The pharmacology of headache

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Abstract

Headache is a common problem which besets most of us at some time or the other. The pharmacology of headache is complex in an overall sense but can be understood in terms of the anatomy and physiology of the pain-producing structures. Migraine can be used as a template to understand the activation of nociceptive systems in the head and thus their neurotransmitter mediation and modulation. In recent years, the role of serotonin (5-HT) in headache pharmacology has been unravelled in the context of both understanding its role in the nociceptive systems related to headache and by exploiting its 5-HT1 receptor subtypes in headache therapeutics. The pharmacology of the head pain systems, as they are known and as they might evolve, are explored in the context of both, the anatomy and physiology of trigeminovascular nociception and in the context of clinical questions, such as those of efficacy, headache recurrence and adverse events. © 2000 Published by Elsevier Science Ltd.

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Abbreviations: 5-HT, serotonin.
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1. Introduction

Headache is perhaps among the commonest afflictions of humans. Its classification runs to 96 pages (Headache Classification Committee of The International Headache Society, 1988) and the number of headache types keeps the most devoted, enthralled. However, the cranial nociceptive system for headache is relatively limited in terms of the structures that are involved so that understanding basic headache pharmacology is a reasonable goal. Headache is broadly divided into primary or idiopathic headache, and secondary or symptomatic headache. Symptomatic headaches rely upon entraining the nociceptive pathways that the primary headache syndromes also employ so that basic headache biology is best considered in terms of the primary headaches. The subject is dealt with more fully in the clinical sense in recent monographs (Lance and Goadsby, 1998; Silberstein et al., 1998) and reviews (Ferrari, 1998; Goadsby, 1998a, 1998b).

Broadly, primary headache can be understood in terms of the pain expression system, the trigeminovascular and cranial autonomic innervation, and pain processing and modulation systems. The pain expression is shared, and to some extent this is why there is so much phenotypic overlap in headache syndromes, yet the central mechanisms, at least those that are causative, hold the individual keys to the syndromes. This review will detail the pain expression systems generic-ally and then attempt to discuss the pain modulation systems (Table 1). Conveniently, this division includes the essential therapeutic options of acute attack and preventative management (Goadsby and Olesen, 1996).

Much of what has been studied has been specifically directed at migraine therapeutics which provides the best data and will be used as a template for understanding headache more broadly. Serotonin pharmacology will be outlined broadly first, this is in some ways historical, although it is impossible to adequately consider the current state of headache pharmacology without some consideration of the role of serotonin (5-HT).

2. Serotonin (5-HT) and headache

Suggestions for the involvement of serotonin in migraine date back to nearly 40 years and stem from certain seminal observations. The most convincing data demonstrated that:

- Urinary excretion of 5-hydroxyindoleacetic acid, the main metabolite of serotonin, was increased in association with migraine attacks (Curran et al., 1965; Sicuteri et al., 1961);
- Platelet 5-HT was found to drop rapidly during the onset of the migraine attack (Anthony et al., 1967);
- Intravenous injection of 5-HT aborts either reser-

Table 1
An anatomical and physiological approach to headache

<table>
<thead>
<tr>
<th>Pain expression systems (treating the acute attack)</th>
<th>Pain response or modulation systems (preventing headache)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranial vessels and dura mater</td>
<td>Frontal cortex</td>
</tr>
<tr>
<td>Trigeminal innervation</td>
<td>Insula cortex</td>
</tr>
<tr>
<td>peripheral terminals</td>
<td>Cingulate cortex</td>
</tr>
<tr>
<td>central terminals</td>
<td>Thalamus</td>
</tr>
<tr>
<td>Cranial parasympathetic innervation&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Disease specific regions</td>
</tr>
<tr>
<td></td>
<td>rostral brainstem&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>posterior hypothalamic grey matter&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Activated particularly in trigeminal-autonomic syndromes, such as, cluster headache and paroxysmal hemicrania (Goadsby and Lipton, 1997).

<sup>b</sup> Migraine.

<sup>c</sup> Cluster headache.
pine-induced or spontaneous headache (Kimball et al., 1960; Lance et al., 1967).

These data suggested since 5-HT drops during migraine and when infused relieves attacks, that a suitable serotonin receptor target might be identified to retain the anti-migraine effects without the unwanted effects of serotonin administration, such as, flushing, nausea, faintness, hyperpnoea and paraesthesiae.

The classification of the 5-HT receptors has received considerable attention in recent years driven in large measure by developments in molecular techniques and the therapeutic roles of specific drugs, such as, triptans (5-HT1B/1D) and 5-HT3 anti-emetics. The current classification (Hoyer et al., 1994) (Table 2) and the alignment of the nomenclature with the molecular data (Hartig et al., 1996) have provided a robust system (Table 3). This alignment of the 5HT-1 subclass nomenclature with the known molecular biology has eliminated some unnecessary complications. The 5HT1Dα, 5HT1Dβ and 5HT1B receptors have been reclassified as 5HT1D and 5HT1B, respectively (Table 3). The human and rat receptors, previously called 5HT1Dβ and 5HT1B, are now called h- or r- 5HT1B to indicated human or rat forms. The Triptans in clinical development or use, viz., sumatriptan, almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan and zolmitriptan, share the pharmacology of being 5HT1B/1D receptor agonists in this nomenclature.

Table 2

<table>
<thead>
<tr>
<th>5HT receptor class</th>
<th>Second messenger</th>
<th>Antagonist</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>↓ Adenylate cyclase</td>
<td>—</td>
<td>Subclasses A, B, D, E, F</td>
</tr>
<tr>
<td>2</td>
<td>↑ Phosphoinositide turnover</td>
<td>Methysergide, pizotifen</td>
<td>Contraction of smooth muscle, Central nervous system excitation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Subtypes: 2α, 2β, 2γ</td>
</tr>
<tr>
<td>3</td>
<td>K⁺, Ca²⁺, Na⁺</td>
<td>Ondansetron, Granisetron</td>
<td>Membrane depolarisation</td>
</tr>
<tr>
<td>4</td>
<td>↑ Adenylate cyclase</td>
<td>GR113808</td>
<td>GI smooth muscle relaxation, Found in striato-nigral system</td>
</tr>
<tr>
<td>5</td>
<td>—</td>
<td>—</td>
<td>Subclasses A and B</td>
</tr>
<tr>
<td>6</td>
<td>↑ Adenylate cyclase</td>
<td>Ro04-6790 (Bentley et al., 1999)</td>
<td>Found in limbic system, Atypical anti-psychotics bind</td>
</tr>
<tr>
<td>7</td>
<td>↑ Adenylate cyclase</td>
<td>SB 258719</td>
<td>Splice variants (Jasper et al., 1997), Vasodilator, Role in circadian rhythms</td>
</tr>
</tbody>
</table>

a Modified from Hoyer et al. (1994).

b GI, gastrointestinal.

2.1. Efficacy and 5-HT receptor activity

Although the Triptans have some variable 5HT1A, 1E or 1F agonist actions (Table 3), it would seem that the commonality of their action is at the 5HT1B/1D sites. It is noteworthy that despite this clear pharmacology and the known heritability of migraine (Honkasalo et al., 1995), each of the 5HT1B, 5HT1D (Marttila et al., 1999) and 5HT1F (vanDenBrink et al., 1998) sites have been excluded as being responsible for migraine and the 5HT1B site from predicting sumatriptan responses (Maassen vanDenBrink et al., 1998b). It may be of research interest that some of the compounds, such as, sumatriptan, almotriptan (Bou et al., 1997) and frovatriptan (SB209509 or VML-251) (Brown et al., 1996), have actions at the vasodilator 5HT7 receptor (Eglen et al., 1997), but at the doses used clinically this action seems largely irrelevant. Relative specificity of action distinguishes the Triptans from the ergots (Tfelt-Hansen et al., 2000) (Table 4). It has been suggested that the 5HT2 receptor may play a role in migraine prevention (Fozard and Gray, 1989; Kalkman, 1994).

2.2. Molecular action of the 5-HT1B/1D agonists

Activation of the 5-HT1 subclass of receptors leads to a reduction in intracellular c-AMP (Pauwels et al., 1997; Pauwels et al., 1998). Studying human 5-HT1B and 5-HT1D receptors in stably transfected C6 glioma cells, John and collaborators established that sumatrip-
Binding produced hyperpolarisation by an increased K⁺ current and this effect could be blocked by the 5-HT₁B/₁D antagonist GR127935 (Clitherow et al., 1994). Moreover, this increase in \( I_K \) could be prevented by a calcium chelator, an endoplasmic reticulum Ca-ATPase inhibitor, and an IP3 receptor blocker, respectively, indicating that the 5HT₁B/₁D current was calcium dependent, \( I_{K/Ca} \).

3. Pain expression in primary headache

Understanding the pharmacology of acute anti-migraine compounds is intimately linked to understanding the pain-producing innervation of the cranial circulation and the intracranial contents that is largely subserved by branches of the ophthalmic division of the trigeminal nerve (Penfield, 1932; Penfield and McNaughton, 1940). The effect of anti-migraine drugs upon the trigeminovascular system is the crucial link.

Table 3
Classification of serotonin (5-HT)-1 receptors*

<table>
<thead>
<tr>
<th>Subtype of 5HT₁ receptor</th>
<th>Agonist</th>
<th>Antagonist</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>8-OH-DPAT*</td>
<td>WAY100165b</td>
<td>Hypotension, Behavioural (satiety)</td>
</tr>
<tr>
<td></td>
<td>Dihydroergotamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sumatriptan</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Eletriptan</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Frovatriptan</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Naratriptan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rat B</td>
<td>CP-93,129b</td>
<td>Central autoreceptor (rat)</td>
<td></td>
</tr>
<tr>
<td>Human B</td>
<td>Dihydroergotamine</td>
<td>SB 216641</td>
<td>Craniovascular receptor</td>
</tr>
<tr>
<td>(Previously 1D₀)</td>
<td>All Triptans</td>
<td>GR127935b</td>
<td></td>
</tr>
<tr>
<td>D (previously 1D₃)</td>
<td>Dihydroergotamine</td>
<td>BRL 15572</td>
<td>Trigeminal neuronal receptor</td>
</tr>
<tr>
<td></td>
<td>All Triptans</td>
<td>GR127935b</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>–</td>
<td>–</td>
<td>?</td>
</tr>
<tr>
<td>F</td>
<td>Sumatriptan</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Eletriptan</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Frovatriptan</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Naratriptan</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Zolmitriptan</td>
<td>LY334370d</td>
<td>Trigeminal neuronal receptor</td>
</tr>
</tbody>
</table>

* Modified from Hartig and colleagues (1996) and assigning activity only for pKi's of 7.0 or greater, see Table 4.

b 8-OH-DPAT (8-hydroxy-2-(di-n-propylamino)tetralin), WAY100165, CP-93,129 and GR127935 are all compounds used in the laboratory for pharmacological purposes and have no current clinical indications.

c Triptans: sumatriptan, almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, zolmitriptan.
d Dose-dependent anti-migraine effect; development stopped for animal toxicity (Goldstein et al., 1999c; Phebus et al., 1997).

Table 4
Comparison of the pharmacology of dihydroergotamine and sumatriptan

<table>
<thead>
<tr>
<th>Serotonergic (5-HT)</th>
<th>Dihydroergotamine</th>
<th>Sumatriptan</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>++ +</td>
<td>+</td>
</tr>
<tr>
<td>1B</td>
<td>++ +</td>
<td>+ +</td>
</tr>
<tr>
<td>1D</td>
<td>++ +</td>
<td>++ +</td>
</tr>
<tr>
<td>1E</td>
<td>+ +</td>
<td>–</td>
</tr>
<tr>
<td>1F</td>
<td>+</td>
<td>+ +</td>
</tr>
<tr>
<td>2A,C</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Adrenergic</td>
<td>3/1a,b</td>
<td>++</td>
</tr>
<tr>
<td>3/2b,c</td>
<td>+ +</td>
<td>–</td>
</tr>
<tr>
<td>3/1,2,3</td>
<td>–/–/+</td>
<td>–</td>
</tr>
<tr>
<td>Dopaminergic</td>
<td>D₁,₂</td>
<td>–</td>
</tr>
<tr>
<td>D₂,₃,₄</td>
<td>++</td>
<td>–</td>
</tr>
</tbody>
</table>

a Based on direct comparative affinity data (Goadsby and Hargreaves, 2000).

Table 5
Current concepts of the pharmacology of acute anti-migraine drugs

<table>
<thead>
<tr>
<th>Target</th>
<th>Receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large cranial vessels</td>
<td>5-HT₁B</td>
</tr>
<tr>
<td>Peripheral terminal of the trigeminal nerve</td>
<td>5-HT₁D/₁F</td>
</tr>
<tr>
<td>Inhibits plasma protein extravasation</td>
<td>5-HT₁D/₁F</td>
</tr>
<tr>
<td>Blocks dural vasodilatation</td>
<td>5-HT₁D</td>
</tr>
<tr>
<td>Inhibits release of trigeminal neuropeptides</td>
<td>5-HT₁D</td>
</tr>
<tr>
<td>Trigeminal nucleus inhibition</td>
<td>5-HT₁B/₁D</td>
</tr>
<tr>
<td>5-HT₁F</td>
<td></td>
</tr>
</tbody>
</table>
in understanding the clinical effects of these drugs and has informed the whole range of headache problems (Table 5) (Goadsby, 1997a).

3.1. Cranial vessels and the dura mater

The role and pharmacology of the large intracranial vessels and dura mater in headache, and specifically in migraine, has been defined by the search for compounds that would mimic the effects of serotonin and ergotamine on the cranial circulation without systemic effects (Humphrey et al., 1990). The role of serotonin is discussed explicitly below. The development of sumatriptan was facilitated by the selective distribution of the ultimate target receptor in the carotid bed (Humphrey et al., 1991) and in the saphenous vein (Bax et al., 1992), which has now been confirmed anatomically using highly selective 5HT1B and 5HT1D receptor antibodies, to be almost exclusively of the 5HT1B sub-type (Longmore et al., 1997b; Nilsson et al., 1999a). Serotonin contracts large human carotid vessels in vivo (Lance et al., 1967) and has potent actions in the monkey cranial circulation (Spira et al., 1978). Sumatriptan, and its immediate predecessor AH25086B (Doenicke et al., 1987), is a potent constrictor of large cerebral vessels (Friberg et al., 1991; Perren et al., 1991) and pial vessels (Connor et al., 1992). It has, however, no effects on resting cerebral blood flow in experimental animals (Goadsby and Edvinsson, 1993; Humphrey et al., 1991) or in humans (Weiller et al., 1995).

The dog carotid vessel has been widely used to evaluate the cranial vasoconstrictor potency of the Triptans. The ED50 for carotid constriction in the dog in µg/kg for sumatriptan is 39 (Feniuk et al., 1989), while in comparison it is ~10 for almogtripran in the cat (Bou et al., 1997), 12 for eletriptan (Gupta et al., 1996), 19 for naratriptan (Connor et al., 1997), 30 for rizatriptan (Williamson et al., 1997c), 10 for zolmitriptan (Martin et al., 1997) and 0.38 for frovatriptan (SB209509, VML-251) (Parsons et al., 1996). On this basis, there is little to choose between the compounds in terms of cranial vasoconstrictor potency, save frovatriptan, which is much more potent, and this may confer some formulation advantages. However, these differences can largely be overcome by careful choice of clinical doses.

It has been suggested that an important aspect of the effect of 5HT1B/1D agonists is through an effect on arteriovenous shunts (Saxena, 1991). It is certainly well documented that this class of drugs closes such shunts (de Vries et al., 1997; Den Boer et al., 1992; Villalon et al., 1992), and it is primarily through this mechanism that cranial flow is redistributed after their administration. The extent to which this change contributes to the anti-migraine action is unclear, although certainly the AVA shunt model has been extremely useful in terms of dissecting the pharmacology surrounding the Triptans' development.

3.2. Peripheral terminals of the trigeminal nerve

The pathway from the pain-producing structures to the level of cortical processing has a peripheral (extra-axial) component and a central dimension. The peripheral element, the trigeminal innervation of pain-producing, mainly vascular, structures (the trigeminovascular system), has been studied in considerable detail in recent years. The inhibition of trigeminal afferents in the periphery may be monitored in three ways: first, an inhibition of neurogenic plasma protein extravasation, second, by monitoring vessels in situ, and third, inhibition of neuropeptide release.

3.2.1. Neurogenic Plasma Protein Extravasation (PPE)

Electrical stimulation of the trigeminal ganglion results in leakage of plasma proteins (Markowitz et al., 1987) from post-capillary venules (Dimtriadou et al., 1992). This plasma protein extravasation (PPE) results in a sterile inflammation in the dura mater that may explain some symptoms, particularly exacerbation of headache by movement (Burstein et al., 1998; Strassman et al., 1996). PPE can be blocked by an array of agents including aspirin (Buzzi et al., 1989), indomethacin (Buzzi et al., 1989; Buzzi and Moskowitz, 1990), sumatriptan (Buzzi and Moskowitz, 1990), valproate (Lee et al., 1995) and neurosteroids (Limmeroth et al., 1996). This effect is mediated by the 5HT1B receptor in mice, since in genetically altered mice with no 5HT1B receptors sumatriptan is ineffective in blocking PPE (Yu et al., 1996).

With respect to the Triptans, the ED50 in µg/kg for inhibition of PPE in the rat is 4 for sumatriptan (Buzzi and Moskowitz, 1990), 200 for almogtripran (Bou et al., 1997), 100 for eletriptan (Gupta et al., 1996), which was a dose for inhibition rather than an ED50, 4 for naratriptan (Connor et al., 1997), 30 for rizatriptan (Williamson et al., 1997c), 10 for zolmitriptan (Martin et al., 1997), and is unknown for frovatriptan (SB209509, VML-251). There is a range of potency that does not directly predict clinical efficacy and other issues which are addressed below.

3.2.2. Intravital durally-evoked vasodilatation

Activation of dural afferents can produce two responses, plasma extravasation and dural vasomotor change. The latter has been specifically examined as an attempt to study pre-junctional trigeminal terminals. Briefly, the model involves local electrical stimulation of the dura mater through a thin bone window. Vessels, branches of the middle meningeal artery, are
observed with a video microscopy-image measurement device to dynamically record vessel calibre. Measurements of calibre can thus be made continuously, as the dural nerves are activated, and various substances administered. It has been shown that sumatriptan and rizatriptan, both potent 5-HT\textsubscript{1B,1D} agonists (Goadsby, 1998a) and effective acute anti-migraine compounds (Ferrari and The Subcutaneous Sumatriptan International Study Group, Ferrari, 1991; Tfelt-Hansen et al., 1998), are inhibitors of neurogenic dural vasodilatation (Williamson et al., 1997b, 1997c).

Moreover, in the same setting neurokinin-1, substance P, mechanisms do not play a role in vasodilatation, rather, calcitonin gene-related peptide (CGRP) is the main vasodilator transmitter (Williamson et al., 1997a). By studying both trigeminal neurons and using intravital microscopy together, it has been shown that CGRP-induced vasodilatation can lead to activation of trigeminal neurons (Cumberbatch et al., 1999), offering some insight into possible mechanisms of sensitisation of dural nociceptors during migraine.

3.2.3. Inhibition of neuropeptide release

Trigeminovascular activation is marked by release of neuropeptides (Edvinsson and Goadsby, 1998). The cranial circulation is innervated by three extrinsic (to the brain) systems which are: the sympathetic, parasympathetic and trigeminal systems. The sympathetic nerves are vasoconstrictor, arise from the superior cervical ganglion, and are marked by neuropeptide Y (Goadsby and Sercombe, 1996). The parasympathetic system is vasodilator, arises from the pterygopalatine (sphenopalatine), optic and internal carotid miniganglia, and is marked by vasoactive intestinal polypeptide (VIP) and other substances (Goadsby and Edvinsson, 1997). The trigeminal vascular system is both sensory and vasodilator, arises from the trigeminal ganglion, and is marked by substance P (SP), calcitonin gene-related peptide (CGRP) and neurokinin A (NKA). The distribution of the neuropeptides is summarised in Table 6.

<table>
<thead>
<tr>
<th>Table 6 Extrinsic innervation of the cerebral circulation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ganglia</strong></td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td><strong>Sympathetic</strong></td>
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<tr>
<td><strong>Parasympathetic</strong></td>
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<tr>
<td><strong>Trigeminal</strong></td>
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</table>

\textsuperscript{a} Vasoactive intestinal polypeptide.  
\textsuperscript{b} Internal carotid.  
\textsuperscript{c} Peptide histidine isoleucine (methionine).  
\textsuperscript{d} Pituitary adenylate cyclase activating polypeptide.  
\textsuperscript{e} Calcitonin gene-related peptide.

3.2.3.1. Calcitonin gene-related peptide. Stimulation of the trigeminal ganglion in cats and humans results in the release of both SP and CGRP (Goadsby et al., 1988). This effect is blocked by dihydroergotamine, sumatriptan (Goadsby and Edvinsson, 1993), avitriptan (Knight et al., 1997) and zolmitriptan (Goadsby and Edvinsson, 1994b) but not by CP122,288 (Gupta et al., 1995), a conformationally restricted analogue of sumatriptan (Knight et al., 1997), or 4991w93 (Giles et al., 1999), a conformationally restricted analogue of zolmitriptan (Knight et al., 1999). In this setting, CGRP release seems a good predictor of clinical outcome possibly because it reflects trigeminal activity directly. Stimulation of the superior sagittal sinus results in release of CGRP in the rat, which is attenuated by sumatriptan (Buzzi et al., 1991) and CGRP and VIP in the cat (Zagami et al., 1990). In humans during migraine, CGRP is released instead of SP (Gal-
3.2.3.2. Substance P. In humans, thermocoagulation (Onofrio, 1975; Sweet and Wepsic, 1974) or injection of alcohol (Oka, 1950) into the trigeminal ganglion (VG) is accompanied by flushing of the skin in the distribution of the appropriate division or divisions of the nerve. Consistent with this flush, increases in skin temperature and capillary pulsation have been observed after thermocoagulation of the VG in humans for tic douloureux (Drummond et al., 1983). Cutaneous flushing and pain can be associated with local release of calcitonin gene-related peptide (CGRP) in patients with facial pain (Goadsby et al., 1992). Stimulation of the trigeminal ganglion in humans causes release of substance P, and calcitonin gene-related peptide levels are increased in the ipsilateral external jugular vein if the patient flushes (Goadsby et al., 1988). However, as observed above, substance P is not released in any detectable level in acute migraine (Goadsby et al., 1990). These clinical observations are consistent with the lack of effect of substance P, neurokinin-1 antagonists in acute migraine (Connor et al., 1998; Diener, 1996; Goldstein et al., 1997; Norman et al., 1998) and in its preventative management (Goldstein et al., 1999b).

Thus, neuropeptide release is a robust method of detecting trigeminovascular activation in vivo, which can be applied to humans. The finding of VIP release implicates activity of parasympathetic nerves which supports our basic observation of the presence of a functional trigeminal-autonomic loop (Goadsby and Duckworth, 1987) within the brain stem. Such a loop would explain the very marked autonomic symptomatology that accompanies certain primary headaches, such as, cluster headache and paroxysmal hemiercianias (Goadsby and Lipton, 1997) and is certainly seen in some patients with migraine (Goadsby et al., 1990).

3.3. The trigeminal nucleus

Electrical (Kaube et al., 1993b) or mechanical (Hoskin et al., 1996b; Kaube et al., 1992) stimulation of the sagittal sinus or dural vessels (Davis and Dostrovsky, 1986) in the cat; and electrical stimulation of the sinus (Goadsby and Hoskin, 1997), or middle meningeal artery in the monkey (Hoskin et al., 1999) or cat (Davis and Dostrovsky, 1988; Hoskin et al., 1999) results in the activation of a group of cells in the trigeminal nucleus caudalis and the superficial laminae of the dorsal horn of the C1 and C2 spinal cord, the trigeminocervical complex. It has also been shown that metabolic activity arising from stimulation of a clearly ophthalmic nerve (trigeminal) innervated structure, superior sagittal sinus (Goadsby and Zagami, 1991), and the greater occipital nerve, a branch of C2 (Goadsby et al., 1997), has a considerable degree of overlap in the trigeminocervical complex. This overlap explains the clinical fact that primary headache often ignores peripheral cutaneous innervation patterns. These neurons then form a target for headache pharmacology.

3.3.1. Serotonin pharmacology

The trigeminocervical complex has receptors that bind \[^3H\]-dihydroergotamine (Goadsby and Gundlach, 1991). Specific binding of \[^3H\]-sumatriptan in cat (Mills and Martin, 1995), guinea pig (Waeber and Moskowitz, 1995) and humans (Pascual et al., 1996) and of \[^3H\]-zolmitriptan in the cat (Goadsby and Knight, 1997) has been demonstrated in the trigeminocervical complex and provides a locus of action for 5HT\_1B/1D agonists. These cells can be inhibited by anti-migraine drugs, such as, dihydroergotamine (Hoskin et al., 1996a), eletriptan (Goadsby and Hoskin, 1999), naratriptan (Cumberbatch et al., 1998a; Knight and Goadsby, 1997), rizatriptan (Cumberbatch et al., 1997) and zolmitriptan (Goadsby and Hoskin, 1996). Sumatriptan does not inhibit the activity of these cells unless the blood–brain barrier is disrupted (Kaube et al., 1993a; Shepheard et al., 1995), an observation broadly consistent with the lack of efficacy of subcutaneous sumatriptan given during the migraine aura (Bates et al., 1994). Given the long-standing interest in serotonin in migraine (as discussed above), it is of some importance that intravenous 5-HT can block trigeminal cell firing, just as those compounds synthesised to mimic its actions, at doses comparable with those used in humans (Goadsby and Hoskin, 1998).

For both, serotonin (Goadsby and Hoskin, 1998) and the 5HT\_1B/1D agonist naratriptan (Knight and Goadsby, 1997), the inhibition of trigeminal activity is blocked by the specific 5-HT\_1B/1D antagonist GR127935 (Clitheroe et al., 1994). Data concerning the effect of 5-HT\_1A agonists suggests that they play no role in inhibiting trigeminocervical transmission (Cumberbatch et al., 1998b).

Considering that all these physiological studies have employed intravenous administration of compounds, it has been essential to question whether the effect of 5HT\_1B/1D agonists may be at some other site than the trigeminocervical complex. Microiontophoretic application of 5HT\_1B/1D agonists, sumatriptan and zolmitriptan, as well as an ergot derivative on clearly defined trigeminovascular nociceptive neurones results in reversible inhibition of firing (Storer and Goadsby, 1997). Using this method, no non-5-HT\_1B/1D agonist activity of the PPE inhibitor 4991w93 (Earl et al.,
1999) could be detected in the trigeminal nucleus (Storer et al., 1999). In humans, zolmitriptan can inhibit the auditory evoked potential (Proletti-Cecchini et al., 1997), which has a degree of serotonergic influence (Wang et al., 1996). There seems little doubt that the more lipophilic brain penetrant Triptans can effect CNS structures, and the trigeminocervical complex is an ideal target for drug action currently proven for the 5HT1B/1D receptor class agonists.

3.3.2. Other receptor systems

The trigeminal nucleus has a rich pharmacology which has begun to be explored. Glutamate is a major source of excitatory transmission within the central nervous system (Seeburg, 1993). N-Methyl-D-aspartate (NMDA), \(\alpha\)-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid (AMPA), kainate and metabotropic glutamate receptors have been identified in the superficial laminae of the trigeminal nucleus caudalis of the rat (Greene-Tallaksen et al., 1993). Furthermore, the pioneering studies of Hill and Salt (Hill and Salt, 1982; Salt and Hill, 1982) showed that iontophoretically applied L-glutamate excited neurons in the trigeminal nucleus caudalis. It has been shown that NMDA and AMPA antagonists can inhibit trigeminal firing (Storer and Goadsby, 1999), Fos expression (Classey et al., 1999) and local spinal cord blood flow (Goadsby and Classey, 1999) due to stimulation of the superior sagittal sinus in the cat. Similarly, Fos expression in the trigeminal nucleus after administration of capsaicin can again be inhibited by NMDA (Mitsikostas et al., 1998) or AMPA blockade (Mitsikostas et al., 1999b). Glutamate receptor blockade (Nicolodi and Sicuteri, 1996) or NMDA receptor modulation, such as glycine site modulation (Carignani et al., 1998; Marret et al., 1999; Miyazaki et al., 1999; Nankai et al., 1998), form an obvious target for acute intervention if adverse event can be contained.

4. Specific pharmacological targets in primary headache

The success of the triptan development programmes have led to demands for further innovative therapies. This is driven by two issues, first, not all patients respond to triptans for reasons far from clear (Visser et al., 1996a), and second, perceived cardiovascular risks (Ottervanger et al., 1997b) have encouraged development of non-vascular acute anti-migraine drugs. The issue of cardiovascular safety is moot and is addressed explicitly below.

4.1. Inhibitors of neurogenic plasma protein extravasation

It was shown very clearly in the rat that sumatriptan blocked neurogenic plasma protein extravasation (PPE) by a prejunctional mechanism since it did not prevent PPE induced by the exogenous substance P (Buzzi and Moskowitz, 1990). This observation and general thinking on the mechanism of action of sumatriptan (Humphrey and Goadsby, 1994) lead to the pursuit of purely neural means of blocking PPE. One such molecule CP122,288, a conformationally restricted sumatriptan analogue, was 1000 times more potent than sumatriptan in blocking PPE and therefore active at doses without vascular effects (Gupta et al., 1995; Lee and Moskowitz, 1993). This compound was studied in a double-blind placebo-controlled study and was ineffective in acute migraine (Roon et al., 1997). A second specific PPE inhibitor, 4991w93, a conformationally restricted analogue of zolmitriptan, which is also a highly potent blocker at doses without vascular effects (Giles et al., 1999), is also clinically inactive in acute migraine (Earl et al., 1999).

Similarly, both bosentan, an endothelin antagonist (Brandli et al., 1996), and substance P, neurokinin-1 (Lee et al., 1994), antagonists are highly effective anti-PPE agents but are also ineffective in acute migraine studies (Goldstein et al., 1997; May et al., 1996). Neither substance P antagonists nor CP122,288 are effective at the central trigeminal synapse described above (Goadsby and Hoskin, 1999; Goadsby et al., 1998). In a study examining retinal extravasation which can be measured in rat retina and blocked by sumatriptan, no extravasation was seen in human retina during acute migraine or cluster headache (May et al., 1998). This human study has important implications. PPE involves at least albumin extravasation since \(^{125}\text{I}-\text{albumin}\) is used for its detection, and PPE is seen in the retina of the rat behaving just as it does in the dura mater. Similarly, fluorescein is bound to albumin and thus leakage on fluorescein angiography would be expected if the human retina had the same pathophysiological processes during migraine and cluster headache, as are seen in the rat when the trigeminal ganglion is stimulated. No changes are seen on fluorescein angiography so that certainly the processes are different and the difference requires explanation.

4.2. 5HT1F receptor agonists

It has been suggested that the 5HT1F receptor (Adham et al., 1993) may be a possible target for an anti-migraine drug (Bancheck and Archa, 1997). The potent specific 5HT1F agonist LY334,370 has been developed (Phebus et al., 1997) and shown to block PPE (Johnson et al., 1997), consistent with early molecular studies (Wainscott et al., 1998). Activation of 5-HT1F receptors does not seem to have vascular effects (Cohen and Schenck, 1999; Razzouque et al., 1999).

LY334,370 has recently been reported to be effective...
in acute migraine, albeit at doses with some central nervous system side effects (Goldstein et al., 1999c). No cardiovascular problems were seen in these studies (Goldstein et al., 1999a), but unfortunately, development has stopped because of a toxicity problem in the dog. Although these studies are of enormous interest, they do not contribute to the PPE issue since there are 5HT1F receptors in the trigeminal nucleus (Castro et al., 1997; Fugelli et al., 1997; Pascaul et al., 1996; Waebcr and Moskowitz, 1995) and trigeminal ganglion (Bouchelet et al., 1996). Moreover, 5-HT1F agonism is inhibitory in the trigeminal nucleus in rat (Mitsikostas et al., 1999a). Anti-migraine drugs not potent at the 5HT1F receptor, such as rizatriptan, are effective anti-PPE agents (Williamson et al., 1997c) and are clinically effective. Yet, it must be borne in mind that sumatriptan and a number of other Triptans, notably eletriptan, naratriptan and zolmitriptan, are also agonists at the 5HT1F site, while almiditan, which is certainly active in migraine (Goldstein et al., 1996) and PPE (Limmoth et al., 1997), but is no longer being clinically developed, is relatively inactive at the 5HT1F receptor (Leyesen et al., 1996). On pre-clinical grounds, the 5-HT1F receptor seems to represent a second target which does not displace what can be concluded about the 5HT1B/1D receptors but provides another useful treatment option.

4.3. 5HT1D receptor

Similar to the 5HT1F agonists, 5HT1D agonists were shown to be potent inhibitors of PPE (Waebcr et al., 1997) and to have no vascular effects. Specific potent 5HT1D agonists have been developed by taking advantage of similarities between human and non-human primate 5HT1B and 5HT1D receptors (Pregenzer et al., 1997). One compound has gone forward into clinical studies, PNU 142633, and was ineffective (McCall, personal communication), although it was a relatively weak agonist when compared to sumatriptan in in vitro studies (Pregenzer et al., 1999). This compound was developed in gorilla receptors and it must, therefore, be asked as to whether this was the correct compound to test the 5-HT1D hypothesis. It is perhaps more remarkable that there were no complaints of adverse events of a cardiovascular nature in the placebo group, with cardiovascular adverse events, including chest pain, in the PNU 142633, treated group. It would be very important to show conclusively that some part of triptan chest symptoms are non-vascular, as these data suggest. A further study with a more potent agonist would clarify this situation enormously.

5. Specific issues in headache pharmacology

5.1. What makes an acute attack drug better?

It seems almost provocative to ask the question as it begs an answer that some drugs work better than others. While there are now a number of direct comparisons between the triptans and differences emerge (Bomhof et al., 1999; Diener et al., 1999; Goldstein et al., 1998b; Tfelt-Hansen et al., 1998), it is possible to understand properties of individual drugs that can answer this question. A comparison of the response rates of sumatriptan for subcutaneous, intranasal and oral formulations, as they have been summarised (Dahlof, 1999; Tfelt-Hansen, 1998), demonstrates that the tablets work less effectively than the nasal spray which is in turn less effective than the injection. Given that the drug is the same with identical receptor affinity and physico-chemical properties, the difference can be only a few. Given time, the area-under-the-curve can be comparable but what is never the same is the T_{max}, the time to reach maximal plasma concentration. Similarly, comparing efficacy rates for naratriptan by oral administration (Goadsby, 1997b; Gunasekara and Wiseman, 1997; Klassen et al., 1997; Mathew et al., 1997) and injection (Dahlof et al., 1998b), there is stark difference between the oral response rates and the much superior injectable response rate; and the difference between the T_{max} is greater for naratriptan. This principle extends to even non-specific therapies, such as aspirin, where again the intravenous formulation (Diener and ASASUMAMIG Study Group, Diener, 1999) with its very rapid T_{max} seems to be superior to oral aspirin (Tfelt-Hansen et al., 1995) in the treatment of acute migraine.

5.2. Headache recurrence

Headache recurrence is the phenomenon of an acute migraine treatment improving, probably strictly abolishing pain and then the pain worsening significantly within 24 h of that improvement. Not all recurrence data have been collected in the same way but the overall concept is of getting distinctly better and then worse. This author takes the view that recurrence might be simpler to study if it necessarily implied headache resolution, and the adoption of the headache free endpoint, as currently suggested by the International Headache Society Clinical Trials Committee (International Headache Society Committee on Clinical Trials in Migraine, 1991), would make the process being examined more homogenous and perhaps easier to study. However, to be practical if patients say that their headache gets better and then gets worse, whatever they mean, they may well be describing recurrence, and the gap between understanding and
characterising recurrence is probably broader than we currently imagine. The mild to moderate transition remains a problem when it comes to understanding the nature of headache recurrence. As it stands, headache recurrence can be seen with all acute attack medications that have been studied properly. It is not a *Triptan* only phenomenon but was recognised as sumatriptan ushered in a new era of controlled clinical trials in migraine. What is its pharmacology?

Sumatriptan has a short half life of 2 h (Fowler et al., 1991) which has been considered responsible for headache recurrence. Recurrence rates for sumatriptan across studies are between 30 and 40% (Visser et al., 1996c, 1996g). Similar rates are seen with rizatriptan (Gijisman et al., 1997; Goldstein et al., 1998b; Teall et al., 1998; Tfelt-Hansen et al., 1998; Visser et al., 1996c, 1996f) and zolmitriptan (Dahlof et al., 1998a; Rapoport et al., 1997; Solomon et al., 1997; Visser et al., 1996d). Naratriptan had a consistently low rate of recurrence across the clinical studies (Goadsby, 1997b), and a significantly lower rate of recurrence when tested against sumatriptan in a double-blind crossover study in a group of patients in whom recurrence was common (Gobel et al., 1997). These data fit the $t_{1/2}$ hypothesis but not all data do.

Frovatriptan (SB209509, VML-251) has as its major reported advantage lower headache recurrence ranging from 8 to 10%, however, in the same study, placebo recurrence was 18% (Goldstein et al., 1998a; Ryan and Keywood, 1997) and thus half what is seen in most large clinical studies. Frovatriptan (SB209509, VML-251) has the longest half life of any of the *Triptans*, in development or use, at 25 h but the recurrence data are unconvincing against placebo and cannot be sustained without a sumatriptan comparative arm. Alniditan had a similar initial highly promising low recurrence rate in its phase II development programme (Goldstein et al., 1996), along with a much longer half life (Goldstein et al., 1996), but has been abandoned because this advantage was not sustained in phase III. Given these results the drug $t_{1/2}$ life hypothesis cannot be sustained.

5.2.1. Ergotamine — back to the future for an answer

Dihydroergotamine (DHE) has a long elimination half life but a short redistribution that sees its plasma level drop 50% within 2 h. It is absolutely clear from the studies of both the nasal and injectable forms of DHE that it has a lower recurrence rate than sumatriptan (Massiou, 1996; Touchon et al., 1996; Winner et al., 1996). Martin et al. (1995) speculated on the basis of experimental work and theoretical considerations that the low recurrence rate of dihydroergotamine may be related to a slow dissociation from the receptor or from its local environment. Yokca et al. (1997) in studying the pre-clinical effects of BMS181885 have shown that the compound has a long duration of action in vivo constricting vessels and a $K_{off}$ that is 50 times slower than dihydroergotamine and 70 times slower than sumatriptan, yet its rate of headache recurrence is identical to sumatriptan in clinical studies.

A plausible explanation for dihydroergotamine or indeed for naratriptan would be that the combination of the pharmacology and their actions at central receptors might contribute to a reduction of headache recurrence by influencing central brain stem areas (Goadsby et al., 1991), which are within the regions active in migraine (Weiller et al., 1995) on PET studies. This view is supported by the outcome across the eletriptan trials with a high early efficacy and relatively less recurrence than sumatriptan in a more lipophilic drug (Pitman, 1999). A reasonable hypothesis might be that recurrence is due to an ongoing central nervous system process which re-activates and thus, the crucial combination in a *Triptan* will be of appropriate pharmacology and good brain penetration.

5.3. P-glycoprotein pump substrates — evidence for central action of triptans

The dose of 80 mg required to obtain clinical effects with eletriptan superior to sumatriptan (Goadsby et al., 2000) seems high given that eletriptan has better bioavailability at 50% (Morgan et al., 1997) compared to that of sumatriptan at 14% (Fowler et al., 1991), and sumatriptan has pK\textsubscript{i}'s at the 5HT\textsubscript{1B} and 5HT\textsubscript{1D} receptors of 7.9 and 7.9, respectively, compared to 8.0 and 8.9, respectively, for eletriptan. Given the superior bioavailability and comparable receptor affinity, the dose might suggest perhaps another receptor or site is involved. However, eletriptan is the most lipophilic of the triptans, either during the development or after its completion (Rance et al., 1997), and as it happens, is a substrate for P-glycoprotein (Pgp) (Hargreaves, personal communication), a membrane glycoprotein that is an ATP-dependent active efflux pump which leads to lower intracellular accumulation of its substrates (Gottesman and Pastan, 1993). Pgp is localised in the luminal membrane of the brain capillary endothelium, and contributes to the function of the blood–brain barrier (Cordon-Cardo et al., 1989; Tatsuta et al., 1992). The gene that codes for Pgp in humans is called *MDR1* and in rodents *mdr1a* and *mdr1b* (Gros et al., 1986). Knock-out mice have been developed that are *mdr1a* (+/−) (Schinkel et al., 1994). Since eletriptan is a Pgp substrate, higher doses are required than would be predicted from bioavailability or affinity data and, moreover, suggest that a crucial aspect of its action must be within the central nervous system.
5.4. Side effects and the coronary issue

The preferential action of triptans, 5HT_{1B/1D} agonists, in the cranial circulation is a direct consequence of their potency and the relative lack of 5HT_{1B/1D} receptors in other vascular beds, particularly the coronary circulation (Longmore et al., 1997a; Maassen vanDenBrink et al., 1998a; Nilsson et al., 1999b). It may be of interest that some of the compounds, such as, sumatriptan, almotriptan (Bou et al., 1997) and frovatriptan (SB209509 or VML-251)(Brown et al., 1996), have actions at the vasodilator 5HT_{7} receptor (Eglen et al., 1997) but are unlikely to be of practical importance at the doses used in clinical studies. There has been considerable discussion of the cardiovascular risks associated with triptan use (Ottervanger et al., 1998, 1997a, 1997b; Visser et al., 1996b) and yet we are no closer to understanding the basis of the symptoms. It has been suggested that some of the chest pain may be oesophageal in origin (Foster et al., 1999; Houghton et al., 1994) and the results of the 5HT_{1D} agonist study (see above) certainly suggest that the question needs re-thinking. However, it seems beyond doubt that there are 5HT_{1B} receptors on human coronary arteries and that all triptans are 5HT_{1B} agonists such that all have the potential to do harm and the sensible contraindications for the use of sumatriptan, uncontrolled hypertension, myocardial infarction, stroke and ischemic heart disease, must apply to the whole triptan class.

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