti situazioni cliniche durante la cefalea
    - nausea e/o vomito
    - fono e fotofobia
5. Presenza di una delle seguenti condizioni
    - l'anamnesi, l'esame obiettivo generale e neurologico escludono la presenza di una causa organica di cefalea
    - l'anamnesi e/o l'esame obiettivo generale e/o neurologico suggeriscono la presenza di una causa organica, ma gli esami strumentali ne escludono la presenza
    - la causa organica e' presente, ma l'attacco emicranico non si presenta in stretta relazione temporale con questa

Tabella 2 - Criteri diagnostici classificativi della Societa' Internazionale delle Cefalee (IHS) per la cefalea di tipo tensivo episodica

1. Almeno 10 attacchi soddisfano i punti successivi
2. Durata compresa fra 30 minuti e 7 giorni
3. Il dolore presenta almeno due delle seguenti caratteristiche
    - qualita' gravativo-costrittiva
    - intensita' lieve o media
    - bilaterale
    - non aggravato dall'attivita' fisica
4. Si verificano entrambe le seguenti situazioni cliniche durante la cefalea
    - nausea o vomito assenti
    - fono e fotofobia possono essere presenti, ma non contemporaneamente
5. Presenza di una delle seguenti condizioni
    - l'anamnesi, l'esame obiettivo generale e neurologico escludono la presenza di una causa organica di cefalea
    - l'anamnesi e/o l'esame obiettivo generale e/o neurologico suggeriscono la presenza di una causa organica, ma gli esami strumentali ne escludono la presenza
    - la causa organica e' presente, ma l'attacco emicranico non si presenta in stretta relazione temporale con questa

Benche' estremamente utili nel mettere ordine in un campo troppo spesso dominato da individualismi basati su esperienze cliniche a volte anche molto disparate, i criteri diagnostici proposti dall'IHS si sono presto rivelati come un ambito, certo semplificato, ma troppo angusto in cui il medico deve muoversi e lo stesso nuovo sottocomitato per la classificazione delle cefalee ha preso atto della necessita' di meglio definire alcune forme di cefalea primaria nella prossima classificazione (2). Vari studi epidemiologici successivi alla pubblicazione della Classificazione IHS hanno infatti dimostrato come tali criteri siano gravati da pesanti limitazioni (3-9). La loro rigidita' previene, anzitutto, la classificazione di una considerevole porzione di cefalee idiopatiche che non soddisfano completamente questi criteri e che, a seconda dei casi, finiscono nel calderone delle cefalee emicraniche o delle cefalee di tipo tensivo non altrimenti classificabili (5), con le conseguenti importanti incertezze nell'approccio terapeutico del paziente che disgraziatamente ne risulta affetto. In secondo luogo, la scelta di escludere dai criteri operativi la possibilita' che esistano forme miste di tipo cronico ha, di fatto, rallentato ed ostacolato il naturale processo di definizione nosografica delle cosiddette "Cefalee Croniche Quotidiane (CCQ)" che, pur essendo osservate con relativa rarità al di fuori dell'ambito strettamente specialistico, rappresentano, da un lato, quadri clinici stimolanti per la migliore comprensione dell'evoluzione nel tempo dell'emicrania e dei suoi rapporti con la cefalea di tipo tensivo e, dall'altro, delle vere e proprie sfide terapeutiche (10-13).

Un'attenta revisione della letteratura recente ha permesso di riassumere le varie terminologie utilizzate per le forme croniche di emicrania e/o cefalea di tipo tensivo (14). Accanto ai termini descrittivi di "emicrania evolutiva", "emicrania cronica", "emicrania con cefalea parossistica" ed "emicrania continua", che si riferiscono a forme continue o subcontinue di natura francamente emicranica (figura 1), quantomeno all'esordio, troviamo le "cefalee miste", in cui caratteristiche francamente emicraniche sono commiste in varia proporzione ad aspetti tipici della cefalea tensiva, per arrivare al gruppo delle "cefalee di tipo tensivo cronico", caratterizzate dalla presenza esclusiva di caratteristiche proprie della forma tensiva.

Per ognuna di queste forme sono stati proposti, da gruppi diversi, criteri diagnostici piu' o meno validati, con il risultato che, applicando la classificazione vigente, i pazienti affetti dalle forme elencate nel paragrafo precedente

Figura 1 – I termini (da "cestinare") rappresentano le definizioni, alcuni delle quali ancora in uso, per le CCQ che derivano da forme di emicrania cronica o cronicizzata (da G. Nappi et al. J Headache Pain 2000;1(suppl.1):5-10)

possono essere identificati o con la diagnosi riduttiva di "emicrania senza aura" oppure con la doppia diagnosi di "emicrania senza aura" e "cefalea di tipo tensivo", episodica o cronica a seconda del numero di giorni mensili (< o ≥ di 15) in cui e' presente la forma tensiva.
Appare evidente, tuttavia, la diversita' dell'impatto che puo' avere una forma episodica di emicrania o una forma cronicizzata sia sul paziente, in termini di salute e di qualita' di vita, sia sul medico, specie per quanto riguarda l'iter diagnostico e terapeutico. Per questo motivo, negli ultimi anni, si e' diffusa l'esigenza di spostare l'attenzione clinica non tanto sulla diagnosi di un numero esiguo di attacchi cefalalgici, quanto sul paziente e sul livello di gravita' con cui la patologia si manifesta in quell'individuo nelle varie fasi della sua vita (15,16).

Impatto epidemiologico delle forme miste

La forma di cefalea piu' frequente e' rappresentata dalla forma tensiva episodica, che viene riferita dal 63% della popolazione generale, mentre l'emicrania colpisce il 10% circa dei soggetti (17).
E' interessante, pero', osservare che le due forme si presentano associate nel 9% della popolazione generale, che la stragrande maggioranza degli emicranici (83%) risulta essere affetta anche da cefalea di tipo tensivo e che la forma tensiva nei soggetti emicranici si manifesta con una frequenza ed un'intensita' di attacchi maggiore rispetto ai soggetti che non soffrono di emicrania.
In uno studio di alcuni anni fa e' stato di mostrato che, negli adolescenti, un quarto delle forme emicraniche e un terzo circa delle forme tensive non soddisfa appieno i criteri IHS per emicrania e cefalea di tipo tensivo (9), rispettivamente, lasciando intravedere la possibilita' che le forme di confine tra queste due cefalee idiopatiche siano in realta' molto piu' numerose di quanto si pensi, specie nelle fasi iniziali di malattia.
La CCQ colpisce, invece, il 4-5% della popolazione generale, manifestando nella meta' dei casi caratteristiche proprie della forma tensiva e in un terzo le stigmate dell'emicrania cronicizzata (18,19).
Appare ovvio, che in assenza di un preciso inquadramento nosografico delle forme di associazione fra emicrania e cefalea di tipo tensivo, questi dati sono da considerarsi incompleti, ed imprecisi, e dovranno essere integrati con i risultati di futuri studi *ad hoc*.

Aspetti fisiopatogenetici

Vari autori hanno suggerito che emicrania e cefalea di tipo tensivo non siano entita' cliniche separate, ma costituiscano bensi' i due estremi di un *continuum* di disordini cefalalgici di intensita' variabile (20-22). In tale contesto, la cefalea di tipo tensivo rappresenta la condizione clinica di minore gravita', mentre la presenza di emicrania senza aura corrisponde ad un aggravamento del quadro clinico, che sfocia poi nella variante con aura ai gradi estremi di serieta' (teoria del *continuum* della severita') (figura 2). Le forme miste si collocherebbero nella vasta zona centrale dello spettro, accanto all'emicrania senza aura.
L'esistenza di stretti rapporti tra le varie forme di cefalee primarie era, del resto, stata proposta alcuni decenni fa anche da Nappi e collaboratori (23), i

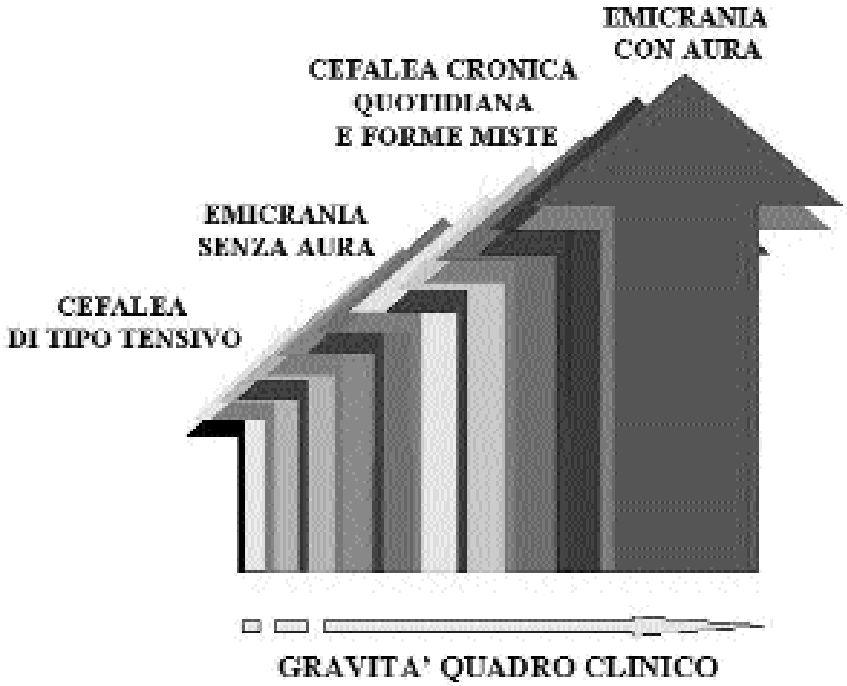

Figura 2 – Teoria del continuum della severita' nell'interpretazione dei rapporti fra emicrania e cefalea di tipo tensivo

quali avevano proposto l'interpretazione delle forme di cefalea idopatiche come elementi costitutivi di uno spettro in cui cefalee francamente vascolari ed episodiche confinano e, talora, sconfinano in forme miste (tensivo-vascolari), tensive pure e psicogene (figura 3a). Tale visione a "spettro" si applica non solo sul piano puramente clinico, ma potrebbe coinvolgere anche quello fisiopatogenetico, spiegando cosi' la stretta relazione esistente fra alcune forme di confine di cefalea con aura e gli accidenti cerebrovascolari, nonche' fra alcune cefalee di tipo tensivo cronico ed i disturbi del tono dell'umore (figura 3b).

Una vasta mole di dati clinici e sperimentali sembra confermare che emicrania e cefalea di tipo tensivo differiscano in termini quantitativi, piu' che qualitativi. Entrambe risultano essere scatenate dallo stress e dalla tensione mentale (24-25). La contrattura muscolare nucale viene spesso riferita come sintomo prodromico degli attacchi emicranici (26,27) e il trattamento della dolenzia muscolare in corso di crisi emicranica induce un netto miglioramento della sintomatologia (28). Dal punto di vista epidemiologico e' stato, inoltre, dimostrato che una porzione sostanziale di emicranie e di cefalee di tipo tensivo non rispondono in toto ai criteri diagnostici dell'IHS oppure presentano caratteristiche intermedie fra le due forme (5).

Ancora piu' intricati sembrano essere i

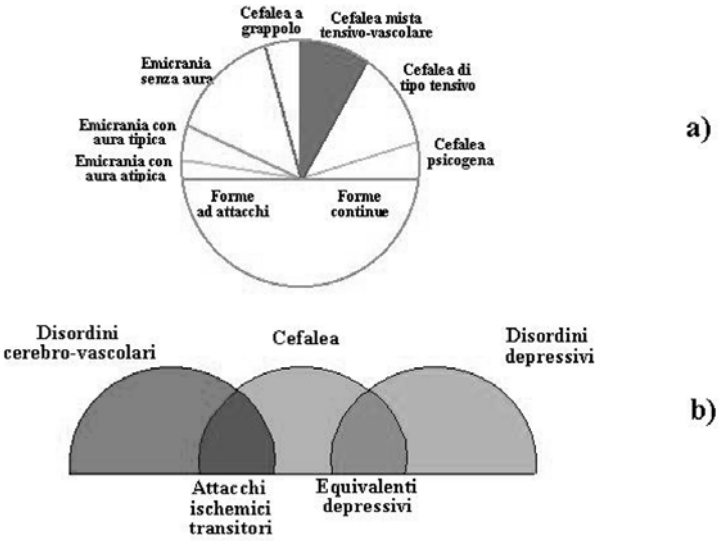

Figura 3 – Visione delle varie forme di cefalee primaria come sub-entita' di un unico spettro che racchiude forme ad attacchi o continue (a). La concezione delle cefalee come espressioni modulari all'interno di un unico spettro di patologia fornisce inoltre interessanti spunti fisiopatogenetici per l'interpretazione di alcune forme di confine con la patologia cerebrovascolare o con quella psichiatrica (B)

rapporti fra emicrania e cefalea di tipo tensivo nei soggetti che presentano cefalea cronicizzata. Negli ultimi anni sono stati condotti alcuni studi (29,30) su un'ampia popolazione di soggetti affetti da CCQ allo scopo di documentare le caratteristiche della cefalea all'esordio, la sua evoluzione nel tempo ed l'outcome finale ha infatti evidenziato che il 63% dei soggetti aveva sviluppato una forma cronica a partire da un'episodica, mentre gli altri avevano sperimentato la comparsa di una cefalea cronica *ad initio.* La trasformazione da forma episodica a cronica si era realizzata mediamente nell'arco di 10 anni. La cefalea episodica iniziale era, in un terzo dei soggetti, di tipo tensivo, mentre, nei rimanenti due terzi di tipo emicranico. Ciononostante, la cefalea quotidiana che i pazienti avevano sviluppato presentava le stesse caratteristiche, indipendentemente dalla tipologia degli attacchi all'esordio.

La sovrapposizione fra le due forme di cefalea primaria sussiste anche in campo fisiopatogenetico. Una riduzione dei livelli serotonina plasmatica e piastrinica e' stata infatti descritta sia nella forma tensiva (31-32) sia in quella emicranica (31) ed entrambe le forme presentano un aumento della sostanza P intrapiastrinica (34). Un'ipofunzione del sistema simpatico e una riduzione del contenuto liquorale dei livelli di endorfine sono presenti sia negli emicranici che nei soggetti con cefalea di tipo tensivo (35-37). Da tempo, inoltre, e' nota l'efficacia in entrambe le forme di farmaci quali l'aspirina, alcuni anti-infiammatori non steroidei e gli antidepressivi triciclici. Di recente e' stato infine dimostrato che il sumatriptan, considerato l'antiemicranico specifico per eccellenza, funziona in un'altissima percentuale di attacchi di cefalea di tipo tensivo (38).

Ashina e coll. (39,40) hanno dimostrato come la somministrazione di nitroglicerina, farmaco donatore di ossido nitrico utilizzato da decenni come test di induzione altamente selettivo per l'emicrania, provoca attacchi simil-spontanei in soggetti con cefalea di tipo

tensivo cronico. La successiva dimostrazione che l'inibizione dell'enzima che sintetizza l'ossido nitrico e' efficace nel trattamento sintomatico di attacchi di CCQ (riducendo sia il dolore sia la dolenzia muscolare) sembra confermare anche nel caso della cefalea di tipo tensivo, oltre che nell'emicrania, un importante ruolo fisiopatogenetico per l'ossido nitrico. Di recente e' stato ipotizzato che, almeno nella forma cronica di cefalea tensiva, si potrebbe verificare un fenomeno di sensibilizzazione centrale (a livello del neurone trigeminale di secondo ordine) attraverso un meccanismo ossido nitrico-mediato associato alla trasmissione glutamatergica al livello spinale, in analogia a quanto gia' proposto per l'emicrania (41,42).

Appare, quindi, evidente che emicrania e cefalea di tipo tensivo non possano essere piu' considerate quali entita' del tutto separate sia sul piano clinico che fisiopatogenetico. Al contrario le due forme di cefalea idiopatica sembrano condividere almeno parte dei meccanismi patogenetici, condivisione che diventa ancora piu' importante qualora si considerino emicrania e forme di cefalea tensiva ad elevata ricorrenza mensile di attacchi.

Nei prossimi anni la ricerca scientifica probabilmente riuscira' a chiarire se le due cefalee sono legate da un semplice fenomeno di coesistenza oppure se la presenza di entrambe in uno stesso individuo non rifletta piuttosto un comune tratto biologico che sottende una condizione di co-morbidita'. In tale caso, ben diverso significato assumerebbe anche il frequente riscontro di psicopatologie (ansia e depressione *in primis*) sia nei soggetti con emicrania che in quelli con cefalea di tipo tensivo (43-47).

Problematiche terapeutiche

Appare evidente come le incertezze in ambito fisiopatologico e nosografico si riflettano sulla scelta dell'opzione terapeutica piu' appropriata, specie per quanto riguarda il trattamento acuto.

Nel caso dell'emicrania e' stato compiuto uno sforzo notevole, specie nell'ultimo decennio, per valutare l'efficacia e la tollerabilità di varie classi di farmaci sintomatici, ciò che ha consentito anche di stilare delle precise linee guide nazionali ed in-

Tabella 3 - Linee guida per la scelta del farmaco sintomatico per il trattamento sintomatico dell'emicrania

ORGANISMO	ANNO	PUBBLICAZIONE
Societa' Italiana per lo Studio delle Cefalee (SISC)	1993	Confinia Cephalalgica Functional Neurology
	1999	Confinia Cephalalgica
Canadian Headache Association (CHS)	1997	Canadian Medical Association Journal
British Association for the Study of Headache (BASH)	1999	sito web
US Headache Consortium	2000	sito web

ternazionali (tabella 3) che consentano, tanto allo specialista, quanto al medico generico, di orientarsi nella scelta del farmaco piu' adatto.
Dalla rielaborazione di tali "decaloghi" e' scaturito un percorso diagnostico che, sulla guida delle caratteristiche degli attacchi nei vari pazienti, consente di restringere, e quindi facilitare, l'opzione terapeutica piu' appropriata, tra quelle disponibili sul mercato italiano (tabella 4) (48,49).
Per la cefalea di tipo tensivo, invece, solo pochi farmaci sono stati sottoposti ad un rigoroso vaglio sperimentale utilizzando una casistica di pazienti adeguatamente inquadrata dal punto di vista diagnostico ed applicando disegni di studio statisticamente affidabili. Al momento attuale sono, pertanto, piuttosto ridotte le opzioni terapeutiche scientificamente validate per il trattamento acuto della cefalea tensiva. Aspirina, paracetamolo, ketoprofene e ibuprofene si sono dimostrati piu' efficaci del placebo (50-52), mentre il ketorolac ha manifestato una tenue efficacia (53). Il naprossene ha mostrato un'efficacia pari a ketoprofene ed ibuprofene (54). Nella realtà quotidiana succede cosi' che i farmaci piu' spesso utilizzati dai pazienti con cefalea di ti-

Tabella 4 – Indicazioni per la scelta del farmaco ad attivita' antiemicranica sulla base delle caratteristiche cliniche degli attacchi (da Nappi et al. Confinia Cephalalgica 1999 e 2000)

CARATTERISTICHE DELLE CRISI	FARMACO (via di somministrazione) prima scelta	seconda scelta
Crisi lievi (senza nausea)	▪ Analgesici comuni (os)	▪ Diidroergotamina (spray nasale)
Crisi con nausea (indipendentemente dall'intensita' del dolore)	▪ Lisina acetilsalicilato+ metoclopramide (os)	▪ Triptano (os, rettale) ▪ Diidroergotamina (e.v.)
Crisi con vomito precoce	▪ Triptano (rettale, s.c.)	▪ Diidroergotamina (e.v.)
Crisi precedute da: - sbadigli - nausea - ipotensione ortostatica	▪ Lisina acetilsalicilato+ metoclopramide (os)	▪ Indometacina + proclorperazina+ caffeina (os, rettale)
Crisi moderate o severe in fase Avanzata	▪ Triptano (os, rettale, s.c.)	▪ Diidroergotamina (e.v.)
Crisi prevedibili	▪ Lisina acetilsalicilato+ metoclopramide (os)	▪ Indometacina+ proclorperazina+ caffeina (os, rettale) ▪ Diidroergotamina a lento rilascio (os) ▪ Naprossene (os, rettale)

po tensivo siano i prodotti da banco, in cui il principio attivo viene per lo piu' associato a caffeina o sedativi, con il conseguente rischio di assuefazione ed aumento della frequenza delle crisi per comparsa di cefalea da "rimbalzo" (55). Anche l'azione sintomatica dei miorilassanti

Ancora piu' scarsi sono i dati sperimentali relativi all'uso dei farmaci sintomatici delle forme miste, siano esse episodiche o croniche, problematica certo non trascurabile qualora si consideri il ben noto ruolo facilitante dei sintomatici "sbagliati" nell'evoluzione di una forma di cefalea idiopatica (emicrania o tensiva) da episodica in cronica.

Sulla base delle recenti segnalazioni relative all'efficacia di antiemicranici specifici nella forma tensiva (34) e del comune substrato fisiopatologico fra le due forme (v. paragrafo precedente) e' possibile elaborare una serie di considerazioni, che seppur non (ancora) sostanziate da un forte supporto sperimentale, possono essere utilizzate nella pratica clinica, allo scopo di realizzare un flusso virtuoso di informazioni che fornisca al terapeuta un maggiore numero di opzioni e, al tempo stesso, rappresenti per il ricercatore una valida fonte di ispirazione.

In questo contesto, sembra lecito la proposta di valutare il possibile inserimento, fra le opzioni terapeutiche delle forme tensive o miste, di alcuni antiinfiammatori non steroidei che abbiano dimostrato di possedere una componente centrale nel loro meccanismo d'azione nella terapia. E' il caso della nimesulide, un inibitore preferenziale dell'enzima ciclo-ossigenasi 2, che svolge un'azione anti-nocicettiva a livello spinale con un meccanismo che prevede anche un'interferenza con la sintesi dell'ossido nitrico (56). Se la mancanza completa di studi che confermano l'efficacia della nimesulide negli attacchi di cefalea di tipo tensivo rende per ora improponibile la promulgazione del suo impiego in questa forma su vasta scala, ben diversa risulta essere la situazione dell'associazione di aspirina con metoclopramide. L'azione dell'aspirina sia negli attacchi di cefalea tensiva che negli attacchi emicranici e' infatti nota da decenni. Piu' di recente e' stato inoltre dimostrato che l'azione anti-nocicettiva dell'aspirina prevede una componente di tipo centrale che si estrinseca sia a livello del nucleo trigeminale caudale che nella corteccia cerebrale (57-59). D'altronde, la presenza dell'antiemetico nell'associazione appare un particolare tutt'altro che trascurabile se si considera che il sintomo nausea e' presente in almeno un terzo dei pazienti affetti da cefalea di tipo tensivo pura (60) e, sulla base della teoria del continuum di severita', sembra verosimile che esso sia ancora piu' rappresentato nelle forme miste.

Aggiungendo quindi l'associazione aspirina-metoclopramide fra le opzioni terapeutiche per le cefalee miste o di tipo tensivo, appare possibile elaborare un approccio finemente modulato sulla base della tipologia degli attacchi e della loro ricorrenza (tabella 5). L'elevato impatto economico dei triptani ed il frequente riscontro di fenomeni di ricorrenza della cefalea suggerisce il loro uso selettivo negli attacchi di tipo francamente emicranico, di intensita' media o severa, non rispondenti ai comuni analgesici. La presenza di fenomeni di rebound, unitamente all'elevata incidenza di effetti collaterali, suggerisce di limitare l'uso degli ergot-derivati alle stesse indicazioni.

Aspirina, acetaminofene e alcuni FANS

Tabella 5 – Proposte per la scelta del farmaco per il trattamento acuto della cefalea di tipo tensivo e delle forme miste

CARATTERISTICHE DEGLI ATTACCHI	PRIMA SCELTA	SECONDA SCELTA	TERZA SCELTA
Forme tensive pure, con dolore lieve, senza nausea (criteri IHS)	▪ Acido acetilsalicilico (os) ▪ Ibuprofene (os) ▪ Ketoprofene (os) ▪ Naprossene (os)	▪ Ketorolac (os)	
Presenza di nausea	▪ Lisina acetilsalicilato+ metoclopramide (os)	▪ Triptani (os, rettale)	▪ Acido acetilsalicilico (os) ▪ Ibuprofene (os) ▪ Ketoprofene (os) ▪ Naprossene (os) ▪ Ketorolac (os)
Forme a frequenza ingravescente	▪ Lisina acetilsalicilato+ metoclopramide (os)	▪ Acido acetilsalicilico (os) ▪ Ibuprofene (os) ▪ Ketoprofene (os) ▪ Naprossene (os) ▪ Ketorolac (os)	
Forme che, pur esordendo come tensive, possono talora evolvere in emicrania	▪ Lisina acetilsalicilato +metoclopramide (os)	▪ Triptani (os, rettale)	▪ Acido acetilsalicilico (os) ▪ Ibuprofene (os) ▪ Ketoprofene (os) ▪ Naprossene (os) ▪ Ketorolac (os)
Forme non classificabili con almeno una delle seguenti caratteristiche: - dolore pulsante - nausea - sbadigli	▪ Lisina acetilsalicilato +metoclopramide (os)	▪ Triptani (os, rettale)	▪Acido acetilsalicilico (os) ▪ Ibuprofene (os) ▪ Ketoprofene (os) ▪ Naprossene (os) ▪ Ketorolac (os)
Forme non classificabili con almeno una delle seguenti caratteristiche: - dolore gravativo lieve - assenza di sintomi vegetativi	▪ Acido acetilsalicilico (os) ▪ Ibuprofene (os) ▪ Ketoprofene (os) ▪ Naprossene (os)	▪ Ketorolac (os)	

(ibuprofene, ketoprofene e ketorolac) trovano indicazione negli attacchi lievi o moderati delle forme di tipo tensivo. L'associazione aspirina-metoclopramide potrebbe, invece, trovare una naturale indicazione in quelle forme di cefalea di tipo tensiva o mista di intensita' lieve o media che si manifestano fra attacchi emicranici di elevata intensita'. Il loro impiego potrebbe essere esteso anche agli attacchi francamente emicranici intensi, limitatamente alla finestra temporale che occorre rispettare nella somministrazione di due dosi successive di triptani. L'associazione potrebbe essere poi utilizzata nelle crisi che, pur iniziando con caratteristiche tensive, subiscono, col pas-

sare delle ore, una trasformazione in forme tipicamente emicraniche. In considerazione del suo scarso o nullo effetto rebound, l'associazione aspirina-antiemetico può inoltre essere utilizzata nelle forme di cefalea di tipo emicranico, miste o di tipo tensivo in cui si assista ad un progressivo incremento della frequenza degli attacchi con l'utilizzo altri farmaci sintomatici.
Infine, in considerazione della dimostrazione che l'incidenza di nausea nel soggetto con cefalea di tipo tensiva tende ad aumentare passando dall'età adolescenziale a quella adulta, contemporaneamente ad un incremento dell'uso di analgesici, la combinazione aspirina-metoclopramide riveste un possibile ruolo terapeutico nelle forme tensive dell'eta' adulta, specie nel caso in cui si verifichi un pattern in crescendo del consumo di analgesici.

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organizzazione e comunicazione

Introduzione

In questo numero di Confinia Cephalalgica pubblichiamo la seconda parte degli atti del Simposio celebratosi lo scorso anno a Paestum con tema i meccanismi per cui il dolore si trasforma da segnale di allarme, fondamentale per l'adattamento all'ambiente, a motivo di sofferenza per se stesso, rovinando letteralmente la vita a coloro che ne sono affetti. In alcune situazione la sensazione dolorifica è completamente sine materia, non essendo documentata da una qualsivoglia causa che ne giustifica la presenza, la durata, la intensità. E talvolta è difficile spiegare al paziente che per il suo dolore, magari di intensità severa o persistente fino alla cronicità, non vi sia una causa documentabile. Negli ultimi anni un netto avanzamento è stato compiuto nella comprensione dei meccanismi per cui queste condizioni sono prodotte. Di grande rilevanza sono stati gli studi di neurofisiologia che sempre più mettono in risalto e chiariscono concetti quali la duttilità plastica, pur non replicativa, del sistema nervoso, prima invece pensato come sistema che diviene statico alla fine delle fasi dello sviluppo. La farmacologia supporta queste evidenze da un punto di vista dei neurotrasmettitori coinvolti, ma anche chiarisce ed apre sempre più importanti aspetti della trasmissione nocicettiva fornendo prospettive terapeutiche innovative. Le osservazioni cliniche supportate da moderne tecniche di valutazione strumentale, consentono di dare significato agli eventi fisiopatologici che sottendono un sintomo. Infine la genetica, che forse più di ogni altra disciplina sta fornendo possibilità di comprensione di aspetti fino ad ora completamente sconosciuti. In una grande pletora di dati, ipotesi, prospettive, quello che ancora non è stato raggiunto è l'amalgama fra tutte le discipline che orbitano intorno ai problemi sopra descritti. In altre parole la multidisciplinarità. Ma multidisciplinarità non vuol dire che ciascuno degli specialisti delle discipline coinvolte partecipano dando il loro contributo avulso da una visione globale, come svolgere un compito con diligenza, per poi tornare nel proprio recinto. Multidisciplinarità vuol dire integrazione delle esperienze, delle conoscenze allo scopo di fornire la propria parte interpretativa per raggiungere la comprensione di un fenomeno o quanto meno avvicinarsi ad essa. Lo scambio di esperienze sollecita nuove idee, propone nuove soluzioni.

Questa parte è in lingua inglese. Infatti si tratta di contributi più di base rispetto a quelli già pubblicati in italiano. Questa scelta di proporre i contributi in lingua differente ricalca lo spirito con cui era stato progettato il Simposio senza una schema rigido, ma con un meccanismo fluido di interscambio culturale, tra l'altro in un ambiente piacevole e quasi ricreativo, che potesse offrire una occasione poco formale ma costruttiva di confronto reale fra varie esperienze. E proporre collaborazioni interdisciplinari nuove ed innovative. Importanti collaborazioni sono in corso con risultati di rilievo.
I lavori di questa sessione sono molto interessanti ed esplorano vari aspetti del problema legato al dolore patologico e di quelli che abbiamo definito i suoi paradigmi: le Cefalee Primarie. Ringraziamo ancora il prof. Nappi che ha voluto ospitare anche

questi contributi nella sua prestigiosa rivista. Gli siamo grati perchè Confinia Cephalalgica rappresenta la tradizione ed il prestigio italiano nel campo delle cefalee.

Un'ultima considerazione sempre in tema di multidisciplinarità. Sto scrivendo (collaborando via e-mail con il prof. Giacovazzo) questa introduzione mentre mi trovo per lavoro negli Stai Uniti. Il paese che mi ospita è un paese spesso discusso ed a volte discutibile. Ma ha anche pregi fondamentali che contribuiscono a farlo essere il paese leader nel mondo. Fra i pregi vi è la capacità di ciascuno di lavorare in team, ponendo il proprio impegno con quelli di altri in modo sinergico per raggiungere uno scopo comune. E ci riescono, vanno al di là delle individualità, delle piccole rivalità, delle conflittualità spicciole che sono presenti in ciascun essere umano, non comunque escluse anche qui, negli USA. Ma lo scopo del gruppo è più importante. Questo dovrebbe essere lo spirito della multidisciplinarità: ex pluribus unum.

Bruno M. Fusco, Mario Giacovazzo

Emerging concepts in migraine pathophysiology

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This review briefly focuses on recent developments in migraine research with emphasis on new imaging techniques including Blood Oxygenation Level-Dependent (BOLD) functional MR and Laser Speckle Imaging. The importance of cortical spreading depression and sensitization will also be addressed as will the importance of serotonin receptors in acute migraine treatment.

KEY WORDS: cortical spreading depression, imaging, migraine pathophysiology, sensitization, serotonin receptors

Introduction

The pathophysiology and treatment mechanisms in migraine remain understudied and poorly understood in part because experiments are difficult to initiate in humans. However, with the recent advent of functional imaging, new tools are becoming available to study migraine both during the headache and aura. Some investigators have proposed that meningovascular and cerebral mechanisms are of primary importance to the underlying pathophysiology, although with existing information, it is impossible to distinguish the relative contributions of each. This chapter will review topics of emerging importance to migraine mechanisms. New insights into basic pathophysiology and drug mechanisms will hopefully translate into improved quality of life and expanding knowledge about brain function.

Peripheral Sensitization

Chemosensitivity and sensitization within meningeal primary afferents fibers may contribute to mechanical hypersensitivity and throbbing quality of headache pain. Strassman and colleagues recorded from trigeminal ganglion during stimulation of dural venus sinuses (1). They found that chemical stimulation of dural receptive fields by inflammatory mediators directly enhanced mechanical sensitivity of trigeminal afferents and rendered them strongly activated by previously innocuous mechanical stimuli. In addition to central pain transmission, trigeminal C-fibers release vasoactive neuropeptides. Substance P (SP), neurokinin A (NKA) and calcitonin-gene-related peptide (CGRP) levels increase in sagittal sinus blood upon stimulation (2) and mediate neurogenic inflammation (NI) (3-4). This sterile inflammatory response within meninges consists of: endothelial activation with platelet aggregation, leakage of plasma and plasma protein from small vessels into surrounding tissue, vasodilation, and activation of mast cells. NI may be associated with threshold lowering for C-fiber activation and may be one of the mechanisms by which headache is prolonged and intensified.

Preliminary evidence that a meningeal inflammatory response may develop during migraine comes from a recent small series of patients studied during acute migraine attacks with Single Photon Emission Computerized Tomography (SPECT) scan using 10mCi 99Tc Hu-

man Serum Albumin (5). In three cases, the SPECT images taken approximately 3 hrs into unilateral headache showed increased extraparenchymal isotope accumulation within the region of maximal head pain, consistent with neurogenic inflammation.

Central Sensitization

Central inputs from nociceptive fibers increase the excitability of higher order neurons within trigeminal nucleus caudalis (6). Activation of small caliber C-fibers by inflammatory and chemical stimuli causes expansion of receptive field size (7), lowering of thresholds for activation of second order neurons (8), recruitment of inputs from normally non-nociceptive fibers (6) and a heightened response to suprathreshold stimuli. Together, these state changes are known as central sensitization and are reflected clinically in the pain associated phenomena of spread of cutaneous sensitivity to uninjured areas, hyperalgesia (lowered pain threshold) and cutaneous allodynia (the generation of a painful response by normally innocuous stimuli). Recent animal studies by Burstein and coworkers (9) have shown that chemical irritants applied to the meninges lower the threshold of second order neurons to subthreshold low-intensity mechanical and thermal stimuli. Furthermore, noxious chemical stimulation of the dura lowers the threshold for generation of cardiovascular response (such as blood pressure elevation) by previously innocuous skin stimulation (10). Recent data also suggest that the responses of neurons within trigeminal nucleus caudalis receiving convergent inputs from face and dura are enhanced following dilation of meningeal arteries by CGRP infusion (11). If true, then neurogenic vasodilation may also contribute to the phenomenon of central sensitization in humans. Furthermore, antimigraine 5-HT1 agonists (L-741,604) attenuate these augmented responses to cutaneous stimulation either by inhibiting vasodilation or by actions directly on neuronal receptors (11).

Recent clinical data support a relationship between migraine and central sensitization. Repeated measurements of mechanical and thermal pain thresholds were performed in periorbital and forearm skin during and in between attacks in 42 migraineurs. Seventy-nine percent of subjects exhibited cutaneous allodynia (12). Hence, sensitization may represent an important new therapeutic target for migraine.

Imaging

New discoveries using functional imaging are rapidly expanding our knowledge of changes in human brain during a migraine attack. One such technique, Blood Oxygenation Level-Dependent (BOLD) imaging is based on changes in deoxyhemoglobin content and its corresponding MRI signal changes (13). The BOLD technique, widely employed in the generation of brain activation maps, was used recently by Cao to investigate the occipital cortical response to flashing lights in migraineurs. Cao and colleagues (14) studied 10 patients with aura and two patients without aura. In 5 subjects, the onset of headache or visual change (but not aura) was preceded by suppression of initial activation with spreading inactivation across occipital lobe at a slow rate (3-6 mm per minute). Sanchez del Rio et al (15) re-

ported results during two spontaneous migraine visual auras. In these studies, loss of activation to a visual stimulus developed in occipital lobe contralateral to the symptomatic visual field in all patients. With resolution of symptoms, activation within the affected occipital lobe gradually returned to normal. The occipital lobe ipsilateral to the visual field defect responded normally at all time points. The inducible subject was imaged before the onset of symptoms and for the full duration of visual symptoms and into the headache phase. With onset of visual symptoms, suppression of activation was observed first in area V3a, a region sensitive to motion (16). This area of suppression expanded across areas of contiguous occipital cortex at a rate of 3.5 mm per minute to involve both primary visual and association cortices. The area of BOLD perturbation within striate cortex corresponded to the retinototopic visual disturbance. Perfusion defects observed at the end of all four auras were present in areas that had exhibited abnormal BOLD activation.

The MR findings described above resemble cortical spreading depression in the following ways: 1) Both CSD and the migraine visual aura are characterized by an initial hyperemia lasting about 3 to 4.5 minutes; 2) the hyperemia in both CSD and migraine aura is followed by mild hypoperfusion lasting 1-2 hours; 3) the hyperemia/hypoperfusion signal spreads across the cortex at a slow rate (2-5 mm/min); 4) both the BOLD signal complex during aura and induced CSD's in animals abort at major sulci; 5) evoked visual responses during CSD and during aura are suppressed and take about 15 minutes to recover; 6) finally, in both CSD and migraine aura, the first affected area is the first to recover normal evoked responses. Hence, these studies suggest that cortical spreading depression (CSD) or at least a human analogue of CSD may underlie the migraine visual aura. Whether CSD is either necessary or sufficient to generate headache remains for further study.

Serotonin receptor subtypes and abortive treatment

5-HT is the neurotransmitter most frequently mentioned in relation to migraine. However, most of the evidence for a direct role of this amine in pathophysiology is circumstantial (17). For example, platelet 5-HT levels are reduced by 30% during attacks, while plasma concentrations are 60% lower, and the biogenic amine depleting drugs such as reserpine cause a "typical headache" in migraineurs, probably by inducing 5-HT release from intracellular stores. Similarly, m-chlorophenylpiperazine (m-CPP), a major metabolite of the antidepressant trazodone, has been reported to cause migraine-like headaches in humans by activating 5-HT2B or 5-HT2C receptors. Perhaps the strongest evidence for a role of 5-HT in migraine has been provided by the fact that some acute (ergot alkaloids and sumatriptan, naratriptan, rizatriptan, zolmitriptan ("triptans") and prophylactic (methysergide, pizotifen, cyproheptadine) antimigraine drugs interact with 5-HT receptors. Fourteen different subtypes of 5-HT receptors have been identified by pharmacologic and molecular cloning techniques (18).

Historically, the antimigraine efficacy of ergots was documented in the 1920's, although their ability to inter-

act with 5-HT receptors was not known until the 1950's. Pharmacologically, however, these drugs are highly nonselective, since they interact no only with 5-HT receptors but also with dopamine and noradrenaline receptors. They were initially employed in migraine based on the belief that migraine resulted from altered sympathetic activity. Graham and Wolff (19) proposed that the efficacy of ergotamine was due to its vasoconstrictive activity on the extracranial vasculature. Sumatriptan is the first of a series of agents (which now includes naratriptan, rizatriptan and zolmitriptan) that was developed by screening agents that would selectively activate "vasoconstrictive" 5-HT receptors (20). However, the importance of vasoconstriction to the antimigraine efficacy of triptans and ergot alkaloids is controversial, and activation of neuronal receptors located on primary afferents (21) or in the brainstem trigeminal nucleus (22) might be of equal or greater significance. More recently, inhibition of neurogenic vasodilation, involving activation of trigeminal A-delta-fibers, rather than inhibition of neurogenic inflammation produced by activation of trigeminal C-fibers, has been proposed to underlie the acute antimigraine activity of selective 5-HT1 receptor agonists (21, 23).

As noted above, neurogenic inflammation has been proposed as a mechanism relevant to vascular headache pathogenesis and treatment (20-21). Blockade of central processing within trigeminal nucleus caudalis has also been proposed (22). The tachykinins induce both an endothelium-dependent vasodilation and enhanced permeability via receptors located on the vascular endothelium. CGRP induces vasodilation by activating receptors on vascular smooth muscle cells. Several factors indicate the relevance of neurogenic inflammation to the acute treatment of migraine. Ergotamine and sumatriptan have been shown to block this process in the dura mater of rodents after electrical stimulation of the trigeminal ganglion. The dosages required to block neurogenic inflammation in rodents are comparable to those efficacious in relieving migraine headache. These drugs block the inflammatory response even when administered 45 minutes after electrical stimulation (23). Finally, other medications effective in the treatment of migraine attacks but inactive at 5-HT1 receptor also block plasma protein extravasation: opiates (24), valproate (25), and acetylsalicylic acid (26). The specific receptor subtype responsible for the antimigraine efficacy of ergot alkaloids and triptans has not been identified with certainty (27).

Most migraine aborting drugs show a high affinity for 5-HT1B and 5-HT1D receptors. The only exception to this rule is the 5-HT1F selective drug LY334370. However, it is worth mentioning that this agent shows antimigraine efficacy at the relatively high dose of 60 mg, but not 20 mg (28). It is thus impossible to rule out a 5-HT1B/1D mediated effect. In addition, the affinity of IS-159 and alnitidan for 5-HT1F receptors is negligible, indicating that activity at this subtype is not required for therapeutic efficacy. Considering that c-fos expression in rat trigeminal nucleus caudalis after intracisternal capsaicin administration (a model commonly used in antimigraine drug development) can be inhibited by both 5-HT1B and 5-HT1F receptors, it is likely that stimulation of either re-

ceptor is sufficient to abort migraine attacks (27). A significant role of 5-HT1A receptors can be ruled out, because these receptors are neither involved in the smooth muscle actions of these drugs, nor in their inhibitory effects on neurogenic inflammation.

Reverse transcriptase polymerase chain reaction techniques (RT-PCR), as well as in situ hybridization experiments, have detected similar amounts of the mRNA for both 5-HT1D and 5-HT1B mRNA in human trigeminal ganglia (29). 5-HT1F receptor mRNA was also found in human trigeminal ganglia, indicating a presynaptic location of these receptors. Interestingly, mRNA's for both 5-HT1B and 5-HT1F receptors, but only trace amounts of 5-HT1D receptor mRNA, were found on cerebrovascular tissues. 5-HT1B mRNA was also found in coronary artery (29-31). In view of the reported cardiovascular side effects of sumatriptan (32), this data suggests that selective 5-HT1D agonists (with no effect at 5-HT1B receptors) might alleviate headache with greatly reduced side effects, provided efficacy in the neurogenic inflammation model is predictive of antimigraine efficacy.

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Referred pain. A Clinical approach

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The term "referred pain" is used for pain localised not in the site of origin of pain but in areas that may be adjacent or et distance from such site, generally comprised in the same metameres. Pain can be referred by deep somatic or by viscera1 structures. Myofascial pain syndrome is a typical syndrome characterised by referred pain from deep somatic structures. Referred pain from visceral organs is the most important from a c1inical point of view. The patterns of referred pain originating from various viscera are important for a correct diagnosis. Different pathogenetic mechanisms may be involved in the onset of referred pain: convergence impulses in the central nervous system, reflexes inducing muscle contraction, sympathetic activation, antidromic activation of afferent fibres which induces the so-called "neurogenic inflammation".

KEY WORDS: myofascial pain, neurogenic inflammation, reffered pain, theory of convergence, visceral pain

The term "referred pain" is generally used for pain localized not in the site of origin but in an area that may be adjacent or at distance from such site. The term "transferred pain" (übertragener Schmerz), used German authors (1) is perhaps more appropriate because it indicates the phenomenon as it is observed. Pain can be referred: a) by a deep somatic; b) by a visceral structure. It has generally a metameric distribution.

Myofascial pain syndrome is a typical syndrome characterized by referred pain from deep somatic structures: pain originating in muscular "trigger point" is referred to " areas of reference" (or "target areas") (2).

Referred pain may also be observed when pain is experimentally induced in deep somatic structures. Kellgren (3) and Lewis (4) carried out a group of interesting experiments in man: they induced referred pain by injection of hypersonic saline solution in muscles, tendons and ligaments. The pattern of pain induced by injection of saline solution into the intespinous vertebral ligaments was especially interesting: a referred pain was observed with a segmental distribution. In recent investigation Vecchiet et al (5) observed that the experimental induction of deep somatic allogenic focus via injection of hypersonic saline solution into skeletal muscles provoked hyperalgesia of the skin, of the subcutaneous tissue and of the muscles in the referred pain area.

Referred pain from visceral organs is the most important from a clinical point of view (6,7). It is especially observed when an algogen process affecting a viscus is intense and long lasting or recurs frequently.

The different aspects of true visceral pain and referred pain are especially evident in some clinical conditions. In

ischemic heart disease, three types of pain my be distinguished: a)true visceral pain; b)deep somatic pain (deep referred pain);c) cutaneous pain (superficial referred pain) (7).
True visceral pain is poorly localized, usually retrosternal or epigastric. Sometimes interscapular. It is accompanied by nausea, vomiting, diffuse sweating and by an intense alarm reaction. This type of pain is the earliest manifestation in most cases of myocardial infarction.
Deep referred pain is constrictive and rather well localized. It is reported by patients as originating in the thoracic wall and/or in the upper limbs: in the chest it may be felt in the precordial, sternal or left interscapular area; in the upper limbs (more frequently the left) it may be diffuse to the shoulder and to the whole limb and/or localized in the forearm, with a sense of numbness and constriction at the elbow and wrist. In myocardial infarction this type of pain often follows the deep visceral pain, in angina pectoris it is usually the first type of pain perceived.
Superficial referred pain is well localized and is felt only in the C8-T1 dermatomes, i.e. in the lunar side of arm and forearm. It may arise both in infarction and angina pectoris. It is nearly always associated with deep referred pain, but it is not frequent.
In painful disease of thoracic visceral organs, differential diagnosis may be very difficult. A clinical problem is to distinguish heart pain from esophageal pain (7). True visceral pain in esophageal diseases is poorly localized, substernal pain, mainly felt at the level of the xyphoid process. The typical areas of reference of esophageal pain are the higher sternum for the disease of the proximal third of the esophagus and the lower sternum for the disease of the distal third. Diseases of the intermediate third may give rise to pain referred to one or another areas. Moreover, esophageal pain may be referred to other areas: the interscapular and the central dorsal areas at the level of the sixth and seventh thoracic vertebrae, the precordium, the epigastrium, and the upper limbs. It is evident that true visceral pain in esophageal diseases may be very similar to heart pain and that many areas of reference of esophageal pain are the same areas on which heart pain may be referred.
Other diagnostic problems may be due to the presence of the so-called "intricate conditions". The concept of intricate conditions was introduced by Froment and Gonin (8) who, studying pain of coronary heart disease, identified some syndromes in which heart pain was mingled with one arising fro other structures. Froment and Gonin called these syndromes with the name of "intricate angina" (angors cornariens intriqués). Intricate angina may be observed when myocardial ischemia is accompanied by cervicothoracic osteoarthritis (vertebro-coronary syndrome), by chest fibromyalgia or by disease of the gastrointestinal tract, such as disease of the esophagus, hiatus hernia, gastroduodenitis, peptic ulcer calculous and non-calculuos cholecystitis (cholecystocoronary syndrome). Intricate conditions may be due to an addition of impulses from different sources in central nervous system or to viscero-somatic and somatovisceral reflexes, which may induce a "vicious circle" between different structures. Typical intricate condition are observed when thoracic referred pain from heart or esophagus is accompanied by fibromyalgia or myofa-

scial pain syndrome involving muscles of the chest wall.

Many hypotheses have been proposed to explain the mechanism of referred pain. Some fundamental concepts were proposed by Head and by MacKenzie.

Head (9) in 1893 assumed that "the localisation of sensation is not physical but psychical phenomenon", According to Head, at the level of spinal cord there is a convergenc of impulses from visceral organs and from more superficial structures: visceral pain is referred to the surface of the body "by a psychical error of judgment" This theory was called by Ruch (10) "convergence-projection" theory.

MacKenzie (11) instead suggested that the impulses from the diseased viscus entering the posterior horn set up an "irritanle focus" by the constant bombardment of the segment in which they enter. This "irritable focus" causes a dimished threshold for the somatic impulses which are constantly entering the same segment of the cord: in such way cutaneous hyperlagesia and referred pain are produced in the corresponding segments. MacKenzie suggested that visceral afferent impulses activate anterior and lateral horn cells, producing muscle contraction, piloerection, vasoconstriction, and other sympathetic phenomena. Ruch (10) called MacKenzie's interpretation "convergence-facilitation" theory.

The occurrence or referred pain from viscera with reflex muscle spasm and deep tenderness was demonstrated in experimental studies on genito-urinary pain in man. MacLellan and Goodell (12) in 1943 observed that follwing a faradic stimulation or local distension of the ureter or the pelvis of the kidney, the muscles of the abdominal wall on th stimulated side remained contracted and, after about half hour, this side began to ache. The ache became quite severe and lasted for six hours, with the side still tender during the following day. It was clear that painful stimulation of visceral structures evoked a viscero-somatic reflex, so that some muscles contracted and became a new source of pain. In ureteral colic due to calculosis, Vecchiet et al.(13) observed that, when pain is long lasting , cutaneous and muscolar tenderness and hyperlagesia are still present when visceral pain is eliminated by medical and surgical means. The observations are important because they demonstrate that referred pain, if longlasting, may become independent from the visceral noxae and persist also when visceral pain disappear, becoming a true muscular pain.

In referred pain from viscera a reflex activation of sympathetic nerves, which modifies the peripheral environment, is often observed. As regards referred pain from somatic structures, Galletti and Procacci (14) observe that a lidocaine block of sympathetic ganglia led to the disappearance or at least, to a strong decrease, of referred pain, hyperalgesia, alterations of dermographia and of a cutaneous electrical impedance in cases of myofascial pain. Hyperactivity in autonomic system is important not only because it can be a starting point for a reflex sympathetic dystrophy or sympathetically maintained pain. Pain of acute myocardial infarction induces the well-known referred pain of muscles and skin and sometimes a scapulo-humeral per arthritis or a complete shoulder-hand syndrome (7,15).

A controversial point is what happens

when a local anesthetic is injected in the site of referred pain. Sometimes referred pain disappears, sometimes not (6). Pain generally disappears when it is accompanied by deep somatic and cutaneous hyperalgesia.

Progress in neuroanatomy and neurophysiology confirmed many of the theoretical assumptions proposed by Head and MacKenzie. Experimental data for the existence of convergence of visceral and cutaneous afferent fibres onto second order neurons were presented by Pomeranz et al.(16) and by Seltzer and Spencer (17). The analysis of the visceral afferent fibres showed that only small myelinated and unmyelinated fibres converged onto spinal cord neurons: These findings were confirmed by several groups (18-19).

In 1937 Morley (20) published a hypothesis on referred pain, based on the concept of the presence of afferent collaterals associated with afferent axons. Eleven years later, Sinclair et all (21) extended the hypothesis of Morley. According to these authors, the branching of afferent axons is such a type that one limb of a branched axon passes to the site to which the pain is referred. This mechanism works in two ways: first by leading to a misinterpretation by the central nervous system of the true origin of the pain impulses and secondly by the antidromic liberation of metabolites at the terminals in the region where pain is experienced, thus giving rise to secondary pain impulses actually having origin at the periphery. Of course, this theory presupposed axon reflexes as postulated by Lewis (22).

An antidromic activation of cutaneous and muscolar afferents was experimentally demonstrated in animals (23-24). The antidromic activation of afferent C fibres induces a neurogenic inflammation, by the release of some neuropeptides (substance P, calcitonin gene related peptide (CGRP), neurokinin A, neurokin B) and probably of other autacoids (25). This neurogenic inflammation may be induced by axon reflex. According to Moskowitz et al. (26) neurogenic inflammation is a primary factor in causing migraine crisis, with release of sensory neuropeptides both in dura mater and in temporal muscle. In experimental arthritis in rat and in rheumatoid arthritis in man Ferrell and Lam (27) observed a release of substance P, CGRP, neurokinin A and vasoactive intestinal is synovial fluid and articular and periarticular tissue have a rich innervations. Ferrel and Lam also observed an activation of sympathetic system and postulated a positive feedback mechanism. Neurogenic inflammation appears to be an important mechanism in referred pain.

In conclusion, referred pain is an important path physiological phenomenon, in which may components intermingle, which of te occurs in clinical conditions. The careful evaluation of this phenomenon is necessary for correct diagnosis in important painful affections.

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The psychogenic factor in primary headache disorders

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The association between personality changes and chronic pain is well accepted. As far as migraine is concerned, in the majority of the investigations a relation was found between this pathology and mood or personality disorders. Data from a longitudinal studies support the hypothesis that this relation is bi-directional. This association is even more pronounced in chronic daily headache and in patients with facial pain disorder (so called " atypical facial pain"). After treatment, most authors found an improvement of personality profile in patients with headache or facial pain. However, this improvement varies conspicuously in the different series, also depending on the pain pathology involved.

KEY WORDS: headache, personality, psychology

Personality alterations and pain

The association between personality changes and chronic pain is well accepted (1-4). By means of various psychometric tests, such as the Minnesota Multiphasic Personality Inventory (MMPI), the Hamilton test, the Eysenk Personality Inventory, the Beck depression test, the State-Trait Anxiety Inventory (STAI) and others, depression and anxiety have in general been found more elevated in a chronic pain populations than in healthy controls (3, 5, 6-7-8-9). The question whether such personality disorders predispose to pain is still debated. however (10-12).

Personality alterations and headache

In patients suffering from headache or facial pain the first question is whether mood or personality disorders, when present, represent a peculiar characteristic of these patients or whether such disorders are simply a consequence of chronic pain. Furthermore, if a relation between head pain and mood or personality disorders exists, the question is whether such relation is unidirectional or bi-directional, that is whether:
1- mood or personality disorders predispose to headache and facial pain;
2- mood or personality disorders are a consequence of headache and facial pain; or 3- both hypotheses are correct.
Characteristic mood or personality alterations have quite extensively been reported in patients with cranio-facial pain and/or headache (5, 13-25). These data were confirmed also in children and adolescents (26-27).
However, while some authors (13-14, 18, 20, 28-29) maintain that such changes predispose to some types of pain, others (17, 30-32) reject this hy-

pothesis and believe that psychopathology is rather a consequence of headache or facial pain.

As far as migraine is concerned, in the majority of the investigations a relation was found between this pathology and mood or personality disorders (33). Using the MMPI in migraine patients, some authors found normal profiles or, at least, a lower scale elevation than in patients with chronic tension-type headache or with migraine and tension type headache superimposed (13-14, 34). Instead, other authors found a marked elevation of several MMPI scales and, in women migraine patients, a typical V configuration of the neurotic triad of the MMPI (with high scores of hypochondria and hysteria, and depression score still high but lower than those of the two other scales) (17). Using the Eysenck Personality Questionnaire higher scores of psychoticism were found (20). In epidemiological studies an association was found between migraine and panic attacks (35) and between migraine and depression and anxiety disorders (20, 36-40). This was confirmed by recent prospective studies (41-42). Mongini et al. in a study (24) in which 43 women with migraine were examined with MMPI, STAI and history including a checklist of psychosomatic symptoms found a general elevation of several MMPI scales and STAI scores. According to the different MMPI profiles obtained, the patients could be divided in four different groups : one group had an elevation of the three scales of the neurotic triad (and of depression in particular) and of psychastenia (indicating anxiety); a second group showed a "conversion V" configuration of the neurotic triad (with definite elevation of hypochondria and hysteria scales with the depression scale been at least 10 T-scores lower) , a third group ("emotionally overwhelmed") had an elevation of the scales of the neurotic triad and of others relative to psychoticism (paranoia, schizophenia, mania), and a fourth group had a normal configuration (the "copers"). The majority of the patients had several symptoms, prevalently psychosomatic in nature: however, these symptoms were less prevalent in the group with normal MMPI configuration . As far as the relation between migraine and depression is concerned, data from a longitudinal study (42) support the hypothesis that this is bidirectional. More recently, Mongini et al. (43) recorded the prevalence of 26 psychosomatic symptoms in 141 migraine female patients and processed the data were through a neural network system (Self-Organizing Map - SOM-). They found two patient clusters with high and low prevalence of psychosomatic symptoms. The cluster with high prevalence showed consistently higher scores of several MMPI scales and of STAI 1,2 scores. They concluded that a distinction could be made between two categories of migraine female patients with high or low personality, respectively.

Cronic tension-type headache, alone or in conjunction with migraine, is often accompanied by alterations of mood (5, 13-14 , 17, 24, 31, 44).

This association is even more pronounced in chronic daily headache (CDH) , that is for headache present all day or most of the day , at least six days a week and since at least six months (45-46). Mongini et al. (23-24, 47) examined with the MMPI patients with CDH and found that approximately one third of the patients had a char-

acteristic "psychosomatic" configuration while the rest of the patients had elevation of all three neurotic scales(and depression in particular) and of psychastenia. Almost all patients had numerous psychosomatic symptoms.
Patients with facial pain disorder (so called "atypical facial pain") are those in whom the coexistence of the pathology with distinct personality changes seems least debatable (5, 16, 48-49). Pain in such patients is usually constant or persistent for most of the day, and is troublesome or poorly defined. At onset, it can be confined to a limited area of the maxilla or the mandible, but it may then spread to a wider area of the face and neck. Typically it is not confined to the distribution of a cranial or cervical nerve root, neither can a structural source of pain be identified.
In research using the Minnesota Multiphasic Personality Inventory (MMPI) to assess personality profiles in patients with different types of headache or facial pain, Mongini et al. (5) found that the group with facial pain disorder had many scales significantly higher than other groups. This datum was independent of the level of pain. Moreover, this was the only group in which all three "neurotic" scales - hypochondria, depression and hysteria - scored above 70 (clearly above normal values), depression being slightly lower than the other two scales. More recently, Mongini et al. (25) using the MMPI-2 came to similar conclusions.
Thus, a tendency to the already mentioned "psychosomatic" or "conversive V configuration" was observed, although in its typical pattern this configuration has the depression score 10 or more points below hypochondria and hysteria scores. Interestingly, a similar tendency to this configuration was found , besides, as mentioned in migraine and CDH, also in other chronic pain pathologies, such as primary fibromyalgia, in which the psychological factor seems to play an important role (6, 10-11).

Personality profiles and treatment outcome

The question of whether headache and facial pain are associated with mood or personality disorders is related to two additional questions, that is: 1) whether personality profiles before treatment might predict treatment outcome, and 2) whether treatment outcome is proportionally accompanied by an improvement of the personality profile of the patient. As far as the first issue is concerned, some authors (50) found that, in headache patients, an elevation of the depression and social introversion scales correlated positively with the biofeedback treatment outcome. However, other authors applying the MMPI conclude that MMPI findings before treatment have no prognostic value of treatment outcome in patients with migraine or with different types of headache or facial pain (24, 30, 44).
As far as the second issue is concerned, most authors found an improvement of personality profile in patients with headache (24, 30, 44, 51). However, this improvement varies conspicuously in the different series, also depending on the pain pathology involved. Mongini et al. (24, 44) administered MMPI and STAI before and after treatment to 96 patients suffering from different types of headache or cranio-facial pain, comparing the data obtained to those concerning improvement in pain after treatment. These authors found a significant reduction

in the whole group, after treatment, of numerous MMPI scores (Hs, D, Hy, Pd, Pt, Sc, Si) and of STAI 1 and 2 scores . Separate analysis confirmed this trend among women but not among men. Profile improvement was more marked in patients suffering from tension-type headache than in those with migraine of facial pain disorder as somatoform disorder. No relation was found between MMPI and STAI changes before and after treatment and the degree of improvement.

In CDH the improvement of the personality is related to its characteristics before treatment. In the above mentioned work, Mongini et al. (24) found in CDH patient a decrease of several MMPI scales after treatment.. However, patients with a conversive V configuration before treatment still showed this configuration after treatment , though at a lower level, while several patients with a depressive MMPI profile showed a conversion V after treatment . Therefore it seems that hysterical traits may be typical of these patients and that they may develop a depressive disorder while headache becomes chronic

The question remains open whether these changes are consequent on symptom improvement or on a third variable.

Ellersten et al. (30) applied the MMPI test to migraine patients treated with biofeedback, and separated the patients into two subgroups: those who showed most and least improvement. These two groups showed strikingly similar profiles before treatment. However, after treatment, the group which had responded best to therapy, compared to the group which had responded poorly, showed a significant decrease in the values of numerous MMPI scales. On the contrary Blanchard et al., (51-52) found , after treatment, an improvement of the psychological profile of headache patients independent of the treatment outcome. Finally, Mongini et al., in the previously mentioned works (24, 44), could not find any statistical relation between changes in MMPI and STAI before and after treatment and the degree of clinical improvement.

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Cluster headache: a clinical and nosographic update

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A recent review showed a progressive reduction in male preponderance, in cluster headache (CH), over the different decades of onset of the disease. In order to establish whether or not that change could be accounted for by time-related variations in referral to the Centre, we selected 610 patients affected by migraine without aura (MO) matched to our CH patients by decade of disease onset.
The pattern of male-to-female ratios over time was not found to be comparable in the two forms of headache and our data analysis showed that the change could not be explained by an increase in the rate of female referrals to the Headache Centre over the last few years.
According to the International Headache Society (IHS) classification, all patients with forms of cluster headache (CH) not matching any one of the diagnostic criteria at 3.1 must be coded as 3.3, or "Cluster headache-like disorder not fulfilling above criteria". We applied the IHS coding parameters to a study population of 652 CH patients in order to: i) determine how many patients fulfilled the diagnostic criteria for group 3.3; and ii) find out any diagnostic elements that could be added to or changed in the upcoming revision of the classification to make it more relevant to current clinical practice. In our opinion, the upcoming revision of the IHS classification should take into consideration such diagnostic elements and have certain criteria of the 3.1 group - i.e., pain location and accompanying autonomic phenomena - modified accordingly.

KEY WORDS: Clinical features, cluster headache, diagnostic criteria, gender ratio, migraine without aura

Gender ratio in cluster headache

Among primary headache forms, cluster headache (CH) is certainly the one with the most distinctive clinical features, which make its recognition comparatively easy. Yet, several aspects of this disease (e.g., epidemiological data) are still quite unclear. The most recent evidence from CH research concerns genetic factors -which are thought to play a primary role in CH pathogenesis (1)-, the possible location of CH pathophysiologic "primum movens" at the CNS level as shown by PET scanning (2) and functional MRI (3), and the observation of a progressive decrease in male preponderance by decade of onset since the 1950s. (4).

The University of Parma Headache Centre has investigated the latter aspect extensively through an in-depth analysis of the phenomenon in order to exclude any interference. In particular, after searching for evidence of the actual preponderance pattern to explain the possible causes of its modification, we found that no changes were introduced over the years in the procedures used at our Centre for patient referral and data collection, nor did any changes occur in male and female distribution in the population from the same area as our CH patients.

The modification of the pattern might then be explained either by a change in gender preponderance for CH among the general population or by the fact that an increasing number of CH females were seeking treatment at our Centre. While the first hypothesis can be verified only through a study of the general population, for the second one it is necessary to determine whether or not the same pattern can also be found for females reporting other forms of primary headaches.

We therefore calculated the male: female ratio by decade of onset in a group of 610 CH patients consecutively referred to the Parma Headache Centre between December 1975 and June 1998, versus a "control" group of patients with migraine without aura (MO). So, we calculated the male: female ratio by decade of onset in 610 MO patients selected at random among all those who had been referred to our Centre over the same period of time, the only inclusion criterion being that they could be matched to CH patients for decade of onset. All pre-1988 diagnoses were revised according to the International Headache Society (IHS) criteria.

The calculation of the gender ratio in the two patient groups surprisingly showed opposite patterns for the two headache forms, confirming the decrease in male preponderance over time for CH – with a male:female ratio of 5:1 for patients with disease onset before 1960 and of 2.0:1 for those with onset after 1990 – and indicating a reduction of the female preponderance over time for MO with a female:male ratio of 6.0: 1 for patients with disease onset before 1960 and of 2.0:1 for those with onset after 1990. For both forms of headache, a sharp reversal of trend was apparent after 1970.

When we calculated mean age at onset and mean age at the first visit by decade for CH patients and for MO patients, we could not find any differences between males and females in the periods considered. Therefore, any influence of those factors on the change in gender ratio should be excluded. Based on our study results, we can: i) dismiss the hypothesis of changes in the gender representation of referrals to our Centre, because if that were so, we would have found the same pattern – or, at least, a similar pattern – in the two primary headache forms; and, ii) demonstrate a sharp trend reversal after 1970.

In the literature there are no studies of non-Italian CH patient samples that corroborate our line of evidence and so it is possible that the phenomenon may be typical of the Italian population. We then re-oriented our research toward a definition of Italy's social an cultural background in the '70s.

In the late '60s, groups of female intellectuals began to question the certainties of a society that was still strongly dominated by male figures. In those same years, the Students' Movement group and the other groups coming in the wake of the 1968 protests brought to the fore the male authoritarianism lingering under new forms inside the groups themselves, stressing the differences still existing between gender roles and, ultimately, the persistence of female subordination in what might otherwise be considered a "revolutionary" movement. Women then felt that what they actually needed was not so much emancipation – meaning an attempt to achieve parity with men – as true liberation – meaning the search for a separate identity of their own as a means of affirming their unique role in society. The rediscovery of female subjectivity obviously undermined the predominant-

ly male values of traditional society, leading to the appearance of several movements that, in spite of different ideologies and goals, shared a concern for such issues as sexuality, family relations, the division of roles, the recognition of housewives' work, the search of new approaches to politics, now all seen from a woman's perspective.

Starting in 1964, people began to talk openly about birth control, sexual education, divorce and abortion. Struggles followed for equal pay for equal work, freedom of access to all careers, planned motherhood, and the creation of day-care centres and other social structures. Then, in 1973, two campaigns were launched to support female employment and a reform of family law. The efficacy of the women empowerment movements is reflected in the large number of laws that were enacted in those years: first, in 1963, the abolition of an employer's right to fire women workers in case of marriage and the removal of the ban on female access to careers in justice administration; then, in 1974, the referendum that called people to vote for or against divorce, followed in 1981 by a similar referendum about abortion on demand. The factors that contributed to strengthening those changes were basically economic and political. Between 1950 and 1970 a boom in manufacturing production had made Italians' per-capita income skyrocket from 100 (taken as a baseline indicator) to 234. A larger number of women were now employed as salaried workers outside the house, with an increasingly stronger female representation in the most productive sectors of industry, the liberal professions, higher schools ad universities. As a result of women working side by side with men and sharing the same rules and the same privileges, males were now facing shrinking career opportunities. The notion of all-male competition in the workplace – crucially, a mainstay of male identity – began to crumble. Radical changes were also bound to occur within the household, with a decrease in the number of children born to each couple and, conversely, an increase in marital separations. Women's greater decision-making autonomy also weakened the notion of fatherhood, which now could only come to be if a woman so desired, if she was determined to accept it as part of her own expectations for her personal life. Housewives began to be seen as workers in their own right, on a par with factory workers. Husbands could no longer claim for themselves the authority associated with their previous role as sole bread-winners.

In the mid-'70s, female school enrolment in Italy – which so far had lagged behind the other countries of Northern and Central Europe – increased dramatically, not only in those fields that had been traditionally reserved to women, but also in what had so far been typically male-oriented higher education, such as schools for accountants or surveyors. The trend was even more marked at the university level and the increase in school enrolment of women in colleges and universities eventually affected men's own prospects for training and job finding, dealing a fatal blow to gender-specific career paths, such as in high-school teaching, the Bench and the Bar, the medical profession, and scientific research. Free access to all school levels also brought changes in women's passage to adulthood, leading them to defer childbearing to a later age.

Our remarks are not at all meant to explain the "cause-effect" relationship between the two patterns observed. In-

deed, they are only aimed at stressing the role that social and cultural factors might play in the pathogenesis of certain disorders, such as headaches. The fact that no similar changes could be found in the epidemiology of primary headache in other countries might well be a consequence of the profound differences characterizing the various protest movements that came to dominate the political scene in Europe and overseas in the '70s, each one of them bringing to the fore different issues from different backgrounds on a different time scale.

As proof of the strict interdependence between environmental and biological phenomena, recent currents of thought have postulated a direct correlation between the mind and the brain, based on a few straightforward assumptions: all mental processes, even the most complex psychological processes, derive from operation of the brain; genes and their protein products are important determinants of the pattern of interconnections between neurons in the brain and therefore exert a significant control over behaviour; just as combinations of genes contribute to behaviour, so can behaviour and social and cultural factors exert actions on the brain by feeding back upon it to modify the expression of genes and thus the function of nerve cells; finally, alterations in gene expression induced by learning give rise to changes in patterns of neuronal connections (5).

Such notion, used as a key to interpret psychiatric disorders, could also apply to "structural" disorders, a term under which many would now like to include also cluster headache (3). It could then be reasonably assumed that the discussed factors may have an influence on the aetiology of headache.

Cluster headache and the International Headache Society classification

In view of the upcoming revision of the International Headache Society (IHS) classification (6), a topical issue is certainly represented by the adequacy of the current diagnostic criteria.

At the Parma Headache Centre, we investigated a large sample of patients in order to: i) determine how many clinically verified CH patients did not fulfill the diagnostic criteria for group 3.1 of the existing IHS classification; and ii) find out any diagnostic elements that could be added to or changed in the upcoming revision of the classification to make it more relevant to current clinical practice.

Our study population consisted of all 652 CH patients (470 men and 182 women) consecutively referred to our Centre between December 1975 and December 1999. Prior to data analysis, we revised all pre-1988 CH diagnoses according to the IHS diagnostic criteria. In our sample, the patients who could be coded to the 3.3 cluster-like group were 99 out of 652 (15.2%), including 59 out of 470 males (12.6%) and 40 out of 182 females (22.0%). The remaining 553 patients (84.8%) were classifiable as 3.1. All 3.3 patients fulfilled the criteria listed under letter heading A, because at the time of their first visit all of them reported more than five attacks. Most of these patients, however, did not match the diagnostic criteria for CH because their headache was not accompanied by any of the autonomic phenomena listed in the classification (in 45.5% of patients, or 45 out of 99), or because pain was not located orbitally, supraorbitally and/or temporally (in 29.3% of patients, or 29 out of 99).

Among the 45 3.3 patients who did not report any of the accompanying autonomic phenomena listed in the IHS classification, eight, or 17.8 per cent – five males and three females – did not report any symptoms associated with pain, while the remaining 37, or 82.2 per cent – 24 out of 29 males, or 82.8%, and 13 out of 16 females, or 82.3% – reported only symptoms other than those listed in the IHS classification, the average being 2.1 symptoms for each patient (range: 1-6). Analysis of the "non-IHS" accompanying symptoms in the 37 3.3 patients and in the 553 3.1 CH patients (411 males and 142 females) showed that restlessness/agitation, nausea and photophobia were more common in both groups. A similar procedure was applied to the study of pain location. In the 29 3.3 patients who did not report pain orbitally, supraorbitally and/or temporally and in the 553 3.1 CH patients, "non-IHS" pain location was more frequently in the frontal, occipital and parietal regions.

Several authors have reported frequent involvement of the frontal region (7-8). These reports are in agreement with our own observation of 57.7 per cent of 3.3 patients and 54.8 per cent of 3.1 CH patients reporting frontal pain. Based on these findings, frontal pain location can be considered as typical of CH patients in general and not only of that group of patients who do not match "classic" pain location characteristics. Similarly, in our sample, occipital region involvement was reported by 30.8 per cent of 3.3 patients and by 26.0 per cent of 3.1 CH patients. CH patients without the typical accompaniment of autonomic phenomena have been repeatedly described after 1988. In their study of patients referred to the Headache Centres of Parma and Pavia, Nappi et al. (9) found a high rate of photophobia (55.8%) and nausea (40.6%), suggesting that the frequent occurrence of "general" autonomic phenomena should indeed focus investigators' attention to the role of CNS involvement in CH pathophysiology - as has recently been demonstrated by a number of interesting neuroimaging studies (2, 3). In 1998, Vingen et al. (10) assessed the increased sensitivity to light and sound of CH patients versus healthy subjects and concluded that photo- and phonophobia are important accompanying symptoms of CH attacks.

Based on these findings and on other reports in the literature, we made an attempt at modifying the criteria under letter headings C and B of the IHS classification. If, for example, restlessness/agitation, nausea and photophobia were added to the list of CH accompanying symptoms under heading C, 31.3 per cent of our 3.3 patients (31 out of 99) could be coded instead to 3.1; if restlessness/agitation and nausea were added, 27.3 per cent (27 out of 99) could; and, finally, if only restlessness/agitation were added, that would be enough to code to the 3.1 group as much as 20.2 per cent (20 out of 99) of our 3.3 patients. We then calculated what percentage of the 99 patients currently coded as 3.3 would fulfill the diagnostic criteria for CH if frontal or occipital pain location or both were added under letter heading B: in the first case 15.2 per cent (15 patients out of 99) could be coded as 3.1; in the second case, 8.1 per cent (8/99); and in the third case, 20.2% (20/99).

In conclusion, we found that bilateral pain location was extremely rare (occurring in 0.8% of our patients, or 5 out of 652). Duration of attacks, as well as

their frequency, could vary in the same patient and in the same cluster period. The IHS classification provides a "snapshot" of the disorder, but fails to describe it as a "feature-length" syndrome. Far from changing the existing criteria and without restoring use of those vague adverbs that were typical of descriptions in previous classifications, a system of percentage ranges could be used that would allow for variability of attack duration and frequency within different patients and within each cluster period of the same patients.

Finally, we believe that, based on the evidence we gathered from a large sample of patients and the review of previous reports in the literature, the letter heading B of the IHS classification should read "Severe unilateral orbital, supraorbital and/or temporal and/or frontal and or/occipital pain lasting 15 to 180 minutes untreated", and letter heading C should also list restlessness/agitation, nausea and photophobia among the accompanying autonomic phenomena. With those modifications, 51 of our 99 patients (51.5%) who had to be coded to group 3.3 of the current IHS classification could actually be classified as CH patients (3.1).

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Genes and pain

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Pain is one of the problems that physicians see most. Pain, though, is a physiological sensation that helps the organism to relate to the environment (acute pain). In some conditions, pain persists over the duration of the pathogen noxa or is produced by an alteration of the nociceptive nerves. This can be defined as pathological pain. An abnormal activation of the central excitatory circuits could be involved in the pathogenesis of the persistent pain. Genetic factors could be involved in the phenomenon. Recent studies have highlighted that the inter-individual differences in pain perception are much more significant than intra-individual differences. Even though many acquired factors may play a role in these variations (e.g. cognitive aspects), a genetic difference is unquestionable. Also experimental findings in animals, have confirmed the inter-individual differences. Different inbred strains showed diverse thresholds of response to various nociceptive stimuli. A bulk of factors could be responsible for the genetic variation. Here, we have mentioned the neurotrophines. The neurotrophines are the growth factors of the nervous system. After the developmental period, they are still found. At this stage, their role could be to modulate (potentiating or inhibiting) the nociceptive function. Genetic studies in animals (transgenic or KO animals) demonstrate the action of these factors in the patho- physiology of the nociception.

KEY WORDS: central sensitization, genetic variability, headache neurotrophins, pain

Acute and pathological pain

Pain is one of the most frequent problems seen in the clinical practice. Also, it is often difficult to manage. Under a pathophysiological point of view we can define two kinds of pain.
Acute pain is an unpleasant sensation, induced by a net and time limited pathogen stimulus. It reflects the direct activation of the nociceptive pathways. It starts with the stimulation of the specific peripheral nociceptor and continues with the excitation of the ascending pathways towards the cortex structures which will make the sensation conscious (1). At the same time, the stimulus will activate the inhibitory network, restraining further nociceptive impulses. Hence the sensation of pain, that opposes the hedonistic principle of the life, is strictly limited in its role as an adequate alarm against a pathogen noxae.
A prolonged presence of the pathological situation that has provoked pain or an exaggerated response of the nociceptive system induce a persistent pain status. This condition can be defined as a pathological pain. The phe-

nomenon is related to structural changes of the system both at peripheral (ganglion) and central levels. Prolonged inflammatory stimuli as well as neuropathic lesions are the principal causes of the pathological pain.
Acute pain can be treated by approaching the stimuli that have caused the occurrence. The pathological pain has to be treated by itself , possibly by interfering with the mechanism which is involved in the pathogenesis. That is an intricate problem, due to the difficulty of understanding the mechanism.
Pathological pain is an expression of a plastic amplification occurring in the somato-sensitive system. The amplification could occur either at a peripheral or central level. In particular, at the central level, the phenomenon could be mediated by the activation of the excitatory circuits. In fact, the inhibitory neurons are involved in the control of the pain signal at the entrance to the spinal cord, instead the excitatory neurons are implicated in the process of the central amplification. Their activation is induced by a prolonged presence of the nociceptive stimuli, increasing the activity level of the central nociceptor and enabling it to respond also to weaker stimuli, or even to discharge in absence of peripheral stimuli (2-3).
The process of the amplification of the pain stimuli is based on two different changes in the neuronal structures: one is due to post-translation events, the other to post-transcriptional condition .
Post-translation events are produced by an extra cellular signal that is translated through a receptor activation inducing reversible modification in the cytosol which increases of the firing level (hypersensitivity). If the stimulus is prolonged, the signal is transduced to the nucleus activating post- transcriptional mechanism and resulting in an altered gene expression.
The post translation events induce a reversible increase of the basal neuronal sensitivity; the post- transcriptional modification further strengthens the firing level also transforming the neuronal phenotype. In both cases, the up-regulation of the system is observed either in the dorsal root ganglion or in the dorsal horn of the spinal cord. An example of phenotype alteration is characterized by the acquired capability of the A fibres of responding to nociceptive stimuli, which before were able to only activate the C fibres (4-6).

The Genetics of pain

Mice and Man (J. Steinbeck)
Before evaluating the available tools that consent to study the genetics of pain, some aspects need to be underlined. The pain sensation is a human experience. In fact, in man the nociceptive stimulus arrives at the conscious level, is symbolized in the mind, and finally it is expressed through the language (7). In man, the pain, symbolized by the language, is the final step of the activation of the nociceptive system. In animal, this activation, lacking the symbolization of the language, could only be indirectly stated .
In man, the study of the nociceptive system is principally based on the evaluation of the subjective parameters connected to the pain referred to by the language. The study of the pain

sensation goes further than the evaluation of the threshold of the pain perception, that will be taken into consideration in this article. In fact, the evaluation of other parameters such as the tolerance, the quality of sensation, the affective evoked response, and the cognitive components is important as well. These parameters are greatly influenced by other cognitive aspects that interfere with the pure physiological function of the nociceptive function (8-9)

In animal, the nociceptive system can be evaluated thorough various methods. A part from the electro- physiological techniques which allow the direct recording the evoked response in the nociceptive neurons after an adequate stimulation, the behavioral studies represent a suitable method to assess the animal nociceptive response. (the combination of both representing the ideal)

The parameters of pain/nociceptive responses evaluation are influenced by a great variability either intra-individual or (and above all) inter-individual. The variability of the responses depends on the complexity of the nociceptive system, including the ascending (conducting the impulse to the cortex) and the descending system (with an inhibitory activity) as the modulatory circuits which control the intensity and the modality of the signal. As it was mentioned above other than this variability which we define as biological, an other aspect of the pain variability is represented by the cognitive component that depends on the acquired experience more than on the genetic factors (8). The cognitive aspects complicate the interpretation of the biological differences.

Studies in Man

Studies on the pain threshold in man have disclosed much biological variability. The pain threshold could be evaluated through a series of nociceptive stimuli: mechanical (pressure on the skin), thermal (increase of temperature until the pain occurs) electrical (administration of stimulation trans and percutaneous with stable frequency and increasing intensity) and chemical (local administration of increasing concentration of irritating agent).

Other forms of testing pain threshold are deep muscolar stimulation and the cold pressure test.

The study on pain threshold have disclosed the following categories of biological variability:

Intra-individual variation (variability degree until 20%)

Topographic variation (stimulation performed in different body areas)

Temporal variation (stimulation performed at different time, chronobiological variation)

Inter-individual variation (variability degree until 50-60%).

A meta-analysis of the studies confirms that the inter-individual features are the most important in the biological variability of the pain feeling; this underlines the factors of gender and race as being much more significant than cultural, anthropological and social aspects. This evidence indicate that the inter- individual variability has a genetic basis rather than environmental (8).

An other observation that permits the evaluation the genetic variability of the nociceptive system is the great variability in the response to the analgesic effect of the morphine. In fact, some individuals scarcely or fail to respond to morphine administrated as

an analgesic. On the other hand, a population of subjects has a great tendency to develop a fast addiction to morphine, whereas another group is resistant to this phenomenon The ? receptors represent one of the most interesting candidates accounting for the biological variability of the nociceptive/pain sensation (10).
The inherited or inheritable diseases characterized by the presence of pain are also special tools for studying the interference of genetic factors in the dysfunction of nociceptive system. For these diseases a familiar pattern of occurrence (either related the mendelian laws or more often an increased familiar distribution) is shown. The search for a responsible gene in direct disease transmission or for the gene polymorphism that is related to the familiar predisposition is the goal of research in this field. An example of the inherited disease is classically characterized by the congenital absence of pain sensitivity. In this disease, an alteration of the gene that code for tyrosyn-kinase receptors of the nerve growth factor was described (11). This alteration inhibits the development of normal nociceptive sensitivity during the embryonic period. For this reason the subjects with this alteration show a diminished or absent capability of feeling the major parts of the pain sensation. Another mendelian disease is represented by the emiplegic familiar migraine, a rare disease which is characterized by migraine attacks accompanied by emiplegia. An alteration of the gene that code for the ?1 unit of the calcium channel was found in the affected subjects (12). Projecting these findings onto the much more common forms of migraine (with and without aura) showed promising results in the direction of the polymorphism of the calcium channel encoding genes.

Studies on the animal
Several studies showed that there is a significant difference in the response to the nociceptive tests (hot plate, tail-flick, formaline tests) among the various strains of rats and mice. The difference is much more noticeable when the observation concerns inbred animals of each single strain than when the outbred strains are studied. These findings suggest a fundamental role played by the genetic factors in the biological variability of the nociceptive system.
The transgenic studies confirm this evidence also indicate the factors that are possibly responsible for the biological variation.
The revolution of molecular technology greatly advance the study of the genetics of the nociceptive system. The fundamental steps in this revolution include: sequencing, mapping and cloning the genes; studying the expression of a gene in relation to the specie-specificity, tissue specificity and to temporal events; modification of the gene expression (application of the mRNA antisense) and the creation of transgenic or knock out (KO) animals.
The last two methods are widely used to analitically study the single factor that are involved in the different functions of the nociceptive system. Transgenic mice are the results of adding an exogenous gene (transgene) to the animal genoma. On the other hand, an endogen gene can be inactivated by an exogen maneuver (e.g. inserting a recombinase in the sites where the gene which has to be inactivated is).
By using these methods, various fac-

tors have been analysed, trying to identify their role in the biological variability of the nociceptive system. In particular, we will describe the neurotrophines (and their receptors). Even though other factors are determinant in the genetic variability of the nociceptive system (e.g. previously we mentioned the opioid receptors), neurotrophins represent the new frontier for the research in this field.

Neurotrophins are growth factors of the nervous system. As growth factors neurotrophines they are fundamental during the embryonic and fetal period of development, and successively, during the maturation of the nervous system (first years of the life). In the 1996 A.M. Davis proposed the neurotrophic hypothesis: during the late stages of the development, the neurons compete between themselves for the growth factors. The cells capable of utilizing an adequate quantity of the growts factors arrive to maturation, the others are eliminated through apoptotic processes. This mechanism explains of explaining why during the late phases of the development a remarkable growth of the nervous cells along with a significant presence of apoptotic elements is observed (11)

The cells of the nervous system are permanent: the duration of their life corresponds to organism life span . When one cell dies, it cannot be replaced with a new one. Neurotrophins should no longer be necessaries after the development phases. Although their concentration decreases, neurotrophins are evident also in adult organisms. Among other functions, a role in the modulation of the activity of the nervous cell was hypothesized. In particular, neurotrophins could be involved in the mechanism of the changes in the sensitivity status of the neurons (see below). The nerve growth factor (identified by Rita Levi Montalcini) represents the most studied factor, however, other neurotrophins also have been described. In particular the NT-3 and the brain derived nerve factors (BDNF) (13).

Receptors of the neurotrophines are present on the sensitivity fibres (either at peripheral or central level) as well as on sympathetic fibers. Usually, on the fibers of a larger diameter there are expressed receptors with a C tyrosin-kinase activity (TrkC), whereas the fibers of a smaller diameter (incuding those with a nociceptive function) express receptors with a A tyrosin-kinase (TrkA). There is a correlation, although not absolute, between the kind of the neurotrophins and the tyrosin-kinase activity of the receptors (14). Finally, another receptor, the p75 without tyrosin-kinase activity has been identified to play an important role in the neurotrophins functions (14). But what is this function in an adult organism? First they have a protective role on the sensitivity fibers. Neurotrophins are involved in the survival of the proximal trunk of the deafferented nerves. Studies carried out on animals models showed that the receptors for the neurotrophins are increased on the deafferented fibres (15). The exogenous administration of the neurotrophins in the central nervous system, regenerates some reflex abolished by the deafferentation (16). This is an indication that the growth nerve factors could be involved in amplifying the level of neuronal firing. Also, the direct application of the neurotrophins at the central level modulate the activity levels of the neurons. In general, the NGF increases and BDNF decreases this activity (17).

The transgenic studies are confirming that neurotrophins play a role in the activity level of the sensory neurons. The most significant studies have been carried out on NGF and on the TrkA and p75 receptors. Mice KO for the NGF die in 4 weeks. They show a dramatic loss of the small diameter sensory fibres. This results in an insensitivity to some nociceptive tests (prinking test) and less sensitivity to thermal stimulation. On the other hand, animals "sense" for the NGF, over-expressing the neurotrophin, show a hyperalgesia (after either thermal or mechanical stimuli). In some animals allodynia is observed (13).
The transgenic studies on the TrkA showed that mice KO for this receptor, also showed a significant decrease in the number of small sensory fibres and sympathetic fibres. The life span is dramatically reduced. They show a complicated alteration of their nociceptive response. These animals are insensitive to the pinprick test and to the hot plate, and less sensitive to chemical stimuli (wiping test after application of capsaicin in the cornea). On the other hand, they showed extensive lesions resulting from automutilating behaviour, as is observed in the deafferented animal: sign of a significant unpleasant sensation.
Mice KO for the p75 receptor have a poor response to thermal or mechanical stimulation. Their life span is normal, but they develop skin alterations, possibly related to a peripheral neuropathy. The cross between these animals with trangenic mice over expressing the human NGF gene creates a population of animals which recovers the sensitivity to nociceptive stimuli (18).

Conclusion

The pain sensation, as well as the animal response to noxious stimulation, is really variable parameters. Part of the variability is due to genetic factors. In particular, these factors could be involved in the mechanisms generating chronic pain, a condition which is seen in some subjects who could be genetically predisposed. Also, the genetic factors could be part of the significant inter-individual difference in the parameters of experimental pain. In animal, direct studies on the possible genes involved in this biological variability have shown interesting results. Even though the evaluation of the nociceptive response in animal is completely different than in man, some factors have been described which can take account for genetic variability. Polymorphism of morphine receptor genes have been described, as well as those of the ionic channel on the surface of the neurons. A new frontier in this line of research is represented by the evidence that neurotrophins play a role, in the functioning of the nervous system in an adult organism as well as in its development. Neurotrophins are particularly active in the nociceptive system, where they have a role in modulating the impulse generated by a noxious stimulation or by a direct damage of the neural structures by themselves.
At the end, what could be the biological finality of the genetic variability in feeling pain? Is it linked to a pre-destined role that the individual should have in relation to the environment (fighter or thinker)? Further, is chronic pain a pathological condition or is a result of the flow of one's existence that permanently modifies (sooner or later) all vital functions?

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Dopamine receptors are involved in the control of opioids antinociception in mice

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An investigation was made on the effects induced by haloperidol and apomorphine on antinociception induced by DAMGO (highly selective m-agonist), U50-488H (highly selective k-agonist) and deltorphin II (highly selective d-agonists).
Haloperidol (a dopamine receptor antagonist) and apomorphine (a dopamine receptor agonist) (0.1-1.0-2.0 mg/kg/i.p.) per se did not change the pain threshold of mice both in the hot plate and in the tail flick test. The antinociception effects of DAMGO (5 mg/kg/i.p.), U50-488H (5 mg/kg/i.p.) and deltorphin II (10 ng/i.c.v./mouse) peaked by 15 min after treatment and was antagonized by haloperidol in a dose dependent manner. By contrast, the dopamine receptor agonist, apomorphine, depending on the doses used, exhibited opposite effects on opiate antinociception. Treatment of mice with low doses of apomorphine (0.1-1.0 mg/kg/i.p.) reduces the antinociception induced by m, k and d receptor agonists whereas a high dose (2 mg/kg/i.p.) potentiates it.
Our results indicate that dopamine receptor are involved in the control of antinociception at both the m, k and d receptor level.

KEY WORDS: antinociception, apomorphine, DAGO, deltorphin II, haloperidol, U50-488H

Introduction

It is well known that opioids induce antinociception by acting at m, d and k opioid receptors (1-2)
Brain dopaminergic system have been widely implicated in many of the pharmacological effects of opioids. Manipulations that alter the activity of dopamine in the central nervous system (CNS) frequently modify the effects of morphine and other opioid drugs (3-4). Although the action of dopamine agonist and antagonists on morphine antinociception has been studied (5- 8), no data are available, to our knowledge, on the effects exerted by dopamine agonist and antagonist on the antinociceptive effects induced by selective opioid agonists.
The experiments described here were undertaken to verify whether the possible interaction of dopamine agonist and/or antagonist on opioid antinociception involves m, k and/or d opioid receptor.
Therefore, the effects of dopamine receptor agonist (apomorphine) and antagonist (haloperidol) were evaluated on opioid antinociception induced by DAMGO (highly selective m-agonist), U50-488H (highly selective k-agonist) and deltorphin II (highly selective d-agonists).

Materials and Methods

Animals
Male CD-1 mice (Charles River, Italy) weighing 25-30 g were used in the experiments. Animal care and use followed the directions of the Council of the European Communities (1986). They were maintained in a climate light controlled room (22+1°C, 12/12h dark/light cycle with lights on at 7:00) and with free access to food and water prior to the experiments. Testing took place during the light phase. The animals were brought to the test room for at least three hours before testing. Each animal was used only in one experimental session.

Pain assays
The pain assays were the hot plate (HP) and the tail flick test (TF). The HP test was performed as previously described (8). Briefly, the hot plate (Socrel Mod. DS37, Ugo Basile, Italy, 25 cm x 25 cm) was set at a plate temperature of 55+1°C to give a latency of 15-17 sec in control animals.
The time of hind paw licking was recorded, and measuring was terminated if the licking exceeded the cut-off time (60 sec).
The tail flick latency (9) was obtained using a tail flick unit (Socrel Mod DS-20, Ugo Basile, Italy).
The animals were gently immobilized by using a glove, and the radiant heat was focused on a blackened spot 1-2 cm from the tip of the tail.
Beam intensity was adjusted to give a tail flick latency of 2-3 sec in control animals. Measuring was terminated if the latency exceeded the cut-off time (10 sec) to avoid tissue damage.

Experimental procedure
In all the experiments mice were tested twice 60 and 30 min before drug administration in the baseline latency determination and afterwards, 15 min after drug administration. DAMGO and U50-488H were administered intraperitoneally at the dose of 5 mg/kg; deltorphin II was administered intracerebroventricularly (i.c.v.) at the doses of 10 ng/mouse alone or 15 min after haloperidol or apomorphine administration (0.1-1.0-2.0 mg/kg/i.p.). On the day of the testing, all drugs used in the experimental sessions were dissolved in 0.9% NaCl solution for i.p. or distilled water for i.c.v. administration. The drugs were injected in a volume of 2.5 ml/mouse for i.c.v. administration which was performed in according to the method of Haley and McCormick (1957) (10). At the end of the experimental session, the injection site was verified by using 1% methylene blue and examining the distribution of the dye in the cerebrum.

Drugs
All drugs were purchased from the Sigma Chemical Co (St. Louis, U.S.A.) with the exception of morphine HCl from Carlo Erba (Milan, Italy), U50-488H (trans-(+)-3,4-dichloro-N-methyl-N-(2-1-pyrrolidinyl)-cyclohexyl-benzeneacetamide) from the Upjohn Co (Kalamazoo, MICH, USA)

Statistical analysis

Data obtained in the experiments were analyzed by using the analyses of variance followed by the Mann-Whitney U-test for between-group differences (9). All the data were expressed as mean+s.e.m. and significance was assumed at a 5% level.

Results

In the HP test as well as in the TF test, saline injected i.p., distilled water injected i.c.v., haloperidol and apomorphine (0.1-1.0-2.0 mg/kg/i.p.) did not change the pain threshold. DAMGO (5 mg/kg/i.p.), U50-488H (5 mg/Kg/i.p) and deltorphin II (10 ng/i.c.v./mouse) produced a significative antinociceptive effect both in the HP and TF test.
Table I and II show the results obtained with haloperidol or apomorphine in animals pretreated with DAMGO, U50-488H or deltorphin II.
The antinociceptive effect of DAMGO, U50-488H and deltorphin II peaked by 15 min after treatment and was dose dependently antagonized by haloperidol (0.1-1.0-2.0 mg/kg/i.p.) (table 1).

Table 1 - The effect of haloperidol (0.1-1.0-2.0 mg/kg/i.p.) with or without DAMGO, U50-488H and deltorphin II on the reaction time in the HP and TF test. Results are expressed as mean+s.e.m. HP and TF latency (sec). ** is for P<0.01 versus saline or distilled water; °° is for P<0.01 versus DAMGO, U50-488H and deltorphin II.

Treatment	Reaction time sec (+ S.E.M) Control		After treatment	
	HP	TF	HP	TF
Saline or Distilled water	16.0+1.7	1.7+0.2	17.3+1.3	2.0+0.9
Haloperidol 0.1 mg/kg	16.5+1.7	1.9+0.6	18.2+1.2	1.7+0.5
Haloperidol 1.0 mg/kg	15.2+1.1	2.2+0.4	19.0+1.8	2.1+1.5
Haloperidol 2.0 mg/kg	16.7+1.5	2.5+0.3	20.1+1.2	1.9+0.4
DAMGO 5 mg/kg	16.5+1.6	2.2+0.2	50.3+1.8**	8.8+1.7**
U50-488H 5 mg/kg	17.3+1.5	2.3+0.4	47.2+1.5**	8.9+1.6**
Deltorphin II 10 ng/mouse	14.6+1.1	2.1+0.6	44.5+1.4**	7.5+1.3**
Haloperidol 0.1 mg/kg+ DAMGO 5 mg/kg	17.3+1.2	2.2+0.5	36.3+1.5°°	5.6+1.0**
Haloperidol 1.0 mg/kg+ DAMGO 5 mg/kg	18.1+1.3	1.7+0.6	27.0+1.8°°	4.6+1.3**
Haloperidol 2.0 mg/kg+ DAMGO 5 mg/kg	16.7+1.5	2.0+0.7	18.5+1.1°°	2.5+0.8**
Haloperidol 0.1 mg/kg+ U50-488H 5 mg/kg	15.3+1.3	2.1+0.8	35.3+1.7°°	6.2+1.0**
Haloperidol 1.0 mg/kg+ U50-488H 5 mg/kg	16.6+1.2	1.9+0.5	26.2+1.5°°	5.1+1.2**
Haloperidol 2.0 mg/kg+ U50-488H 5 mg/kg	14.8+1.6	2.3+0.7	20.8+1.6°°	3.8+0.9**
Haloperidol 0.1 mg/kg+ Deltorphin II 10 ng/mouse	17.4+1.2	1.7+0.7	32.2+1.5°°	4.9+1.3**
Haloperidol 1.0 mg/kg+ Deltorphin II 10 ng/mouse	18.7+1.4	1.6+0.9	24.0+1.0°°	3.5+1.0**
Haloperidol 2.0 mg/kg+ Deltorphin II 10 ng/mouse	17.2+1.2	1.5+0.7	19.7+1.5°°	2.2+0.6**

By contrast, the dopamine receptor agonist, apomorphine, depending on the doses used, exhibited opposite effects on opiate antinociception. Treatment of mice with low doses of apomorphine (0.1-1.0 mg/kg/i.p.) reduces the antinociception induced by DAMGO, U50-488H and deltorphin II whereas a high dose (2 mg/kg/i.p.) potentiates it (table 2).

Discussion

The present study indicates that both haloperidol (dopamine receptor antagonist) and apomorphine (dopamine receptor agonist) induce significant effects on opiate antinociception in mice thus confirming an important involvement of dopamine receptors in the con-

Table 2 - The effect of apomorphine (0.1-1.0-2.0 mg/kg/i.p.) with or without DAMGO, U50-488H and deltorphin II on the reaction time in the HP and TF test. Results are expressed as mean+s.e.m. HP and TF HP and TF latency (sec). ** is for P<0.01 versus saline or distilled water; °° is for P<0.01 versus DAMGO, U50-488H and deltorphin II.

Treatment	Reaction time sec (+ S.E.M) Control		After treatment	
	HP	TF	HP	TF
Saline or Distilled water	15.0+1.7	1.5+0.2	5.6+1.2	2.2+0.8
Apomorphine 0.1 mg/kg	16.9+1.5	1.8+0.7	16.5+1.3	1.6+0.7
Apomorphine 1.0 mg/kg	18.4+1.3	2.1+0.5	16.0+1.4	2.0+1.0
Apomorphine 2.0 mg/kg	5.5+1.0	2.3+0.4	19.3+1.5	1.5+0.9
DAMGO 5 mg/kg	18.3+1.4	2.0+0.8	46.6+1.6**	7.9+1.2**
U50-488H 5 mg/kg	19.5+1.1	2.1+0.9	45.2+1.7**	9.2+1.3**
Deltorphin II 10 ng/mouse	15.9+1.5	2.5+0.4	43.4+1.9**	8.9+1.7**
Apomorphine 0.1 mg/kg+ DAMGO 5 mg/kg	19.2+1.5	2.4+0.7	39.1+1.3°°	4.7+1.3**
Apomorphine 1.0 mg/kg+ DAMGO 5 mg/kg	16.7+1.7	1.9+0.7	29.0+1.4°°	4.8+1.6**
Apomorphine 2.0 mg/kg+ DAMGO 5 mg/kg	18.4+1.3	2.4+0.9	55.5+1.4°°	9.7+0.6**
Apomorphine 0.1 mg/kg+ U50-488H 5 mg/kg	15.7+1.6	2.5+0.8	39.5+1.6°°	7.1+1.2**
Apomorphine 1.0 mg/kg+ U50-488H 5 mg/kg	16.9+1.4	1.7+0.6	28.4+1.2°°	6.2+1.1**
Apomorphine 2.0 mg/kg+ U50-488H 5 mg/kg	15.7+1.6	2.5+0.7	57.8+2.8°°	9.6+0.9**
Apomorphine 0.1 mg/kg+ Deltorphin II 10 ng/mouse	19.4+1.3	2.2+0.3	45.2+1.3°°	5.5+1.1**
Apomorphine 1.0 mg/kg+ Deltorphin II 10 ng/mouse	16.4+1.2	1.8+0.6	33.0+1.3°°	3.7+1.0**
Apomorphine 2.0 mg/kg+ Deltorphin II 10 ng/mouse	19.6+1.4	1.7+0.6	58.7+2.6°°	9.7+0.8**

trol of opioid effects (3-7). Under our experimental conditions, haloperidol was able to reduce antinociception induced by DAGO (m-agonist), U50-488H (k-agonist) and deltorphin II (d-agonist). The reduction by haloperidol of opioid antinociception was dose-dependent consistent with an action mediated by a dopamine receptor.

Interrestingly, our results with apomorphine showed a reduction of opiate antinociception at the lowest doses (0.1-1.0 mg/kg) whereas at the highest dose (2 mg/kg) potentiates it.

The results of the present experiments could be explained on the basis of actions on pre- and post-synaptic receptors suggesting that the inhibition induced by haloperidol is related to presynaptic receptor (D2) block whereas the inhibition by apomorphine may be related to postsynaptic receptor (D1) stimulation.

Regarding the possible mechanism by which dopamine receptor agonist and antagonist control opiate antinociception, it is hypothesized that the effects observed are related to alterations in the levels of adenosine 3':5'-cyclic monophosphate (cyclic AMP). Cyclic AMP has frequently been implicated as an intracellular messenger for the receptor-mediated actions of opioids. Biochemical observations has indicated that opioids inhibit adenylate activity and decrease the level of cyclic AMP (11). Dopamine receptors are coupled to adenylate cyclase and stimulation of D1 receptors causes an increased production of cyclic AMP, whereas stimulation of D2 receptors causes a decrease of cyclic AMP (12). However, the ability of haloperidol and apomorphine to reduce opioid antinociception with the ability of highest dose of apomorphine to potentiates opioid antinociception are difficult to relate to changes in cyclic AMP production.

Finally, whatever the mechanism may be, our data indicated that the dopaminergic system exerts an important control on the opioid antinociception. Further study are in progress in order to better understand the interaction dopamine and opioid system.

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Novel pathways to activate the vanilloid receptor-1 on nociceptors: anandamide, eicosanoids and protein kinase C activators

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Primary sensory neurons play a key role in pain transmission and possibly in the pathogenesis of primary headaches. Several membrane bound proteins (either channels and receptors) transduce pain signalling in sensory neurons. The vanilloid receptor-1 (VR1) is a non selective cation channel that is activated by noxious heat and protons and mediate inflammatory thermal hyperalgesia. More recently, it has been recognized that several derivatives of arachidonic acid may directly activate the VR1. In addition, intracellular pathways activated by both G protein-coupled receptors and tyrosin-kinase receptors may upregulate VR1. These novel stimulants and upregulation mechanisms may be important regulators of VR1 functions and play a major role in different pathologies.

KEY WORDS: anandamide, CGRP, sensory neurons, substance P, vanilloid receptor-1 (VR1)

The capsaicin receptor on sensory nerve terminals

Some primary afferents form a unique subpopulation of sensory neurons because they are characterised by nerve terminals suitable for a dual sensory-effect function. The generation of an orthodromic impulse to the central nervous system (CNS) evokes nociceptive transmission (or pain in man), whilst, antidromic invasion of collateral fibres or direct stimulation of the nerve terminal result in the local release of peptide neurotransmitters, including the tachykinins, substance P (SP) and neurokinin A (NKA), and calcitonin gene-related peptide (CGRP). The constellation of effects produced by stimulation of tachykinins NK1, NK2 and NK3 receptors and CGRP receptors on effector cells by sensory neuropeptides at the vascular and extravascular level is referred to as neurogenic inflammation (1). A number of mediators acting on excitatory and inhibitory prejunctional receptors or channels limit the sensory and local inflammatory actions of primary sensory neurons. Among these inhibitory mechanisms, activation of cannabinoid (CB) receptors have been found to limit both neurogenic inflammatory responses and sensory transmission (2-3). The most extensively studied primary sensory neurons are those with cell bodies located on dorsal root ganglia (DRG). Similar neurons are, however, present on vagal (nodose and jugular) and trigeminal ganglia. Neurons present in sensory ganglia consist of heterogeneous subpopulations of

cells with diverse electrophysiological, morphological neurochemical and functional characteristics. Peptidergic neurons have small cell bodies, giving rise to unmyelinated C or thin-myelinated Ad fibers, and are further characterised by their unique sensitivity to the neurotoxin capsaicin (4-5), which acts on them by activating the non-selective cation channel. This effect of capsaicin results in a first phase of excitation that may be followed (in a concentration-dependent manner) by channel/cell desensitisation and eventually cell death (4-5). Different molecules with a vanilloid moiety were recognized to be active on the capsaicin-channel and some molecules, including resiniferatoxin (5) were found to be super potent activators.

Recently, a cDNA that encodes a vanilloid receptor (VR1) in rat DRG, denominated as vanilloid receptor-1 (VR1) (6); has been cloned. VR1 is a vanilloid-gated, nonselective cation channel that resembles the members of the transient receptor potential (TRP) channel family (7) (figure 1). Studies with the cloned VR1 receptor (6, 8) confirm previous electrophysiological, functional and neurochemical observations that noxious heat (>43ºC) and acidosis (pH<6) (1, 9-10) selectively activate VR1. More recently studies using VR1 knock out mice showed that these animals exhibited reduced thermal hyperalgesia as compared to their littermate controls (6, 11). Thus, the hypothesis that VR1 contributes to senses and signal variation (increase)

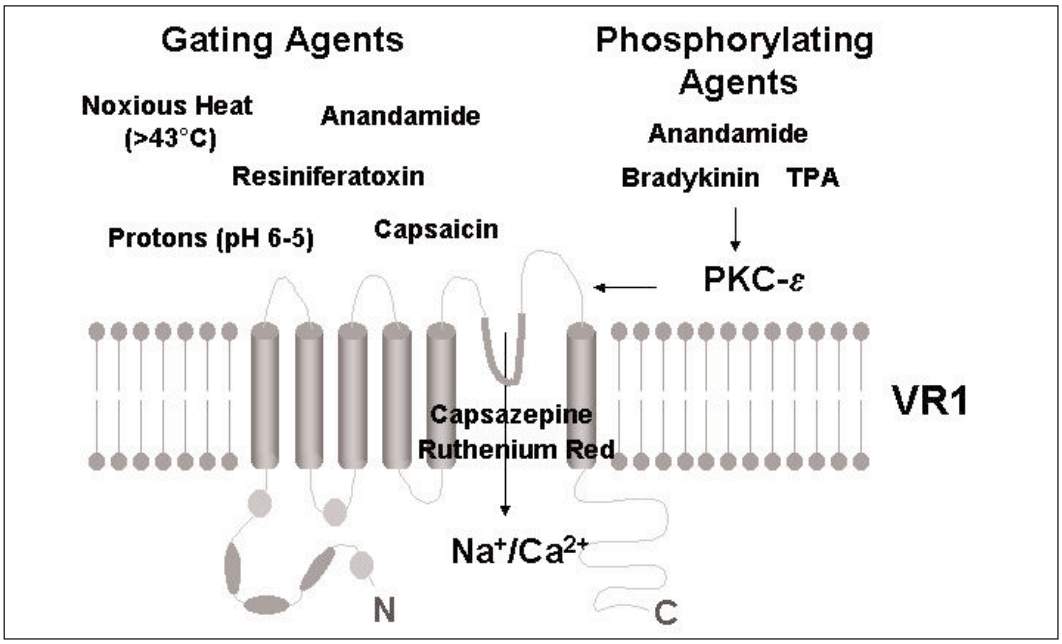

Figure 1 - Schematic rapresentation of vanillod receptor-1 (VR1). Its activation that causes influx of Ca^{2+} and Na^{+} into the nerve terminal may result aither from direct channel gating or by phosphorylation via protei kinase C-ε (PKC-ε) activation.

in temperature and (decrease) in pH in the surrounding medium as proposed in early studies (12-13) has been confirmed by molecular approach. However, in addition to the possibility that physio-chemical stimuli activate VR1, the search for one or more endogenous molecules that could stimulate this unique sensory pathway is ongoing.

Anandamide, an endogenous activators of the VR1

Anandamide is the prototype of a family of N-acylethanolamines (NAEs), and exhibits common properties with other polyunsaturated NAEs (14). NAEs activate G-protein-coupled cannabinoids (CB1 and CB2) receptors. CB1 receptors are found predominantly in the brain and peripheral nervous system, whilst the CB2 receptor appears to be present outside of the CNS (15). The most famous agonist for CB1 and CB2 receptors is d9-tetrahydrocannabinol (d9-THC) (16), of which anandamide (but somewhat less potent) is thought to posses a similar biochemical and pharmacological profile. Anandamide formation involves an increase in intracellular calcium that activates an N-acytransferase, promoting the transfer of arachidonate from arachidonoyl phospholipids to phosphatidylethanolamine. The N-arachidonoyl phosphatidylethanolamine serves as a substrate for Ca2+-activated phospholipase D (PLD), possibly liberating anandamide on hyperpolarization via K+ channel activation (17). In a number of assays the duration of action of anandamide is relatively short-lived. One of the factors towards this phenomenon is its rapid hydrolysis by amidohydrolase to ethanolamine and arachidonate (18-20). The antihyperalgesic and antiinflammatory actions of anandamide are due, at least in part, to the activation of inhibitory CB1 receptors on central and peripheral endings of capsaicin-sensitive primary sensory neurons (2-3). In contrast to the inhibitory action, recently, it has been reported that elevated concentrations of AEA excite peripheral terminals of capsaicin-sensitive primary sensory neurons via CB receptor-independent mechanisms (21).

Because the VR1 antagonist, capsazepine (22), selectively abolishes both AEA-induced release of CGRP in rodent peripheral arteries and AEA-induced activation of VR1 transfected in Xenopus oocytes or HEK293 cells, the proposal was advanced that elevated concentrations of AEA excites capsaicin-sensitive primary sensory neurons via VR1 activation (21). In addition, chemical similarities between AEA and certain ligands of VR1 (23-25) and the observation that AEA behaves as a full agonist at the VR1 (26) supported this hypothesis.

Isolated rodent arteries containing peripheral terminals of primary sensory neurons (21) and heterologous systems (Xenopus oocytes and HEK293 cells) (21, 26) expressing the VR1 were the initial preparations used in the discovery that anandamide stimulates VR1. Furthermore, anandamide is produced in endothelial cells, macrophages and other peripheral cells (16). More interestingly, anandamide is also produced in the CNS neurons (19) and high expression of VR1 has been detected on central terminals of capsaicin sensitive primary sensory neurons (6, 27). For this reason we studied whether anandamide could excite central endings of primary sensory neurons via the activation of VR1.

We found that anandamide could release both SP and CGRP from slices of

rat dorsal spinal cord in a concentration-dependent, capsaicin-sensitive and Ca2+-dependent manner. In addition, anandamide-induced neuropeptide release was inhibited by the VR1 antagonist, capsazepine, but not affected by the two CB receptor antagonists, AM281 and AM630 (28). Similar findings were obtained when mobilization of intracellular Ca2+ ([Ca2+]i) was measured. Thus, anandamide concentration-dependently increased [Ca2+]i, an effect that was again selectively inhibited by capsazepine, but not influenced by CB receptor antagonists (28). Of particular interest, was the finding that excitation of central terminals of primary sensory neurons (neuropeptide release) or [Ca2+]i in DRG neurons in culture was obtained with high (~µM) concentrations of anandamide. In contrast with this excitatory action, lower (~nM) concentration of anandamide were able to inhibit both neuropeptide release and the increase in [Ca2+]i induced by application of electrical stimuli. This later response of anandamide was reduced by CB receptor antagonism, but not affected by capsazepine (28). In conclusion, anandamide seems to have a dual effect on primary sensory neurons. The factor that dictates the final response appears to be the concentration of the lipid molecule. It is likely that low concentrations required to activate the CB-dependent inhibitory mechanism can be physiologically found in the brain and peripheral tissues, however it is less likely that the high concentrations necessary to excite the neurons via the VR1 activation are likewise produced.

Additional regulating factors of VR1 activity

A recent study reported that additional lipid derivatives could activate VR1 in a capsazepine-dependent manner (29). These molecules included metabolites of 12- and 15-(S)-hydroperoxyeicosatetraenoic acid (HPETE), 5- and 15-(S) hydroxyeicosatetraenoic acid (HETE) and leukotriene B4 (LTB4), in a decreasing order of efficacy, excited transfected VR1 (29). Of interest is the observation that in these studies anandamide was less efficacious than several of these lipoxygenase derivatives, thus implying that these molecules could be better candidates than anandamide as possible endogenous agonists of VR1 (29). Metabolic or other kinetic factors may also be important to determine the potency and efficacy of anandamide at VR1. We observed that phenylmethylsulfonyl fluoride (PMSF), a selective inhibitor of the fatty acid amide hydrolase (FAAH), did not increase the potency and efficacy of anandamide to contract the isolated guinea pig bronchus via VR1 activation. However, in the presence of PMSF the short-lived effect of anandamide was transformed in a long-lasting contraction that was not abated despite the extensive washing of the preparation (30). It is also possible that active uptake mechanisms markedly regulate the ability of anandamide. As shown for capsaicin (31) anandamide acts at an intracellular site of action on VR1 (32). This mode of activation of VR1 may, thus, be heavily regulated by mechanisms that control anandamide trafficking and metabolism.

A very recent paper shows that protein kinase C (PKC) activators, including 12-O-tetradecanoylphorbol-13-acetate (TPA) activate VR1 in DRG neurons as well as in Xenopus laevis oocytes

transfected with rat VR1 (33). Activation by PKC, possibly via channel phosphorylation, was able to 'sensitize' VR1 to make it more susceptible to agents that can directly gate the channel, including capsaicin and anandamide. Anandamide and bradykinin by stimulating PKC-e could also upregulate their ability to stimulate VR1 or the activity of additional gating agents such as low pH. The key role of PKC, and particularly of the PKC-e isoform, in the modulation of the sensory function of primary sensory neurons and hyperalgesia has been reported (34). The novel activity of PKC-e in controlling the gating and responses of VR1 may offer a novel molecular basis to the association between VR1 and different models of hyperalgesia (11). Repeated application of capsaicin in order to desensitize sensory nerve terminals have been used in different painful diseases, including cluster headache (35). How much of this beneficial activity may depend on these novel molecular mechanisms described in this article remains to be determined.

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Central nervous system pharmacological effects of plants from northern peruvian Andes: *Valeriana adscendens, Iresine herbstii and Brugmansia arborea*

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Traditional medicine is a primary source for the study of medicinal plants. In some countries, the knowledge about the therapeutical use of medicinal plants is very deep and very often "magical" plants also are used to diagnose and to treat illnesses. The study of these plants can help in the research of metabolites active on central nervous system.
Valeriana adscendens Trel. (Valerianaceae), Iresine herbstii Hook. (Amaranthaceae) and Brugmansia arborea (L.) Lagerheim (Solanaceae) are used in the northern peruvian Andes for magic-therapeutical purposes.
The traditional healers use V. adscendens and I. herbstii with the ritual aim to expel bad spirits from the body; furthermore, I. herbstii was used in association with other plants, such as Trichocereus pachanoi Britt. et Rose, for divination, to diagnose diseases, and to take possession of another identity. Also, species of Brugmansia have been reported to be used during ritual practices for magical and curative purposes.
Considering that there are no data in literature about the chemical composition and pharmacological properties of these plants, the present paper reports the results of some pharmacological tests performed with V. adscendens, I. herbstii and B. arborea and a chemical study of these plants in order to ascertain the nature of their central nervous system activity.
The tests considered to evaluate the central nervous system activity were: locomotor activity, motor coordination, pentobarbital-induced sleep, stereotyped behaviour, catalepsy, nociceptive assays and transmurally stimulated guinea-pig ileum. We also evaluated the effects of V. adscendens extracts on GABA uptake and amino acids neurotransmitters content in mice synaptosomes.
The results of our experiments indicate that all the above tested plants were able to reduce significantly the central nervous system activity of the animals. Furthermore, the chemical study performed for B. arborea indicated the possible constituents responsible for the central activity.
The reduction of motor coordination and stereotyped behaviour together with induced locomotor activity support the possibility that all the studied plants act as psychotropic agents, thus confirming their ritual use.

KEY WORDS: brugmansia arborea, central nervous system, ethnopharmacology, iresine herbstii, psychotropic agents, valeriana adscendens

Introduction

Man has always sought and found remedies for his illnesses in nature, usually in the vegetable kingdom. Every people has accumulated deep knowledge of natural drugs, how to recognise, gather and prepare them.

One can still find this situation in communities that are culturally and geographically isolated, where it is difficult or impossible to find medical doctors who practice "official" medicine, and in those countries still economically emerging, where there are very few medical and social facilities due to the limitation of economic factors. In these areas, the treatment of diseases is based essentially, and sometimes exclusively, on medicines that have a natural origin; among these, vegetal drugs constitute the majority.

The recognition and the use of medicinal plants are an untouchable heritage of most preliterate cultures. Therefore, in the past centuries, and presently in some cultures, the practice of using plants for medicine has assumed a "sacred" characteristic: it is secretly kept and conveyed by priests and other religious figures, who are very knowledgeable about herbs and who combine their botanical, phytotherapeutical and toxicological knowledge with religious elements and rituals based on magic, superstition and ancestral beliefs (1).

In rural communities of the Northern Peruvian Andes, the herbalist or "curandero", the individual who is knowledgeable about all healing and harmful plants, assumes a primary role. He is considered a priest, an intermediate figure between our world and the world of the spiritual forces. At the same time he is also a therapist and an expert on all healing plants, psychotropic plants (used to awaken religious spirits or to gain an altered state of mind) and harmful plants (2). There is a daily contact between the priest and the plant world, from which he receives most of his remedies; hence, his power over the rest of the community.

The shamanic culture in the Andean area of Peru is very old. Its origin certainly date back to pre-Columbian eras and, since then, have been enriched by continuous intercultural and interethnic relationships. In a relatively recent time, it has also been enriched by the Spanish and the other European contacts and by the academic medicine. Still today, this culture is alive and often represents the only medical practice that a population can refer to daily. This makes the "curandero" the only medical doctor that the Andean man can go to treat an illness.

In the traditional medicine of the Northern Peruvian Andes the psychoactive plants play a pivotal role, because they are seen as intermediaries between human and supernatural (1) and the Andean shamans associate the action of these plants with a supernatural depersonalisation or dissociation of body and spirit; this conception has been reported for other cultures (3).

Independent of the purposes of their consumption and application and of the psychopharmacological differences between them, the psychoactive plants are used in ritual context intimately related to religion. It is probable that the fundamental property of these plants, the alteration of the habitual state of consciousness, has led them to be considered special, divine or sacred and appropriate for use in religious and curative ceremonies. The objectives of the rituals centred around psychodysleptics are several. Sacramental practices imply the intention of establishing contact with the sacred to produce ecstasy. On the other hand, divinatory rituals are carried out soon to enable the shaman to detect the origin and treatment of a disorder or the whereabouts of a missing object or person. Finally, in the context of magic

and sorcery, there are rituals for the purpose of inflicting harms ("daño"), purification and exorcism which involves the internal or external use of plants (1, 4).

The most important psychoactive plants in traditional practices of the Northern Peruvian Andes are the cacti *Tricocereus pachanoi* Britt. et Rose and *T. peruvianus* Britt. et Rose ("San Pedro"). These cacti contains the alkaloid mescaline (5-6) and other phenethylamine derivatives (7-8) with well known hallucinogenic properties.

Very few reports are available in ethnobotanical literature on other hallucinogenic plants, usually used in association with "San Pedro".

We carried out studies on some of these psychoactive plants, usually used in magical-therapeutic rituals in traditional practices of the Northern Peruvian Andes (9-12).

The aerial parts of *Valeriana adscendens* Trel. (Valerianaceae) are added to "San Pedro" decoction to enhance its hallucinogenic power. A decoction of the whole plant, traditionally called "hornamo morado", is claimed to act as a drastic purge. The plant is considered a very effective medicinal plant, but its use, as well as the knowledges about its properties, are strictly reserved to the shamans ("curanderos"), due to its strong effects on the central nervous system (1). There are no data in literature about chemical or pharmacological characteristics of this plant, whereas several pharmacological effects are reported for *Valeriana officinalis* L. In fact, it is well known that preparations from *V. officinalis* are widely used in medicine as they exert a mild sedative action on the central nervous system. This plant has been reported to be very useful to treat the states of psychic or sensorial excitability (neurasthenia, hysteria, distress, epilepsy, etc.) (13-19) and a possible effect on GABA transaminase has been suggested (20-21). The aqueous extract of the plant inhibits the GABA uptake in rat synaptosomes and induces a release of GABA previously accumulated, resulting in a decreased extracellular concentration of the neurotransmitter in synaptic cleft at levels sufficiently high to activate GABA receptors (22-24). Also, *V. officinalis* is able to block the convulsion induced both by strychnine and brucine (13) and preparations with chlorpromazine or barbiturates induce a potentiation of its neurodepriment activity (25). Furthermore, the same preparations are also used in heart trouble, menstrual disorders, pregnancy, diabetes insipidus, acidosis, acetonuria (13). Recently, it was shown that *V. officinalis* extracts can interact at other presynaptic components of GABAergic neurones (19). Valepotriates isolated from *V. alliariifolia* also showed neurotropic effects, related to the increased level of the GABA inhibition mediator (26).

In order to validate the traditional use of *V. adscendens*, we carried out some pharmacological tests with an aqueous extract of the plant. Furthermore, we also performed a comparative study with *V. officinalis* and *Passiflora incarnata* L. as standard drugs.

Iresine herbstii Hook. (Amaranthaceae), "cimora señorita", is used in black magic (1). Also, it is employed in association with other species, such as *Trichocereus pachanoi* ("San Pedro") for divination (1, 27-28), to diagnose diseases, and to take possession of another identity (29). Its leaves are applied externally as a skin depurative, whereas the aerial part decoction is claimed to be an antipyretic (1). There are no data in the literature about the

chemical or pharmacological properties of *I. herbstii*.
The present paper report the results of some pharmacological tests performed with an aqueous extract of the plant in order to ascertain the nature of its central nervous system activity.
There are no data in literature about pharmacological properties of *Brugmansia arborea* (L.) Lagerheim (Solanaceae), whereas some tropane alkaloids (30) and cuscohygrine (31) were isolated from the plant.
The south-American species of the genus *Brugmansia* are known with the vernacular names "floripondio", "campanchu", "yerba del diablo" and are used in the traditional therapeutic and magical practices of the folkloric Peruvian medicine to reach altered states of consciousness (1).
Brugmansia species have been reported to be used also in other ethnies during ritual practices for magical and curative purposes in several zones of the amazonic forest (32-38). In Andean zones, the ritual use of *B. sanguinea* was reported by Schultes (39) and Bristol (40), in the Sibundoy Valley, Colombia.
Previous studies founded in the genus tropane and nicotinic alkaloids (30, 41-43) and in literature, studies on the activity of a hydroalcoholic decoction of the flowers of *B. candida* on the mouse behaviour are reported (44).
B. arborea is known in the Northern Peruvian Andes as "misha oso", "misha toro" and "misha galga" and, in addition to ritual use, the decoction of its leaves and flowers, is used externally as an analgesic, antirheumatic, vulnerary, decongestant and antispasmodic and to cure pimples and other skin eruptions (1).
Therefore, the present study was carried out to examine the pharmacological activity of the plant in order to verify its possible effects on the central nervous system. It was considered the activity of methanolic and aqueous extracts, some chromatographic fractions of MeOH extract and pure isolated compounds on the electrically-induced contractions of isolated guinea-pig ileum, a method widely used to study the activity of substances which interact with cholinergic system (45); the influence of these extracts, chromatographic fractions and pure compounds on Ach-induced contractions of guinea-pig ileum was also evaluated.

Materials and Methods

Plant materials
V. adscendens and *I. herbstii* were collected in September 1990 in the Sierra of Huancabamba, Piura Department, Perú, and identified by Dr. V. De Feo. Voucher specimens of the plants are deposited at the herbarium of the School of Pharmacy, University of Salerno, labelled as DFP 90/65 and DFP 90/88, respectively. Leaves and flowers of *B. arborea* were collected in September 1991 near Huancabamba City, Piura Department, Northern Perú. The plant was identified by Dr. V. De Feo. A voucher specimen of the plant (DFP 91/98) is deposited at the herbarium of the School of Pharmacy, University of Salerno (Italy). *Valeriana officinalis* and *Passiflora incarnata* were a generous gift of Prof. F. Capasso.

Extraction and isolation
Five-hundred g of the air dried aerial parts of *V. adscendens* were extracted for 10 days sequentially with methanol and water, at room temperature, giving 13.57 and 8.19 g of residues, respectively. The methanolic extract was resuspended in distilled water, obtaining the hydromethanolic extract (A-

ME), or in methanol (ME). The aqueous dried material was resuspended in distilled water (0.5 mg/mL), obtaining the aqueous extract (AE). Each extraction was carried out for 3-4 h at room temperature and the solutions centrifuged and filtered. *V. officinalis* and *P. incarnata* were extracted at room temperature with distilled water for 10 days.
The aerial parts of *I. herbstii* were air dried, cut in small pieces and extracted (400 g), at room temperature, with distilled water for 10 days. The extract was filtered and then lyophilised with a Edwards Modulyo apparatus to give 6.52 g of residue.
Air-dried and powdered leaves and flowers of *B. arborea* (480 g) were sequentially extracted at room temperature with methanol and water, to give 13.04 and 7.03 g of residues, respectively. Part of methanolic extract (3.2 g), in 2 g lots, was chromatographed on Sephadex LH-20 column, eluting with methanol. Seventy-two fractions of 8 ml were collected and combined by tlc similarity in *n*-butanol:acetic acid:water (60:25:15) (BAW) and in $CHCl_3$:MeOH:H_2O (80:18:2), in 4 main fractions, 1 (mg 345), 2 (mg 477); 3 (mg 547), and 4 (mg 274). Fraction 2, that exhibits the greater biological activity, was chromatographed on tlc and the alkaloids revealed by the Dragendorff reagent, showing the presence of three compounds Dragendorff-positive, with Rf values of 0.2, 0.4 and 0.5, respectively, in BAW.
Fraction 2 was dried and extracted with chloroform, obtaining the pure nor-hyoscine. Atropine and scopolamine were obtained by plc eluting with BAW.
The obtained compounds were then treated with aqueous NH_4OH (pH 10) and extracted with diethyl ether, giving free atropine (mg 7.9), scopolamine (mg 5.3) and nor-hyoscine (mg 8.2).
The identification of the compounds was performed by comparison of spectral data (^1H NMR, ^{13}C NMR and ^{13}C DEPT NMR) with those reported in literature (46-47) and, for atropine and scopolamine, with those obtained from standard compounds (Sigma, Milano, product number A 9547 and S 1875, respectively).

Pharmacological of *V. adscendens* extracts on GABA uptake

Preparation of synaptosomes
Crude synaptosomes were prepared from brain of male Wistar rats (180-220 g), according to the method of Hajos (48) with some modifications. After animal decapitation, the whole cerebral cortices were rapidly removed and homogenised in 10 volumes of 0.32 M sucrose buffered at pH 7.4 with Tris. The homogenate was centrifuged at 1,000 g for 10 min and the synaptosomes were isolated from the supernatant by centrifugation at 12,000 g for 20 min. The white and fluffy synaptosome layer was then resuspended, respun and resuspended in the sucrose medium at a protein concentration of 15-20 mg/mL, as determined by the biuret method. Experiments were carried out within 2 h of preparation.

Incubation conditions
Synaptosomes were incubated at a concentration of 3-4 mg/mL, for 10 min at 30° C in a standard medium containing (in mM): 135 NaCl, 3 KCl, 1.2 $MgCl_2$, 1 NaH_2PO_4,1.2 $CaCl_2$, 10 glucose and HEPES adjusted to pH 7.2 with Tris. The incubation was terminated by centrifugation (120 s in an Eppendorf microcentrifuge), and the levels of total amino acids were measured after the extraction of synaptosomal pellets

with cold perchloric acid. The acid extract was centrifuged at 15,800 x g and for 3, at 0-4° C and the supernatants neutralized with 10 mM KOH in 5 mM Tris. After centrifugation the supernatants were assayed for amino acids by separation in a reverse phase H-PLC.

[^{3}H] GABA uptake
Synaptosomes were incubated in a standard medium for 5 min at 30° C, and the uptake reaction was started by the addition of [^{3}H] GABA + GABA (final concentration 0.5 mM, 9.25 KBq/mL). The extracts were included in the medium before the addition of [^{3}H] GABA and the time of reaction was 15 min. The reaction was stopped by rapid filtration of aliquots of 0.25 ml through Whatman GF/B filters prewashed with 5 mL of sucrose medium maintained at 30° C. The radioactivity was measured in a Packard 2000 spectrometer with dpm correction. All the media used contained 10 mM aminooxyacetic acid, an inhibitor of GABA transaminase, to prevent the degradation of GABA.

HPLC determination of amino acids
Amino acids were analyzed in a Gilson-ASTED system according to the manufacture manual. The amino acids derivatives resulting from the precolumn derivatization with OPA/MCE (orthophtaldialdehyde/2-mercaptoethanol) were separated on a Spherisorb ODS column (particle size 5 mm; 150 mm long; 4.6 mm i.d.), at a flow rate of 2.5 mL/min, using the following ternary solvent system: buffer A (250 mM sodium phosphate, 15%; 200 mM propionic acid, 20%; acetonitrile, 7%; DMSO, 3%; pH 6.2); buffer B (acetonitrile, 40%; methanol, 33%; DMSO, 7.1%) and buffer C (250 mM sodium phosphate, 25%; 250 mM propionic acid, 20%; acetonitrile 7.1%; DMSO, 3.1%; pH 5.5). The effluent was monitored by a fluorescent detector, Gilson model 121 (excitation and emission wave lenghts at 340 and 410 nm, respectively). The integration of the amino acids peaks area and further calculations were performed by the Gilson system software and quantification was allowed by running standard amino acids solutions in the same conditions. The time required for each analysis was 45 min.

Pharmacological activity on animals

Animals
Male Swiss mice weighing 20 to 25 g, or guinea-pigs (180-200 g), supplied by Charles River (Italy), were housed in colony cages (10 mice each) under standard light (light on from 7.00 A.M to 7.00 P.M.), temperature (22±1°C) and room humidity (60%±10%) conditions for at least 1 week before experimentation. Food and water were available *ad libitum*.

Injection Procedure
On the day of the testing the aqueous extracts of *V. adscendens*, *V. officinalis*, *P. incarnata*, *I. herbstii* and *B. arborea* used in the experimental sessions was dissolved in saline for administration. Drugs were injected in a volume of 10 ml/kg, i.p. administrations.
V. adscendens, *V. officinalis* and *P. incarnata* were administered at doses of 25, 50, and 100 mg/kg/i.p. one hour before the beginning of the tests.
On the day of the testing the extracts of *I. herbstii* and *B. arborea* were dissolved in saline and administered at doses of 15, 30, and 60 mg/kg/i.p. one hour before the beginning of the test.

Locomotor activity
The animals were placed in the activity cage for at least a 30 min period for acclimatisation before receiving the injection. Temperature, sound and light conditions were maintained uniformly during the course of the experiments. Locomotor activity of the mice was recorded over a 2 hr period in an activity cage (Basile, Milan, Catalogue No 7400). Measurements were carried out at 10 min and cumulative counts were recorded (49).

Motor coordination
Motor coordination of the mice was evaluated by using a rotarod apparatus (Ugo Basile, Italy) consisting of a bar with a diameter of 3.0 cm, subdivided into five compartments by a disk 24 cm in diameter. The bar rotated at a constant speed of 16 rev/min (50). The motor coordination was assessed on the basis of the endurance time of the animals on the rotating rod. One day before the test, the animals were trained twice. On the day of the test only mice able to stay balanced on the rotating rod between 70 and 120 sec (cut-off time) were selected. The performance time was measured before and at 20, 40, 80 and 120 min after treatment (51).

Pentobarbital-induced sleep
One hour after administration of the above extract, mice were given an i.p. dose of 50 mg/kg of pentobarbital. The time between loss and recovery of the righting reflex was taken as the sleeping parameter and recorded for the saline (0.9% NaCl solution) and drug pretreated animals (52).

Stereotyped Behaviour
Rearing (RE), Grooming (GR), Social response test (SRT), Crossing (CR), Smelling (SM), Washing Face (WF), Scratching (SC), Bar holding (BH) were performed as previously reported (53). The frequency of all behaviours were recorded manually by one observer who did not know the treatment given to the animals. The test was conducted for a period of 120 min after extracts injection and each mouse was observed in the following sequences: 10-20 min post-injection (PI), 40-50 min PI, 70-80 min PI, 100-120 min PI. To check social responsiveness of the treated mouse, each session contained a social response test. An untreated mouse was placed for 5 min in the experimental cage together with the drug-treated mouse. The presence or absence of common social behaviour was recorded (sniffing, play or aggression) (54).

Catalepsy
The presence of a state of catalepsy was detected using the abnormal posture test (54). In mice, catalepsy was quantitatively estimated by placing the forepaws of the animals on a horizontal rod which was mounted 3 cm above the floor of the experimental box. The test was regarded as positive if the animal remained in this position for at least 45 sec. Latency to step down was recorded before and at 20, 40, 80, and 120 min after drug treatment. A maximum cut-off time of 45 sec was used. Cataleptic responses were calculated as a percent of the maximum possible response (%MPR) defined as (R-B)/(45-B)x100%. B is for mean baseline latency, R is for post-treatment response latency (55).
Nociceptive assays
The nociceptive assays performed were the hot plate (HP) and the tail flick test (TF).
The HP test was performed as previously described (56). Briefly, the HP

(Socrel Mod. DS-37, Ugo Basile, Italy, 25 cm x 25 cm) was set at a plate temperature of 55±0.5 C° to give a latency of 17-20 sec in control animals. The time of hind paw licking was recorded, and measuring was terminated if the licking exceeded the cut-off time (60 sec). The TF test was performed as previously described (57). Briefly, the TF latency was obtained using a TF unit (Socrel Mod DS-20, Ugo Basile, Italy). The animals were gently immobilized by using a glove, and the radiant heat was focused on a blackened spot 1-2 cm from the tip of the tail. Beam intensity was adjusted to give a tail flick latency of 2-3 sec in control animals. Measuring was terminated if the latency exceeded the cut-off time (10 sec) to avoid tissue damage. In all the experiments mice were tested twice, 60 and 30 min before drug administration in the baseline latency determination and 30 min after drug administration.

Transmurally stimulated guinea-pig ileum test.
The longitudinal smooth muscle and attached myenteric plexus were prepared as described previously (58). The preparation was placed between platinum electrodes and connected to a model 301 A Anapulse stimulator (Ugo Basile, Italy). A force-displacement transducer and unirecord model poligraph (Ugo Basile, Italy) were used for measuring isotonic contractions. A resting tension was applied of 0.5 g. After a 30 min equilibration period, the preparation was stimulated by a 5 ms pulse delivered transmurally every 10s at a supramaximal voltage (25 V).
The extracts used were added to the bath solution and left to equilibrate for an additional 15 min. During this period, the preparation was under continuous electrical stimulation. Intervals between successive doses were 30 min.

Acetilcholine-induced contractions of guinea-pig ileum
It was performed as previously described (59). Briefly, guinea-pig isolated ileum was placed in a 10 ml organ bath and connected to an isotonic transducer: the resting tension was 0.5 g and maintained throughout the experiment. Acetilcholine (Ach) was added to the bathing fluid and allowed to remain in contact with the tissue until the maximal effect occurred in 2 min and then washed out. After at least three control contractions, alkaloids isolated from fraction 2 of the methanolic extract were added to the bath 5 min before the next addition of agonist.

Statistical Analysis

All data (expressed as mean ± SEM) were analyzed by the analysis of variance (ANOVA) and Dunnett's procedure for multiple comparisons with a single control group. When the analysis was restricted to two means, Student's t-test (Two-tailed) was used.
The Fisher exact test was used to analyze the rotarod data. Significance was assumed at a 5% level.
In the electrically-stimulated of guinea-pig isolated ileum (E.C.I.), regression methods were used for statistical analysis and critical significance set at $P<0.05$. In the Ach-induced contractions of guinea-pig ileum, the inhibition of ileal contraction by alkaloids was expressed as a percent of the corresponding control (mean ± SEM); a paired two-tailed Student's-test was used for statistical analysis of corresponding values.
ED_{50} values were calculated according to Litchfield and Wilcoxon (60).

Results

Valeriana adscendens

Figures 1 and 2 show the effects of the three extracts of *V. adscendens* on GABA uptake in rat synaptosomes. At 40 mM HEPES-Tris the addition of methanolic extract to the reaction medium decreases the pH value from 7.2 to about 6.75. At 10 mM HEPES-Tris the change was from 7.2 to 5.3. The addition of a similar volume of methanol to the control medium has not effect on the uptake of [^{3}H] GABA. The methanolic extract causes a dramatic inhibition of GABA uptake, while the aqueous extract seems not active.

Table 1 reports the amino acid content of the three extracts of *V. adscendens*. The aqueous extract contains the major amounts of all detected amino acids.

Table 2 shows the effects of the incubation of the synaptosomes with the three extracts. In comparison with control, the methanolic extract causes a strong decrease in the content of GABA, alanine, taurine, serine and glutamate, while aqueous and hydromethanolic extracts shows no significant differences with the controls.

In presence of methanolic extract, no significant changes in histidine and tyrosine contents occurred, suggesting that the change in pH value observed is not responsible for the observed effect of the extract in the amino acids content and [^{3}H] GABA uptake. These data may contribute to explicate

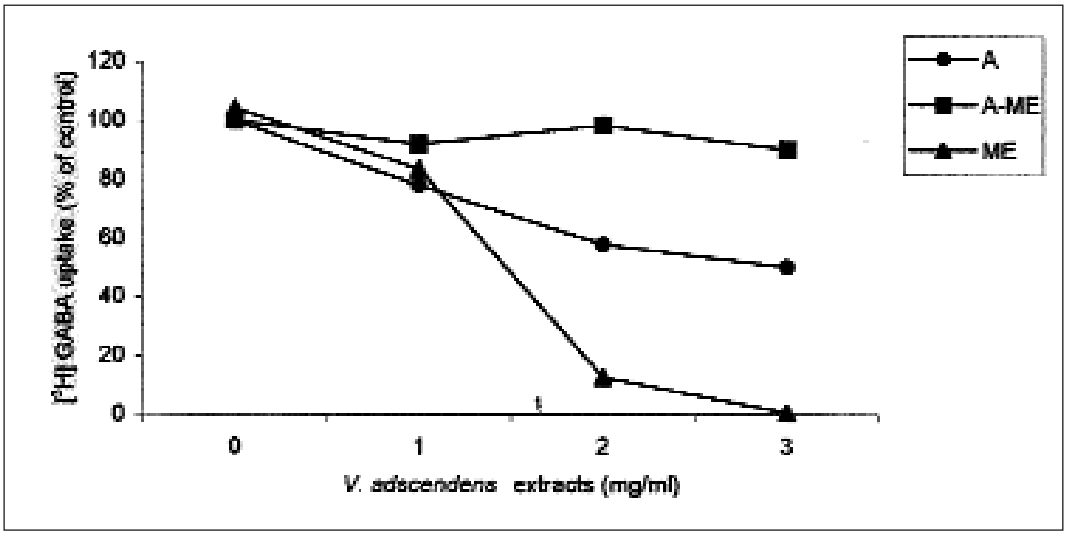

Figure 1 - Effect of the extracts of V. adscendens on the uptake of [^{3}H] GABA in synaptosomes. The preparation of synaptosomes and uptake experiments were performed as described in Material and Methods. V. adscendens concentrations are expressed as mg of original extract resuspended in water; ***AE****, aqueous extract;* ***A-ME****, methanolic extract resuspended in water;* ***ME****, methanolic extract resuspended in methanol. Values are the mean ± SEM of three to six different experiments run in duplicate. The amount of [^{3}H] GABA accumulated by synaptosomes in control conditions was 67.29 ± 2.26 nmol/mg protein.*

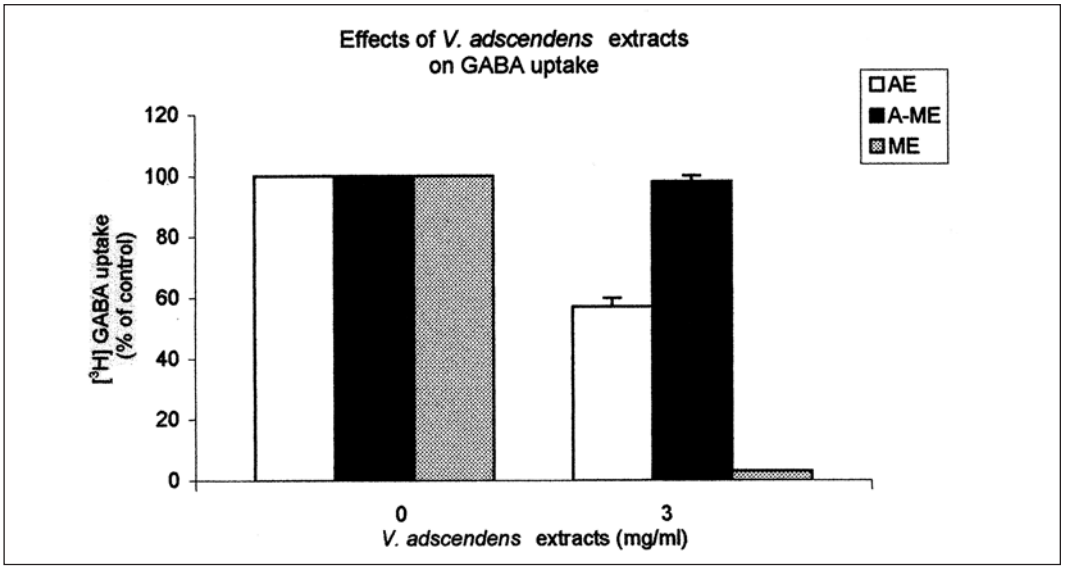

Figure 2 - Effect of the extracts of V. adscendens on the uptake of [^{3}H] GABA in synaptosomes. The preparation of synaptosomes and uptake experiments were performed as described in Material and Methods except that the concentration of HEPES-Tris was 40 mM. V. adscendens concentration was 3 mg of original dried extract per mL of final solution; ***AE****, aqueous extract;* ***A-ME****, methanolic extract resuspended in water;* ***ME****, methanolic extract resuspended in methanol. Values are the mean ± SEM of two different experiments run in triplicate.*

Table 1 - Amino acid content of extracts from Valeriana adscendens

	Aqueous extract (AE)	Hydromethanolic extract (A-ME)	Methanolic extract (ME)
Amino acid	Concentration (mM)		
Aspartate	375.0 ± 27.4	18.4 ±1.7	17.25 ± 0.9
Glutamate	217.7 ± 22.7	8.8 ± 1.7	8.27 ± 0.4
Serine	71.1 ± 13.7	12.0 ± 1.0	11.5 ± 0.5
Alanine	120.6 ± 12.7	59.0 ± 2.1	68.7 ± 11.5
Tyrosine	29.0 ± 6.5	n.d.	n.d.
GABA	36.7 ± 4.9	3.5 ± 1.1	4.4 ± 1.35

Values are the mean ± SEM of determinations performed in three extracts prepared separately. n.d. = not detected.

a neuroleptic-like property of methanolic extract of *V. adscendens*. Probably, the extract contains substance(s) which inhibits the uptake of [^{3}H] GABA and decreases the intracellular content of amino acid neurotransmitters namely, aspartate, glutamate, taurine and GABA. These data agree

Table 2 - Amino acid content of synaptsomes incubated with extracts from Valeriana adscendens

	Control	Aqueous extract (AE)	Hydromethanolic extract (A-ME)	Methanolic extract (ME)
Amino acid	(nmol/mg protein)			
Aspartate	27.9 ± 1.3	35.7 ± 2.2*	27.4 ± 2.4	4.3 ± 1.3*
Glutamate	35.9 ± 1.5	35.7 ± 2.3	28.3 ± 2.1	7.9 ± 2.5*
Serine	3.7 ± 0.2	3.9 ± 0.2	3.9 ± 0.3	2.4 ± 0.1*
Histidine	10.5 ± 2.0	14.2 ± 0.6	12.9 ± 1.7	13.9 ± 0.1
Glutamine	2.3 ± 1.2	n.d.	n.d.	n.d.
Alanine	3.2 ± 0.3	3.2 ± 0.2	2.7 ± 0.2	1.4 ± 0.1*
Taurine	15.2 ± 1.4	17.0 ± 1.3	16.3 ± 1.2	3.1 ± 0.3*
Tyrosine	1.9 ± 0.6	2.4 ± 0.5	3.2 ± 0.1	2.0 ± 0.5
GABA	11.35 ± 0.8	10.5 ± 0.5	11.4 ± 0.8	1.3 ± 0.4**

Values are the mean ± SEM of determinations performed with three aqueous and hydromethanolic extracts and two methanolic extracts prepared separately. Values statistically different from control (* $p<0.05$; ** $p<0.005$). n.d. = not detected.

with the data available in the literature on other *Valeriana* species. In fact, the possible role of the inhibition of GABA-transaminase in the sedative-spasmolytic activity of *V. officinalis* has been proposed (19-24).

The experiments performed with locomotor activity indicate that *V. adscendens* dose-dependently and significantly reduced the locomotor activity of mice when compared to saline-control mice (Figure 3). The reducing effect induced by *V. adscendens* aqueous extract is very similar to that induced both by *V. officinalis* and *Passiflora incarnata* extracts, although these latter are able to induce a slight reduction of locomotor activity also at the lower dose (25 mg/kg/ip - Figure 3).

V. adscendens, at the doses used, induced a significant and dose dependent reduction of the motor coordination of mice on the rota-rod bar when compared both to the saline treated mice and to the respective pre-drug (Figure 4).

Both *V. officinalis* and *P. incarnata* induced a significative reduction of motor coordination of mice also at the lower dose (25 mg/kg/ip). Significative results were also obtained in the stereotyped behaviour study, since *V. adscendens* dose-dependently and significantly reduced all the behaviour elements of the mice (table 3).

The reduction of stereotyped behaviour induced by *V. adscendens* is very similar to that induced both by *V. officinalis* and *P. incarnata* (data not shown). Finally, both *V. adscendens* and *V. officinalis* show a similar potency on the sleep induced by pentobarbital whereas the effect of *P. incarnata* is less marked when compared to the both *Valeriana* species.

In all the above experiments, the reduction induced by *V. adscendens* aqueous extract is significant 10-20

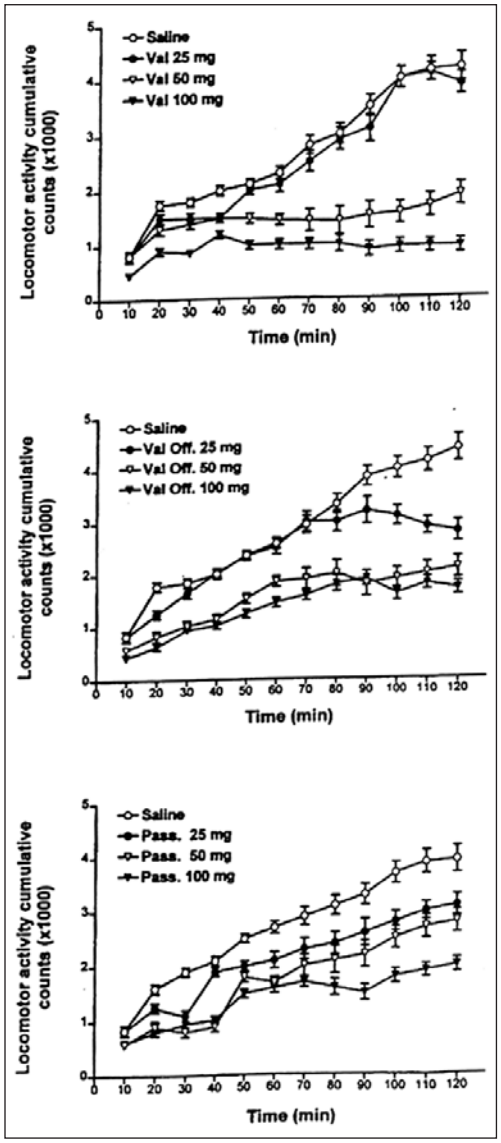

Figure 3 - Time- and dose-effect curves of Valeriana adscendens (VAL), Valeriana officinalis (Val off.) and Passiflora incarnata (Pass.) aqueous extracts on locomotor activity in mice. Abscissa: time in minutes; ordinate: cumulative counts every 10 min. Results are ± SEM (n=6).

min after the beginning of the test and lasted for all the recording period (120 min).

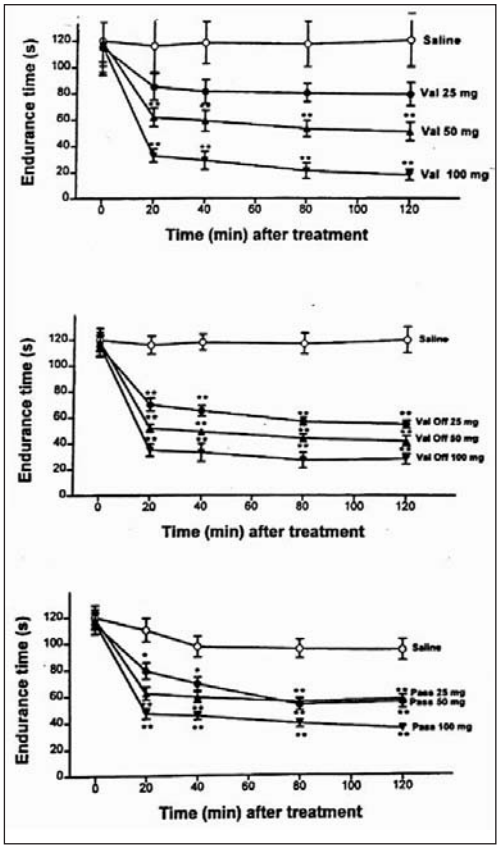

*Figure 4 - Time- and dose-effect curves of Valeriana adscendens (VAL), Valeriana officinalis (Val off.) and Passiflora incarnata (Pass.) aqueous extracts on motor coordination in mice. Abscissa: time in minute; ordinate: endurance time in second (S). Results are mean ± SEM (n=6); *P<0.05, **P<0.01.*

The results indicate that *V. adscendens* induced a significative reduction of the mice behaviour such as locomotor activity, motor coordination, and stereotyped behaviour. An increase of pentobarbital-induced sleep was also observed thus indicating that this plant exerts important depressant effects on the central nervous system.
Furthermore, the plant did not induce analgesia, catalepsy or alteration of guinea-pig ileum preparation electrically stimulated (data not reported).

Table 3 - Effect of saline and Valeriana adscendens aqueous extract (25, 50, 100 mg/kg/ip) on the stereotyped behavior of mice

	RE	GR	SRT	CR	SM	WF	SC	BH
10-20 min PI								
Saline	89±9.0	59±7.0	51±6.0	47±8.0	85±9.0	46±7.0	41±6.0	44±8.0
Val 25 mg	57±8.0	32±7.0	39±9.0	30±9.0	55±4.0	40±8.0	30±9.0	35±7.0
Val 50 mg	32±5.0	29±6.0	20±5.0	25±4.0	53±6.0	20±5.0	20±3.0	23±4.0
Val 100 mg	22±4.0	20±5.0	20±3.0	16±5.0	22±7.0	19±3.0	18±6.0	18±3.0
40-50 min PI								
Saline	65±8.0	48±9.0	47±6.0	39±5.0	76±9.0	55±6.0	43±5.0	37±5.0
Val.25 mg	37±4.0	31±9.0	30±9.0	25±7.0	47±5.0	39±4.0	35±9.0	26±8.0
Val 50 mg	29±6.0	21±8.0	21±9.0	20±6.0	27±7.0	21±5.0	19±3.0	18±2.0
Val 100 mg	20±4.0	18±2.0	18±4.0	21±6.0	19±3.0	15±3.0	12±2.0	11±3.0
70-80 min PI								
Saline	70±9.0	50±7.0	49±6.0	42±7.0	67±8.0	59±9.0	45±8.0	43±7.0
Val.25 mg	39±3.0	35±9.0	27±9.0	31±8.0	43±9.0	34±6.0	31±5.0	30±7.0
Val 50 mg	25±3.0	23±5.0	20±4.0	16±3.0	50±4.0	27±3.0	22±4.0	24±4.0
Val 100 mg	22±5.0	21±4.0	20±7.0	25±5.0	30±4.0	20±2.0	21±3.0	19±5.0
100-120 min PI								
Saline	68±9.0	55±7.0	50±8.0	45±6.0	65±7.0	60±8.0	47±7.0	45±6.0
Val.25 mg	50±3.0	49±9.0	45±9.0	46±8.0	56±9.0	47±8.0	52±9.0	47±5.0
Val 50 mg	33±5.0	35±5.0	29±5.0	30±9.0	45±5.0	30±9.0	24±6.0	26±9.0
Val 100 mg	23±3.0	19±4.0	21±3.0	26±5.0	24±4.0	27±6.0	21±5.0	24±4.0

Stereotyped behavior are dose-dependently and significantly reduced by *V. adscendens*. Results are mean ± SEM (n=6). The abbreviations are as follows: RE = Rearing; GR = Grooming; SRT = Social response test; CR = Crossing; SM = Smelling; WF = Washing Face; SC = Scratching; BH = Bar holding.

V. adscendens seems to possess pharmacological properties very close to *V. officinalis* as it was able to induce a significative reduction of the neuronal activity of mice. If the reduction of motor coordination and stereotyped behaviour registered are considered together with those induced in locomotor activity and on pentobarbital-induced sleep, they support the hypothesis that *V. adscendens* might act as a mild neurosedative drug.

The comparative study performed with *P. incarnata* further enforced the above hypothesis as its neuropharmacological profile is different than that of both *Va-*

leriana. In fact, *P. incarnata* induced both neurosedative and antinociceptive activity (61) whereas both *Valeriana* did not induce antinociception.

Iresine herbstii

The locomotor activity of the mice treated with an aqueous extract of *I. herbstii* was significantly reduced in a dose dependent manner (Figure 5).

This reduction was significant 10 min after the beginning of the test for all three doses (% of inhibition was 30.5, 43.8 and 57.4, respectively) and lasted for all the recording period (120 min).

The motor coordination of treated mice demonstrated a significant and dose dependent reduction of the motor coordination of mice on the rota-rod bar when compared both to the saline treated mice and to the respective predrug, (Figure 6).

The reduction induced by the plant was significant 10-20 min after the beginning of the test and lasted for the remaining 120 min period. A significant reduction was observed for the doses of 30 and 60 mg/kg,i.p.

I. herbstii aqueous extract administered to mice at doses of 15, 30, and 60 mg/kg,i.p. did not modify the sleep induced by pentobarbital.

The extract dose-dependently and significantly reduced all the behaviour el-

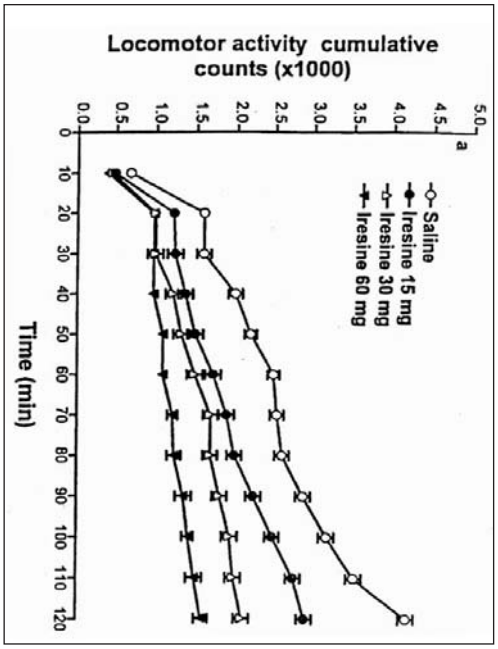

*Figure 5 - Time- and dose-effect curves of Iresine herbstii aqueous extract on locomotor activity in mice. Abscissa: time in minutes; ordinate: cumulative counts every 10 min. Fig. 1b: Locomotor activity counts on the 120th minute. Results are ± SEM (n=6), *P<0.05; **P<0.01 compared with saline-control mice.*

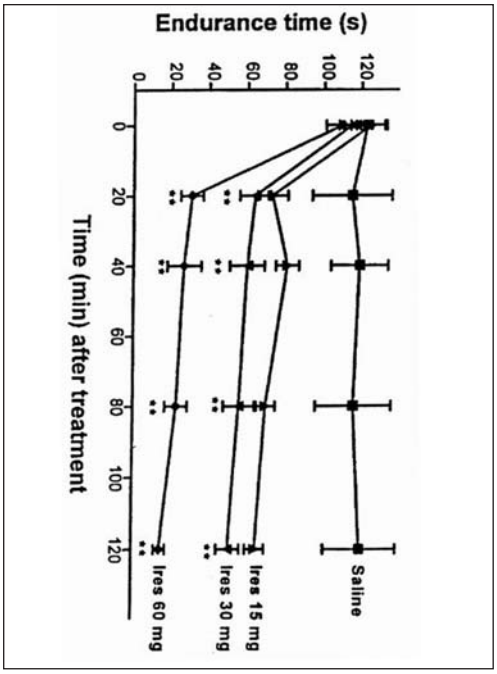

Figure 6 - Time- and dose-effect curves of *Iresine herbstii* aqueous extract on motor coordination in mice. Abscissa: time after treatment in minutes; ordinate: endurance time in second (S). Results are mean ± SEM (n=6), **P<0.01 compared with saline-control mice.

ements of the mice considered in our study (table 4). The reduction is significant 10 min after the beginning of the test and lasted for all the recording period (120 min).
I. herbstii at all the doses used did not induce a significant cataleptic effect in mice during the observing period, 120 min, when compared to saline-control mice (data not shown).
I. herbstii 15, 30, 60 mg/kg,i.p. did not induce significant changes in the nociceptive threshold both of the both hot plate and tail flick test. In fact, the re-

Table 4 - Effect of saline and Iresine herbstii aqueous extract (15, 30, 60 mg/kg/os) on the stereotyped behavior of mice

	RE	GR	SRT	CR	SM	WF	SC	BH
10-20 min PI								
Saline	89±7.	3 79±9.3	61±6.4	67±7.7	80±8.8	66±6.7	63±6.9	74±6.9
Ires 15 mg	50±4.7	41±5.5	42±4.8	35±2.7	33±3.6	36±2.9	38±3.1	41±3.6
Ires 30 mg	44±3.5	36±2.5	31±2.8	29±2.2	46±3.3	39±3.8	27±2.1	36±3.1
Ires 60 mg	25±1.6	15±1.2	18±1.6	15±1.7	12±1.0	16±1.2	12±1.0	11±1.4
40-50 min PI								
Saline	85±7.8	78±7.4	77±6.8	79±6.4	86±7.2	65±6.8	63±5.7	57±6.1
Ires 15 mg	46±4.9	42±4.5	35±3.1	40±4.6	37±3.9	31±3.9	30±2.7	24±1.9
Ires 30 mg	23±2.6	27±3.1	25±3.7	21±1.9	31±3.7	20±3.2	17±1.9	19±2.4
Ires 60 mg	10±1.2	15±1.7	11±1.6	10±1.8	11±1.5	15±1.7	13±1.4	16±1.9
70-80 min PI								
Saline	80±9.4	78±8.4	79±8.2	62±7.3	77±8.2	69±7.3	75±7.7	73±8.1
Ires 15 mg	49±5.3	43±4.9	37±4.1	41±5.2	33±3.7	37±3.5	33±4.3	20±2.6
Ires 30 mg	25±2.7	26±3.5	22±3.6	20±2.5	32±3.3	21±2.6	12±1.7	14±1.8
Ires 60 mg	12±1.9	11±2.4	10±1.6	15±1.8	10±1.7	10±2.3	11±1.7	12±1.8
100-120 min PI								
Saline	78±8.3	75±8.6	80±8.9	75±8.1	85±8.9	70±8.1	87±8.9	75±8.8
Ires 15 mg	40±4.7	44±5.3	35±4.6	36±4.4	32±4.1	37±4.7	32±4.2	27±3.8
Ires 30 mg	23±2.8	25±2.7	19±2.2	24±2.7	25±2.8	20±1.9	14±2.3	16±2.6
Ires 60 mg	13±2.1	11±2.4	11±2.5	16±2.9	44±3.8	17±2.3	11±1.9	44±3.7

Stereotyped behavior are dose-dependently and significantly reduced by *I. herbstii*. Results are mean ± SEM (n=6). The abbreviations are as follows: RE = Rearing; GR = Grooming; SRT = Social response test; CR = Crossing; SM = Smelling; WF = Washing Face; SC = Scratching; BH = Bar holding.

action times registered after injection of the extract were similar to those seen for animals treated with saline (data not shown).
These results indicate that *I. herbstii* induced a significative reduction in mouse behaviour such as locomotor activity, motor coordination, and stereotyped behaviour thus indicating that this plant exerts important effects on the nervous system, confirming popular beliefs (1).
Furthermore, *I. herbstii* extract did not induce analgesia, catalepsy or pentobarbital-induced sleep indicating a selective CNS effect similar to that observed with some psychotropic agents.
The reduction of motor coordination and stereotyped behaviour together with induced locomotor activity, support the possibility that *I. herbstii* might act as a psychotropic agent. In fact, it is already known that many psychotropic agents tend to reduce locomotor activity as well as motor coordination and stereotyped behaviour (62).
We are in the process of attempting to isolate and identify the active constituents of responsible for this psychotropic-like alteration of mouse CNS activities.

Brugmansia arborea
Brugmansia arborea methanolic extract significantly reduced and in a dose dependent manner the locomotor activity of mice (Figure 7). This reduction was significant 10 min after the beginning of the test and lasted for all the recording period (120 min).
Also, the motor coordination of treated mice was dose dependently reduced on the rota-rod bar when compared both to the saline treated mice and to the respective pre-drug, (Figure 8). The reduction induced by *B. arborea* methanolic extract was significant 10-20 min after the beginning of the test and lasted for the remaining 120 min period.
B. arborea methanolic extract administered to mice at doses of 15, 30, 60 mg/kg,i.p. did not modify the sleep induced by pentobarbital.
The methanolic extract dose-dependently and significantly reduced all the behaviour elements of the mice con-

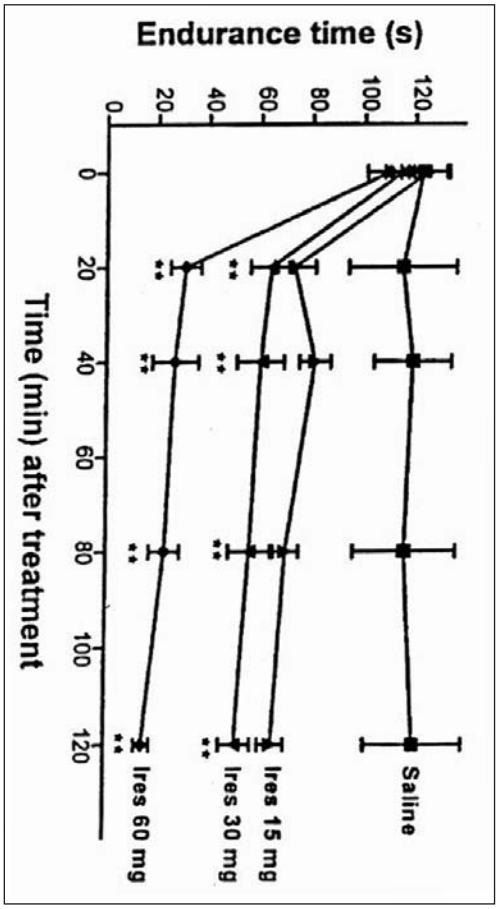

*Figure 7 - Time- and dose-effect curves of Brugmansia arborea methanolic extract on locomotor activity in mice. Abscissa: time in minutes; ordinate: cumulative counts every 10 min. Fig. 1b: Locomotor activity counts on the 120th minute. Results are ± SEM (n=6), *P<0.05; **P<0.01 compared with saline-control mice.*

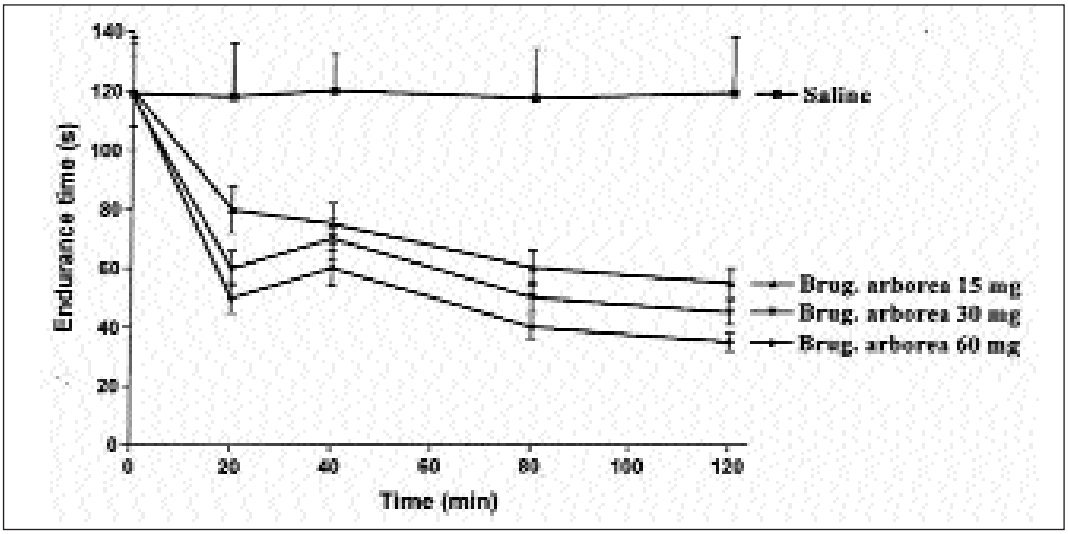

*Figure 8 - Time and dose effect curves of Brugmansia arborea methanolic extract on motor coordination in mice. Abscissa: time after treatment in minutes; ordinate: endurance time in second (S). Results are mean ± SEM (n=6), **P<0.01 compared with saline-control mice.*

sidered in our study (table 5). The reduction induced by *B. arborea* is significant 10 min after the beginning of the test and lasted for all the recording period (120 min).

B. arborea extract at all the doses used did not induce a significant cataleptic effect in mice during the observing period, 120 min, when compared to saline-control mice (data not shown).

The methanolic extract 15, 30, 60 mg/kg, i.p. significantly changes in the nociceptive threshold both of the both hot plate and tail flick test. In fact, the reaction times registered after *B. arborea* injection were higher to those seen for animals treated with saline (data not shown). In all these behaviour tests in mice, aqueous extract was less active (data not shown).

Both MeOH and H_2O extracts, at the concentrations used, dose-dependently reduced the electrically-induced contractions of guinea-pig ileum (E.C.I.). The inhibition began 2-4 min after the extracts administration, and it was enhanced with time and lasted for the whole recording period (15 min). MeOH extract was more potent in E.C.I. inhibition than H_2O extract; in Table VI, the ED_{50} calculated for the extracts, were reported.

As the MeOH extract was more active in inhibiting the ileum contractions, it was purified by Sephadex LH-20 column and four main fractions were collected and tested for E.C.I. activity. Only fractions 2 and 3 were able to reduce significantly the E.C.I., whereas fractions 1 and 4 did not produce significant modification on the preparation contractions (data not shown). The inhibition induced by the fraction 2 was more potent than that induced by fraction 3.

Also in this case, the inhibition appeared 2-4 min after the administration, and it was enhanced with time and lasted for all the recording period (15 min). Table 6 showed the ED_{50} calculated for the active fractions.

Figure 9 shows that the three compounds purified from the fraction 2 of methanolic extract, exert a strong in-

hibiting activity on the E.C.I. Atropine was able to reduce dose-dependently the E.C.I. of guinea-pig ileum at concentrations of 10^{-7}, 5 x 10^{-7} and 10^{-6} M; scopolamine, at concentrations of 5 x 10^{-6}, 5 x 10^{-5} and 10^{-5} M; and nor-

Table 5 - Effect of saline and Brugmansia arborea methanolic extract (15, 30, 60 mg/kg/os) on the stereotyped behavior of mice

	RE	GR	SRT	CR	SM	WF	SC	BH
10-20 min PI								
Saline	59±7.1	82±4.7	77±5.8	55±3.9	50±3.7	47±6.8	57±5.7	79±6.4
Brug 15 mg	36±3.7	59±5.3	62±5.8	47±3.5	44±2.9	50±3.5	35±2.9	57±4.3
Brug 30 mg	39±2.5	37±3.5	52±3.2	39±3.2	36±2.6	42±2.7	30±3.1	39±2.4
Brug 60 mg	25±1.6	19±1.2	12±1.9	10±1.2	16±1.7	17±1.6	11±1.5	13±1.7
40-50 min PI								
Saline	77±6.8	88±7.5	89±7.8	81±7.3	80±6.8	69±7.1	81±8.7	90±8.1
Brug 15 mg	51±3.9	63±7.5	67±7.1	77±7.3	57±7.9	41±3.9	44±3.6	32±3.5
Brug 30 mg	32±1.9	42±3.9	47±3.7	51±5.9	39±3.2	19±1.2	24±1.3	20±1.4
Brug 60 mg	22±1.5	26±2.3	23±1.8	27±1.4	21±1.7	13±1.0	10±1.1	13±1.4
70-80 min PI								
Saline	79±3.1	88±7.2	74±6.2	72±6.4	86±8.4	76±6.3	85±6.5	77±6.9
Brug 15 mg	57±6.3	53±3.	5 48±4.3	39±4.2	62±4.7	38±2.5	45±3.5	41±3.6
Brug 30 mg	36±2.3	23±3.1	34±2.9	25±1.5	42±4.1	27±2.1	22±1.3	24±1.4
Brug 60 mg	22±1.3	10±1.4	15±1.2	18±1.5	20±2.3	12±1.3	10±1.2	11±12
100-120 min PI								
Saline	75±6.4	79±7.5	85±8.3	77±7.5	85±7.9	75±7.1	67±8.0	76±7.8
Brug 15 mg	35±2.9	39±4.2	39±2.6	44±3.6	42±3.1	47±3.2	42±5.3	47±4.8
Brug 30 mg	29±1.8	20±2.0	14±1.2	19±1.5	15±1.3	16±1.3	18±1.3	19±1.4
Brug 60 mg	12±1.4	15±1.6	17±1.9	12±1.9	11±2.0	15±1.3	18±1.6	21±1.1

Stereotyped behavior are dose-dependently and significantly reduced by *B. arborea*. Results are mean ± SEM (n=6). The abbreviations are as follows: RE = Rearing; GR = Grooming; S-RT = Social response test; CR = Crossing; SM = Smelling; WF = Washing Face; SC = Scratching; BH = Bar holding.

hyoscine at concentrations of 10^{-7}, 5 x 10^{-7} and 10^{-6} M. Also in this case, the inhibition appeared 2-4 min after the administration, it was enhanced with time and lasted for all the recording period (15 min); in table 7, the ED_{50} calculated for the active pure com-

Table 6 - ED_{50} calculated for the extracts, chromatographic fractions and alkaloids isolated from B. arborea on the electrically-induced contractions of guinea-pig ileum

	ED_{50}	Confidence limits	
		Lower	Upper
MeOH extract	0.28 mg	0.22	0.35
H_2O extract	6.3 mg	4.6	8.6
Fraction 2 of MeOH extract	0.054 mg	0.044	0.065
Fraction 3 of MeOH extract	0.52 mg	0.44	0.62
Atropine	7.3×10^{-8} M	4.1×10^{-8} M	1.0×10^{-7} M
Scopolamine	8.4×10^{-6} M	6.7×10^{-6} M	1.0×10^{-5} M
Nor-hyoscine	3.1×10^{-7} M	2.4×10^{-7} M	4.0×10^{-7} M

The ED_{50} and 95% confidence intervals were computed from dose-response curves by the method of Litchfield and Wilcoxon with the aid of a computer program.

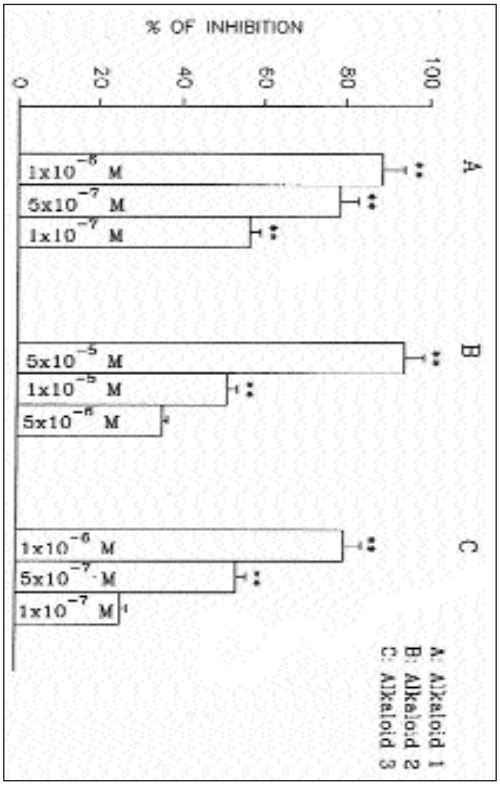

*Figure 9 - Dose-response curve of the alkaloids isolated from Brugmansia arborea on the electrically-induced contractions of guinea-pig ileum. Results are expressed as means ± SEM (n=6), *P<0.05, ** P<0.01.*

pounds were reported. Results presented in table 7 show that the three alkaloids after 5 min contact with ileum, reduced dose-dependently the contractions induced by a submaximally effective concentration of Ach (10^{-6} M). All inhibitory effects of the alkaloids were completely lost after washing out six times in 6 min from the bath.

Our data indicate that *B. arborea* induced a significative reduction in mouse behaviour such as locomotor activity, motor coordination, analgesia and stereotyped behaviour thus indicating that *B. arborea* exerts important effects on the nervous system, confirming popular beliefs (1). Furthermore, *B. arborea* did not induce catalepsy or pentobarbital-induced sleep indicating a selective CNS effect similar to that observed with some psychotropic agents. The reduction of motor coordination and stereotyped behaviour together with induced locomotor activity, support the possibility that *B. arborea* might act as a psychotrpic agent. In fact, it is already known that many psychotropic agents tend to reduce locomotor activity as

Table 7 - Effect of the alkaloids isolated from B. arborea on the Ach-induced contractions of guinea-pig ileum. Results are expressed as a percent of inhibition of Ach contraction

Concentration of compounds	Ach contraction (% inhibition)
Atropine (1.0 x 10^{-7} M)	82.0 ± 6.7
Atropine (5.0 x 10^{-8} M)	51.6 ± 5.5
Atropine (1.0 x 10-8 M)	30.3 ± 4.6
Scopolamine (1.0 x 10^{-5} M)	85.0 ± 7.2
Scopolamine (5.0 x 10^{-6} M)	47.3 ± 6.3
Scopolamine (1.0 x 10^{-6} M)	33.2 ± 5.2
Nor-hyoscine (5.0 x 10^{-7} M)	82.0 ± 5.5
Nor-hyoscine (1.0 x 10^{-7} M)	53.1 ± 6.1
Nor-hyoscine (5.0 x 10^{-6} M)	29.7 ± 4.1

well as motor coordination and stereotyped behaviour (62).

The results of the present study also indicate that both MeOH and H_2O extracts, some chromatographic fractions of the methanolic extract and three tropane alkaloids from *B. arborea* are able to reduce the electrically-stimulated contractions of guinea-pig ileum. Furthermore, the alkaloids were also able to reduce the Ach-induced contractions of guinea-pig ileum thus indicating their anticholinergic activity. Between the tested extracts, MeOH extract was more active than H_2O extract in inhibiting the ileum electrical contractions; therefore, the MeOH extract was submitted to a further purification by Sephadex LH-20 column to yield four main fractions, which were tested under the same experimental conditions. All the fractions tested showed a different potency in inhibiting the E.C.I. The relative order of potency was: fractions 1 and 4 inactive; fraction 3 < fraction 2. In comparison to the whole methanolic extract, its fractions 2 and 3 were much potent, thus indicating that the fractions contain a mixture of the active components which caused a marked inhibitory activity on the E.C.I. In order to identify the molecules responsible for the activity, the fractions were submitted to a purification and by means of rp-hplc, three compounds (atropine, scopolamine and nor-hyoscine) were purified. The experiments performed indicated that all the tested pure alkaloids were able to reduce the E.C.I.

In this respect it is well known that tropane alkaloids antagonize the muscarinic actions of Ach and they are known as antimuscarinic or muscarinic cholinergic blocking agents. Because the major effects of the most members of this class of drugs are quantitatively similar to those of its best known member, the term atropine-like is also used (63). The relative order potency was atropine>nor-hyoscine>scopolamine. Therefore, in order to assess their ability to antagonize the muscarinic actions of Ach, they were tested on Ach-induced contractions of guinea-pig isolated ileum. In these experiments all three alkaloids were able to reduce the Ach-induced contrac-

tions. Taken together, the above results indicate that the inhibitory activity of MeOH and H_2O extracts and of fraction 2 form methanolic extract of *B. arborea* was due to the presence of a combination of active principles. This is confirmed by the experiments performed with this fraction which resulted more active when compared to the fraction 3 (less active) or to fractions 1 and 4, completely inactive. Furthermore, the results of the present study also indicate that the inhibitory activity on the E.C.I. is due to the alkaloids, whose ability inhibiting the Ach-induced contractions indicate an anticholinergic activity related to the presence of the tropane nucleus.

Discussion

The results of our experiments indicate that all the above tested plants were able to reduce significantly the central nervous system activity of the animals, indicating a significative CNS effect similar to that observed with some psychotropic agents.
The reduction of motor coordination and stereotyped behaviour together with induced locomotor activity, support the possibility that all the studied plants act as psychotropic agents.
Our data on these psychoactive plants represent a validation of popular beliefs (1). It appears very important, to collect document and try to save medicinal and ritual plants. In fact, a part the significance of a basic knowledge, the study of plants with medical properties is specially meaningful in tropical lands, due to their great variety of animal and vegetal species, a factor that increase the number of available resources (64). On the other hand, tropical areas, are regarded as a primary source of undiscovered pharmaceuticals (65) and ethnobotanic data may constitute the basis for developing new active metabolites, also in the fascinating field of psychoactive plants.
Thus, it results the fundamental importance of the knowledge of ethnobotany, that Schultes (66) recently called "the prolific and promising treasure-trove of the ethnopharmacological knowledge".

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10th Congress of the International Headache Society (IHC 2001)

New York, 29 Giugno - 2 Luglio 2001

Il decimo Congresso della International Headache Society ha registrato una straordinaria affluenza di partecipanti giunti veramente da ogni angolo del globo, a dimostrazione dell'interesse scientifico e clinico che il capitolo delle cefalee, in anni non lontani Cenerentola delle neuroscienze, riesce oggi a suscitare. Al successo del Simposio ha inoltre certamente contribuito la splendida cornice in cui si è svolto, una sfavillante Manhattan dalla skyline ancora integra…
Un record è stato sicuramente raggiunto anche per quanto riguarda la quantità dei contributi scientifici proposti: tra comunicazioni orali e poster, mediamente di buona qualità, nei quattro giorni del Congresso sono stati presentati circa 550 lavori, molti dei quali da ricercatori italiani, come sempre intervenuti in forze.
Nella prima sessione di comunicazioni orali, dedicata all'epidemiologia e alla diagnosi, ricordiamo la ricerca di Kruit e coll., che hanno indagato, mediante uno studio caso-controllo su un ampio campione di popolazione generale olandese, la prevalenza di infarti e lesioni della sostanza bianca negli emicranici. Piuttosto inaspettatamente, nell'emicrania, e specialmente nell'emicrania con aura, è stata dimostrata un'elevata prevalenza di infarti cerebellari, il cui significato è tutto da indagare. Granella, a nome di un'ampia coalizione italiana comprendente le Università di Parma, Modena, Torino e Pavia, ha dimostrato che, nelle donne affette da "menstrually-related migraine" (cioè nelle donne che presentano attacchi di emicrania sia durante che al di fuori del periodo perimestruale), le crisi di emicrania senz'aura che capitano nei primi 2 giorni del ciclo sono più lunghe, più gravi e meno sensibili al trattamento sintomatico delle crisi extramestruali. In un altro studio olandese coordinato da Michel Ferrari, condotto su oltre 1000 pazienti affetti da cefalea a grappolo, è stato dimostrato che, contrariamente a quanto finora ritenuto, gli attacchi sono preceduti, in oltre la metà dei casi, da prodromi di tipo sensitivo, vegetativo o concernente il tono dell'umore; nel 26% dei casi era inoltre presente una vera e propria aura.
Di grande interesse, nella sessione riservata alla farmacologia, la dimostrazione, offerta da Ramadan e coll., che il LY293558, un antagonista dei recettori glutammatergici AMPA/KA, è efficace nel trattamento dell'attacco di emicrania: si tratta di un'ulteriore evidenza dell'importanza dell'iperattività glutammatergica nell'emicrania, oltre che di una nuova strategia terapeutica, priva di effetti collaterali cardiaci. Per i farmaci già in uso, novità hanno riguardato il sumatriptan e lo zolmitriptan, nella formulazione spray nasale: il primo è stato trovato efficace nella terapia in acuto della cefalea a grappolo, il secondo in quella dell'emicrania.
Nella terza sessione, dedicata ai meccanismi dell'emicrania, Wood, del gruppo di Welch, ha elegantemente dimostrato, mediante la sofisticata tecnica della microscopia intravitale, che la spreading depression corticale aumenta la permeabilità vascolare della microcircolazione piale nei ratti, mediante la generazione di sostanze ossidanti e l'aderenza dei leucociti all'endotelio. Il ruolo dell'os-

sido nitrico (NO) nell'attacco emicranico è stato indagato in due lavori. Nel primo, presentato da Reuter e coll., è stato dimostrato che l'infusione di nitroglicerina nei ratti determina una risposta infiammatoria ritardata nella dura madre, mediata da NO perlopiù derivato dall'espressione di NO-sintasi inducibile nei macrofagi. Nel secondo, Akerman e coll. hanno trovato che la dilatazione dei vasi meningei successiva a somministrazione di donatori di NO nei ratti presenta un decorso temporale simile a quello della cefalea indotta da NO negli esseri umani.
Nella quarta sessione, riguardante le cefalee primarie ad alta frequenza, Tzourio e coll. hanno riportato l'attenzione sulla componente "vascolare" dell'emicrania, mostrando che un polimorfismo del gene del recettore dell'endotelina tipo A modula il rischio di emicrania, mentre un team di ricercatori spagnoli, guidato da Pascual, ha stabilito la prevalenza della cefalea cronica quotidiana con abuso di analgesici nella popolazione generale: essa si situerebbe tra l'1 e il 2%, con una schiacciante predominanza di donne.
Nella sessione dedicata all'età evolutiva, il gruppo di Guidetti ha presentato un follow-up a 2 anni di bambini e adolescenti affetti da cefalea cronica quotidiana: essa avrebbe in questa età un outcome più favorevole che nell'adulto, anche se l'associazione con disturbi depressivi costituisce un fattore prognostico negativo.
Col bel lavoro vincitore del prestigioso premio HG Wolff, Welch ha dimostrato che l'omeostasi del ferro nella sostanza grigia periacqueduttale è selettivamente, persistentemente e progressivamente alterata nei pazienti con emicrania senz'aura e cefalea cronica quotidiana. Potrebbe trattarsi non di un elemento causale dell'emicrania, bensì della conseguenza del ripetersi delle crisi, che comporterebbe un accumulo di ferro causato dall'azione dannosa dei radicali liberi.
Alla fine del Congresso, gli organizzatori hanno dato appuntamento a tutti gli intervenuti alla prossima manifestazione mondiale dell'International Headache Society, che si svolgerà nel 2003 nella Città Eterna.

Franco Granella

Annual meeting of the Danish Headache Society "Headache and Science. A tribute to Professor Jes Olesen"

Glostrup (Copenhagen, Denmark), 7 Settembre 2001

Il 9 settembre ricorreva il sessantesimo compleanno di Jes Olesen Professore di Neurologia di fama internazionale, brillante ricercatore nel campo delle cefalee primarie e attuale direttore del Dipartimento di Neurolgia e del Centro Cefalee dell'Ospedale di Glostrup - Copenhagen. L´evento non e´ passato inosservato: i suoi collaboratori hanno deciso di commemorare la ricorrenza ricordando i prestigiosi risultati ottenuti, negli ultimi 25 anni, dai vari gruppi di ricerca danesi coordinati dal Prof. Olesen. L'occasione è stata il congresso annuale della Società Danese per le Cefalee che si è tenuto il 7 settembre 2001 a Glostrup e che è stato intitolato "Headache and Science – a tribute to Professor Jes Olesen".

L'incontro è stato aperto da Peer Tfelt-Hansen (Glostrup, Danimarca) con una breve rassegna sull'evoluzione delle conoscenze nell'ambito delle cefalee in Danimarca. Le prime importanti scoperte sono state rappresentate dagli studi di Thorvald Dalsgaard-Nielsen relativi alla cefalea indotta dall'applicazione percutanea di nitroglicerina in controlli sani e in pazienti emicranici (1949). I successivi risultati di maggiore rilievo sono sicuramente rappresentati dai lavori di Olesen che nel 1981 ha evidenziato durante gli attacchi di emicrania con aura una riduzione del flusso ematico cerebrale regionale che origina dalle aree corticali visive associative e diffonde anteriormente, con una velocità costante. Grazie a queste osservazioni è stata postulata la prima ipotesi patogenetica che fa risalire l'aura ad un fenomeno simile alla "cortical spreading depression", registrata da Leao nel 1944 nella corteccia cerebrale del coniglio, cioè ad un'onda di diminuita attività corticale che partendo dalla regione occipitale si sposta in senso postero-anteriore alla velocità di 2-3 mm/min. Anche se la "cortical spreading depression" non è ancora stata visualizzata inequivocabilmente nell'uomo, le ricerche di Lauritzen (Glostrup, Danimarca) del 1994 fanno oggi ritenere che i fenomeni vascolari evidenziati siano secondari a un meccanismo primariamente neurogeno visto che non seguono i territori di distribuzione vascolare.

Tra gli ospiti stranieri, James Lance (Sidney, Australia) ha magistralmente esposto il grande "impatto" che, a livello mondiale, ha avuto un piccolo Paese come la Danimarca sotto la guida scientifica di Olesen. E' sufficiente pensare ai risultati ottenuti nel campo dell'epidemiologia, della genetica, della fisiopatologia e della terapia delle principali forme di cefalea primaria che sono universalmente considerati punti di riferimento fondamentali per neurologi e ricercatori. Da non dimenticare la cospicua produzione letteraria di Olesen che, nell'ultimo decennio, lo ha visto ideatore ed editore del libro "The Headaches", oggi alla sua seconda edizione, considerato un caposaldo irrinunciabile per chiunque voglia conoscere o approfondire l'ampio capitolo delle cefalee sia a livello generico che specialistico.

Una delle pietre miliari nella storia della ricerca e della pratica clinica nel campo delle cefalee è rappresentata dalla "Classification and diagnostic criteria for headache disorders, cranial neuralgia and facial pain" stilata sotto la leadership di Olesen da sottocomitati, costituiti da esperti internazionali, nell'ambito della International Headache Society (IHS). Ad Hartmut Göbel (Kiel, Germania) è stato affidato il compito di illustrare i vari passaggi che hanno portato nel 1988 alla pubblicazione della classificazione, attualmente in via di revisione, e di esporre le principali caratteristiche operative della stessa. Evidenziando parallelismi e divergenze esistenti tra le classificazioni degli elementi inanimati ed animati e la classificazione della IHS, Göbel ha proposto una gradevole ed esaustiva descrizione del sistema nosografico delle cefalee che, pur con qualche modifica, mantiene inalterata la sua validità a distanza di quasi 10 anni dalla sua prima stesura.

Le ultime relazioni sono state tenute dai responsabili dei gruppi di ricerca attualmente coordinati da Olesen: Birthe Krogh Rasmussen (Hillerød, Danimarca) per l'epidemiologia, Michael Biørn Russell (Gentofte, Danimarca) per la genetica, Helle Iversen (Glostrup, Danimarca) per i modelli sperimentali animali e Rigmor Jensen (Glostrup, Danimarca) per la cefalea di tipo tensivo. Rasmussen ha brevemente riportato i dati più signi-

ficativi dello studio epidemiologico da lei condotto nella popolazione generale danese nel 1991, per poi sottolineare in modo più dettagliato i risvolti socio-economici del problema "cefalea". I costi diretti e indiretti legati al mal di testa e l'organizzazione delle strutture sanitarie dedicate sono infatti oggetto di una sempre maggiore attenzione da parte di medici, ricercatori e personale amministrativo del settore.

La ricerca molecolare e genetica rappresenta attualmente uno dei campi di maggiore espansione e il gruppo danese di Russell deve sicuramente essere considerato all'avanguardia in questo ambito. La più approfondita conoscenza del ruolo che i fattori genetici giocano nelle varie forme di cefalee – emicrania, cefalea a grappolo e cefalea di tipo tensivo - ha portato ad enormi passi avanti nella comprensione della fisiopatologia e delle modalità di trasmissione di questi disturbi.

La necessità e lo sviluppo di modelli sperimentali animali ha permesso di studiare in vivo, seppur in un modello non perfettamente sovrapponibile a quello umano, la reattività vasale, il rilascio di neuropeptidi da parte dei terminali nervosi di alcuni nervi cranici, l'espressione di specifici geni in seguito a stimoli adeguati e l'azione di varie sostanze esogene. Iversen ha focalizzato l'attenzione sugli studi condotti nell'ultimo decennio rivolti alla definizione del ruolo dell'ossido nitrico e del calcitonin-gene related peptide (CGRP) nel determinismo dell'emicrania e sui possibili risvolti terapeutici di queste scoperte.

Jensen ha chiuso il convegno riassumendo i meccanismi patogenetici che sottendono l'insorgenza della cefalea di tipo tensivo.

L'utilizzo di avanzate tecnologie, appannaggio quasi esclusivamente danese, ha portato a definire con una migliore chiarezza il ruolo dei fattori periferici e centrali nella nelle due forme attualmente codificate: i fattori muscolari e miofascali e la sensibilizzazione periferica avrebbero un peso maggiore nel determinismo della forma episodica, mentre la sensibilizzazione centrale probabilmente ha un ruolo di rilievo nell'insorgenza e soprattutto nel mantenimento della forma cronica. Vista la relativa carenza nell'armamentario farmacologico nell'ambito della cefalea di tipo tensivo cronico, i futuri campi di espansione potrebbero essere rappresentati dallo sviluppo di sostanze in grado di prevenire o far regredire la sensibilizzazione centrale.

Al termine delle relazioni la giornata si è conclusa con il cambio d'abito del festeggiato, dei relatori e degli auditori che sono stati ospiti per la cena in un delizioso ristorante sulle rive di uno dei tanti laghetti che illuminano e rinfrescano la campagna danese.

Paola Torelli

CIRNA FOUNDATION
FOR THE RESEARCH ON HEADACHE AND BEHAVIOURAL NEUROLOGY

CEFALEE TODAY

e-bulletin www.cefalea.it

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OTTOBRE 2001

TOSSINA BOTULINICA: DA VELENO A FARMACO. UNA NUOVA POSSIBILITA' PER IL MAL DI TESTA...

La cefalea tensiva è una patologia frequente e non sempre responsiva ai trattamenti farmacologici convenzionali. Le cause patogenetiche alla base del disturbo non sono ancora del tutto chiarite, ma risulta evidente che la contrazione/tensione protratta della muscolatura pericranica gioca un ruolo determinante nella genesi del dolore.

Perché un nuovo farmaco per il mal di testa?

La tossina botulinica è un farmaco che riduce la contrazione muscolare.

La tossina agisce a livello della giunzione neuromuscolare, cioè dove l'estremità del nervo si divide in tante diramazioni terminali che raggiungono le fibre muscolari e ne controllano l'attività tramite una sostanza detta neurotrasmettitore. A questo livello, la Tossina effettua un blocco del rilascio del neurotrasmettitore con inibizione della contrazione muscolare. Il muscolo, quindi, per effetto della Tossina, rimane indebolito in forma variabile a seconda della quantità di Tossina iniettata. Tale effetto è transitorio poiché nel giro di pochi mesi avviene lo smaltimento della tossina, la rigenerazione della terminazione nervosa e il recupero della normale contrattilità muscolare.

Come nasce la tossina botulinica-farmaco.

Durante la Seconda Guerra Mondiale, negli USA, sono state effettuate ricerche sotto stretto controllo militare per lo sviluppo di adeguate misure difensive nei confronti delle armi batteriologiche, in particolare contro

la più potente di tutte, cioè la tossina botulinica. Durante queste ricerche, alcuni oftalmologi di S. Francisco, fra cui il Dr. A. Scott, hanno visto un possibile utilizzo terapeutico di questa neurotossina, come potente mioralassante da utilizzare nello strabismo, in alternativa alla chirurgia tradizionale. Nel 1979 la Food and Drug Administration (l'ente americano che regola la sperimentazione e l'utilizzo dei farmaci) ha autorizzato l'uso della tossina botulinica in ambito clinico per la cura dello strabismo e nel 1989 ne è stato approvato l'uso per il blefarospasmo, un disturbo del movimento che determina una frequente e involontaria contrazione dei muscoli palpebrali.
Da circa 10 anni, quindi, la Tossina Botulinica viene impiegata come farmaco di prima scelta nel trattamento dei disordini del movimento, ma appare sempre più evidente la sua utilità in altre patologie caratterizzate da iperattività muscolare o ghiandolare (eccessiva sudorazione, eccessiva salivazione).
Alcuni pazienti con movimenti involontari e distonie del volto (blefarospasmo ed emispasmo facciale) che presentavano emicrania o cefalea, riferivano una riduzione dell'intensità del dolore e della frequenza delle crisi successivamente ai trattamenti con tossina botulinica al volto. In seguito a questi casi, sono iniziati degli studi controllati per valutare l'efficacia delle infiltrazioni di tossina nei muscoli pericranici in soggetti affetti da cefalea tensiva ed emicrania.
L'iperattività della muscolatura pericranica, infatti, è attualmente ritenuta un fattore associato alla cefalea tensiva cronica e che può aggravare la sintomatologia dolorosa nell'emicrania.
Nella maggior parte degli studi effettuati fino ad ora, la tossina botulinica ha dimostrato una discreta efficacia nel ridurre, sia acutamente che come trattamento di profilassi, il dolore dell'emicrania e della cefalea per circa 4 mesi.
Non sono stati riscontrati effetti collaterali significativi.
La terapia con tossina botulinica rappresenta, quindi, una nuova possibilità terapeutica nel campo delle cefalee.
Indubbiamente, il suo utilizzo deve ancora essere perfezionato, soprattutto in relazione all'adeguata selezione dei pazienti da trattare.
E' importante ricordare che la terapia con tossina deve essere effettuata solamente nei Centri Neurologici specializzati, dove sia disponibile un'idonea attrezzatura per l'adeguata conservazione e lo smaltimento del prodotto e dove sia presente un'équipe di medici esperti nella somministrazione di questo farmaco e nel monitoraggio dei vantaggi e degli eventuali effetti collaterali dei pazienti cui viene somministrata.

Francesca Mancini

EMICRANIA, ANSIA E DEPRESSIONE: UN TERRENO COMUNE?

Le caratteristiche con cui l'emicrania si manifesta sono assai variabili: tale eterogeneità clinica e' anche spiegabile sulla base del fenomeno della comorbidità, ovvero dell' associazione non casuale di altre condizioni patologiche nei pazienti emicranici. Questo fenomeno suggerisce l'esistenza di fattori eziologici comuni, e condiziona fortemente la diagnosi ed il trattamento dell'emicrania. Tra i disordini più frequentemente osservati negli emicranici vi sono i disturbi dell'umore e d'ansia. Diversi studi di prevalenza hanno evidenziato una stretta relazione tra la depressione dell'umore e l'emicrania, ed in particolare che
1) i pazienti emicranici hanno un rischio di sviluppare depressione maggiore di 4.5 volte più elevato rispetto ai soggetti di controllo;
2) la frequenza con cui i pazienti emicranici senza depressione sviluppano manifestazioni depressive è 3 volte maggiore rispetto alla popolazione generale dei pazienti;
3) pazienti depressi senza emicrania sviluppano l'emicrania con frequenza di 3 volte maggiore rispetto a pazienti non depressi.
L'associazione delle due condizioni ha generato diverse ipotesi. Ad esempio, l'intenso dolore che caratterizza l'emicrania potrebbe predisporre il soggetto allo sviluppo di manifestazioni depressive; d'altro canto, il disturbo dell'umore potrebbe esso stesso comportare una riduzione della soglia del dolore e della tolleranza al dolore, favorendo il ripetersi degli attacchi emicranici. E' inoltre possibile che l'emicrania e la depressione siano entrambe legate ad alterazioni che coinvolgono la serotonina, neurotrasmettitore che gioca un ruolo fondamentale nella patogenesi di numerosi disordini. In ogni caso, il medico deve considerare con la massima attenzione la contemporanea presenza di emicrania e depressione in un paziente: è noto, ad esempio, che farmaci utilizzati nel trattamento dell'emicrania possono causare sintomi depressivi, e sono pertanto controindicati in caso di comorbidità. D'altra parte, un trattamento dell'emicrania disgiunto da quello del disturbo dell'umore può lasciare inalterati sintomi (ad

esempio i disturbi del sonno, o la ridotta concentrazione) che compromettono la qualità della vita del paziente. Pertanto, un trattamento efficace dei pazienti emicranici con depressione dell'umore deve essere basato su principi che riducano al minimo le complicanze associate ad entrambe le condizioni. In alcuni casi, può essere efficace la monoterapia: ad esempio, vi sono evidenze di una buona risposta dei pazienti emicranici a farmaci antidepressivi triciclici come l'amitriptilina. Anche i pazienti con disturbi d'ansia sono affetti da emicrania con frequenza elevata, ma non è noto se la presenza dell'ansia rappresenti un fattore di rischio o piuttosto una conseguenza dell'emicrania, o se le due condizioni siano caratterizzate da un terreno patogenetico comune. Chi è affetto da un disturbo da attacchi di panico è maggiormente suscettibile all'emicrania, e i pazienti con sintomatologia da panico più intensa e frequente rappresentano il 25% dei soggetti con emicrania nell'ambito dell'intero campione studiato. Questi dati, confermati anche da studi svolti presso il Centro Cefalee di Pavia, sono in linea con altri studi di popolazione, che mostrano una associazione significativa tra emicrania ed attacchi di panico, se si considera la prevalenza nell'arco della vita. Anche la comorbidità tra emicrania e disturbi d'ansia ha importanti implicazioni in ambito terapeutico. Alcuni dei farmaci efficaci nella profilassi dell'emicrania sono in grado di attenuare la sintomatologia del disturbo da attacchi di panico; è quindi possibile, in questi casi, fare ricorso alla monoterapia. Invece, alcuni farmaci anti-emicranici, come ad esempio i beta-bloccanti, non sembrano essere efficaci nel trattamento degli attacchi di panico, e non rappresentano pertanto una scelta ottimale. Dati recenti suggeriscono che la combinazione di disturbi dell'umore e disturbi d'ansia è significativamente associata all'emicrania: pazienti con elevati livelli d'ansia nell'infanzia presentano un più alto rischio di essere affetti da emicrania nell'adolescenza o in età adulta, ma anche di sviluppare disturbi depressivi. La ricerca scientifica e' attualmente incentrata sui fattori, in primo luogo di tipo genetico, che fanno da comune denominatore a queste condizioni, strettamente e reciprocamente collegate.

Alfredo Costa

"Dalla Letteratura Internazionale"

Gli anestetici per via intranasale nella cefalea a grappolo: nuove possibilità di terapia?

(a cura di A. Costa)

Un possibile coinvolgimento del ganglio sfenopalatino nei meccanismi della cefalea a grappolo (CH) e´ stato proposto anni fa, ed alcuni studi non controllati hanno suggerito l'utilità dell'applicazione intranasale di alcuni anestetici nel trattamento abortivo degli attacchi. Uno studio italiano, svolto presso il Centro Cefalee di Pavia, ha valutato l'efficacia del trattamento sintomatico con lidocaina e cocaina per via intranasale, in crisi di CH indotte dalla nitroglicerina (NTG). Quindici pazienti sono stati sottoposti a test di induzione (con 0.9 mg di NTG sublinguale). Nei 9 soggetti con cefalea simil-spontanea e' stato effettuato un secondo test, e non appena il dolore raggiungeva un valore significativo, si procedeva in rinoscopia anteriore all'applicazione in fossa sfenopalatina di un tampone imbevuto di una soluzione contenente 1 g di cocaina idrocloride, o lidocaina 10%, o soluzione salina. Nei due gruppi di pazienti trattati con cocaina o lidocaina e´ stata evidenziata una riduzione di intensità del dolore significativamente più rapida e marcata rispetto ai soggetti trattati con salina. I dati ottenuti confermano il coinvolgimento del ganglio sfenopalatino nella CH e suggeriscono che cocaina e lidocaina rappresentano una possibile alternativa terapeutica per il trattamento sintomatico di questo tipo di cefalea, specie nella variante episodica.

(A. Costa et al., Cephalalgia 2000; 20:85-91)

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DICEMBRE 2001

Sommario

Cefalea da week-end: mito o realtà?

La cefalea da weekend, frequentemente riferita dai pazienti che afferiscono ai centri specializzati, è una forma di cefalea che insorge esclusivamente o quasi esclusivamente durante il fine settimana. Esiste o non esiste la cefalea da weekend? E' sicuramente questo il primo quesito che ci si deve porre trattando l'argomento. La letteratura scientifica a tal proposito è contraddittoria ed alcuni autori ne negano l'esistenza considerando la maggiore ricorrenza delle crisi il sabato e la domenica solamente un dato soggettivo, riferito dai pazienti, privo di significato. L'analisi dei diari compilati dai soggetti che ne sono affetti permette di smentire le correnti di pensiero più scettiche evidenziando una reale maggior frequenza degli attacchi nel fine settimana.

Le cause del peculiare pattern temporale che caratterizza la cefalea da weekend sono state ricercate sia

sul versante organico che su quello psichico. Il ruolo, nella genesi delle cefalee, degli stati emotivi in generale è noto sin dall'inizio del secolo scorso.

In linea con queste teorie, alcuni autori hanno messo in relazione la cefalea da weekend direttamente con lo stress ricavando l'ipotesi che sia correlata alla caduta dello stress da lavoro che si verifica nel fine settimana.

Tra i possibile fattori organici coinvolti, un certo rilievo è stato attribuito alla minore assunzione di caffeina e al risveglio ritardato, abitudini che caratterizzano il fine settimana di molti individui. Al termine

delle varie analisi, però, l'ipotesi più accreditata è quella che riconduce la cefalea da weekend ad una perdita, da parte dei pazienti, della loro organizzazione settimanale.

Nel nostro Centro ci siamo occupati in modo approfondito del problema cercando di delineare con maggiore precisione il quadro clinico ed i possibili fattori implicati nella genesi.

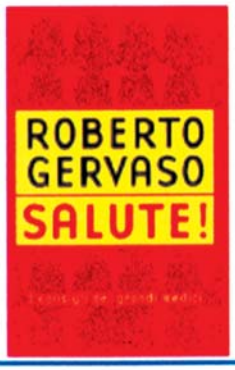
Cosa differenzia il weekend dagli altri giorni della settimana? Per rispondere al quesito abbiamo analizzato le abitudini di vita nel loro complesso e le differenze che eventualmente si evidenziano tra la settimana lavorativa e il fine settimana prendendo in esame: a) lo stress letto non solamente come "caduta nel weekend dello stress lavorativo", lavorativo", ma come "differenti livelli di stress tra settimana lavorativa e weekend"; b) le caratteristiche dell'attività lavorativa nei suoi molteplici aspetti oggettivi e soggettivi; c) il vissuto individuale del tempo libero settimanale e del weekend.

Dalle valutazioni effettuate è emerso che l'attività lavorativa spesso non risulta gratificante e genera tensioni emotive che si ripercuotono sul tempo libero e sulla vita familiare determinando contemporaneamente aspettative di appagamento e rilassamento per il fine settimana. L'ambito domestico impone, in maggior misura per le donne, impegni e compiti da portare a termine nel fine settimana generando ulteriore fonte di insoddisfazione per la scarsa possibilità di seguire i propri interessi. In questo contesto è possibile che i soggetti con cefalea da weekend, forse per predisposizione personale o per meccanismi acquisiti, neutralizzino le frustrazioni scaricando le emozioni negative su se stessi determinando l'insorgenza della cefalea nel fine settimana. È possibile, inoltre, che le crisi che si verificano il sabato o la domenica assumano una connotazione di maggiore gravità proprio perché quei giorni dovrebbero essere vissuti come rilassanti.

La cefalea da weekend sarebbe l'espressione di una mancanza di meccanismi di difesa efficaci oppure potrebbe essere essa stessa un meccanismo di difesa che permette al soggetto di isolarsi dal mondo esterno attenuando in questo modo le frustrazioni per le aspettative mancate.

Paola Torelli

Letture consigliate



"Salute!"
I consigli dei grandi medici

di Roberto Gervaso

Arnoldo Mondadori Editore

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Al.Ce. Alleanza Cefalalgici

CONCORSO LETTERARIO

Cefalee in cerca D'Autore

II Edizione

Questa iniziativa intende offrire al paziente cefalalgico l'opportunità di estrinsecare il proprio problema attraverso un momento di creatività. Di certo, questo non ci aiuterà a guarire, ma siamo convinti che, anche attraverso la cultura della cefalea, si possa far emergere una realtà spesso sottovalutata e che coinvolge, in modo più o meno grave, dieci milioni di italiani.
I concorrenti dovranno presentare racconti inediti sul tema "le cefalee". Il genere letterario (autobiografico, epistolare, d'avventura, realistico, giallo, rosa) potrà essere liberamente scelto dall'Autore.

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Verranno premiati, entro giugno 2002, i 6 racconti migliori (1 supervincitore e 5 vincitori ex aequo). E' prevista la pubblicazione delle opere su un numero speciale di Confinia Cephalalgica.

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"Dalla Letteratura Internazionale"

(a cura di A. Costa)

Le proteine Gi nelle cefalee primarie: mito o realtà?

Il coinvolgimento delle proteine Gi nella modulazione del dolore è un dato diffusamente noto, così come il loro ruolo nei meccanismi patogenetici di molte condizioni patologiche. Un recente studio italiano ha cercato di verificare se nelle forme di cefalea primaria (emicrania con aura e senza aura, cefalea a grappolo) possa manifestarsi una carenza o un alterato funzionamento di queste proteine. L'attività ed il grado di espressione delle proteine G sono stati misurati nei lifociti dei pazienti: è stata così osservata una ridotta capacità di inibire l'attività adenilciclasica indotta dalla forscolina. Inoltre, i pazienti con emicrania hanno evidenziato livelli basali di cAMP di ben quattro volte superiori a quelli dei soggetti di controllo. La ridotta attività delle proteine Gi non sembra essere legata ad una riduzione dei loro livelli, visto che non è stata osservata una diminuzione delle unità Gi-alfa. Questa alterazione può quindi rivestire un ruolo patogenetico nell'emicrania e nella cefalea a grappolo. Va tuttavia segnalato, vista la risonanza che questo studio ha avuto tra i pazienti affetti da cefalea, che l'applicazione di questi risultati alla pratica clinica, e quindi in primo luogo a fini terapeutici, non sembra essere immediata.

(N. Galeotti et al., Cephalalgia 2001; 21:38-45)

Cefalee Today

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Scopo della rivista

La rivista è interamente dedicata allo studio interdisciplinare delle sindromi cefalalgiche e dei disordini adattativi; essa pubblica contributi provenienti da cultori delle branche principali della medicina (medicina interna, neurologia, anestesiologia, etc…) che si interessano al problema del dolore cefalico. L'obiettivo del giornale è quello di costituire un forum in cui idee e competenze diverse possano confrontarsi, nella convinzione che un aperto dialogo fra esperti di differenti discipline possa contribuire in modo sostanziale all'avanzamento delle conoscenze. La rivista ha periodicità trimestrale e contiene articoli originali, casi clinici di interesse e casi impossibili (ovvero storie cliniche di casi rari, complessi o comunque difficili da diagnosticare), rassegne, editoriali, note terapeutiche e storiche, informazioni sui congressi, recensioni librarie.

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TABELLE - Le tabelle (in numero non eccedente la metà delle pagine di testo) devono avere un titolo conciso ed essere numerate con numeri romani. Ogni tabella deve essere scritta su un foglio separato. Tutte le abbreviazioni usate devono essere chiaramente definite.

FIGURE - I grafici ed i disegni devono essere di qualità professionale; le fotografie devono essere inviate su copia cartacea o diapositiva. Sia per i disegni che per le fotografie devono essere inviate tre copie di cui una in originale; le restanti due copie possono essere fotoriproduzioni. Le figure devono essere numerate con numeri arabi; sul retro delle illustrazioni vanno riportati a matita il relativo numero progressivo, il nome del primo Autore e l'indicazione del lato superiore. Le didascalie delle figure devono essere scritte in ordine progressivo su un foglio separato; tutte le abbreviazioni ed i simboli che compaiono nelle figure devono essere adeguatamente spiegati nelle didascalie. Le figure devono essere in numero non superiore alla metà delle pagine di testo.

BIBLIOGRAFIA - I riferimenti bibliografici devono devono essere segnalati nel testo tra parentesi e in numero (es: …"come recentemente riportato" (1) oppure (1,2)..). Le voci bibliografiche devono essere riportate alla fine dell'articolo e numerate consecutivamente nell'ordine in cui sono menzionate per la prima volta nel testo. Nella bibliografia vanno riportati:
1) tutti gli Autori eventualmente citati nel testo e nelle didascalie di tabelle/figure;
2) tutti gli Autori fino a un massimo di sei. Se sono in un numero superiore, riferire il nome dei primi tre seguiti dalla dicitura "et al.";
3) i titoli delle riviste abbreviati seguendo la convenzione in uso nell'Index Medicus (Medicine). I periodici non indicizzati da questo repertorio devono avere il titolo per esteso. Si invitano gli Autori ad attenersi ai seguenti esempi:
per riviste:
1) Anthony M, Hinterberger H, Lance JW. Plasma serotonin in migraine and stress. Arch Neurol 1967; 16:544-552.
Per libri:
2) Kudrow L. Cluster headache: mechanism and management. New York: Oxford University Press 1980; 1-18.
3) Barzizza F, Cresci R, Lorenzi A. Alterazioni ECGrafiche in pazienti con cefalea a grappolo. In: Richichi I. & Nappi G. eds. Cefalee di interesse cardiovascolare. Roma: Cluster Press 1989; 7:133-137.
Per abstract:
4) Caffarra P, Cammelli F, Scaglioni A et al. Emission tomography (SPECT) and dementia: a new approach. J Clin Exp Neuropsychol 1988; 3:313, abstract.