The specific cause of common forms of migraine headache is unknown but studies on families suffering from familial hemiplegic migraine (FHM) have suggested that genetic factors may be involved.\(^1,2\) In FHM, a rare subtype of migraine with aura, missense mutations in a neuronal specific P/Q calcium channel gene that give rise to amino acid substitutions in the pore-forming and voltage sensor regions of the alpha 1a subunit of the channel have been identified. It was hypothesized that these changes may provide the basis for channel and consequent brain dysfunction in FHM sufferers. Recent studies from Hans and colleagues\(^3\) have shown that these mutations produce a constellation of changes in channel expression and kinetics that result both in a net gain and a net loss of function. FHM is

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thought to be a genetically simple (autosomal dominant) disorder, whereas the more common migraine variants are likely to be genetically complex (multifactorial polygenic) with a substantial influence from ‘environmental factors’ that increase genetic penetrance to produce the observed phenotype. The study of FHM has nonetheless given a framework for the study of other migraine disorders (see review by Kathy Gardner, this supplement). There is, however, no doubt that deciphering the genetic basis of common migraine with and without auras is going to be a monumental task.

It has been suggested that it is theoretically possible for all individuals to suffer a migraine attack. The occurrence and frequency of attacks in any individual will be governed by the sensitivity of their CNS to migraine specific triggers (e.g. certain foods, hormones, changes in levels of stress, consciousness and even exposure to light and sound). It has been hypothesized that genetic abnormalities result in a lowered threshold of response to these specific trigger factors in migraineurs. The trigger factors can thus be conceptualized as modulators of the genetic set point that predisposes to migraine. Conversely, in normal individuals, who lack genetic deficits relevant to migraine, exposure to the same trigger factors would not breach the ‘migraine threshold’ and so an attack would not be initiated. It is possible that the abnormal hyporesponsivity of the brain of migraineurs, like FHM, may be a consequence of genetic abnormalities in ion channels that regulate neuronal excitability. This has given rise to the description of migraine as a channelopathy.4

The theory suggests that, as a result of this channelopathy, migraine specific triggers can provoke marked CNS dysfunction that can characterize and initiate the early stages of a migraine attack. In this respect, the presence of blood flow changes, both oligemia and hyperaemia, have been taken to indicate of altered CNS activation and have supported a role for spreading depression, or indeed activation, in migraine (particularly with altered CNS activation and have supported a role for spreading depression, or indeed activation, in migraine).10 These nuclei are selectively activated in the brain stem of migraine patients (raphe nuclei, locus coeruleus, periaqueductal grey) to be involved in signal integration within pathways that modulate craniovascular status and that provide endogenous pain control. Such an activation of the trigeminal sensory nerves that then relay pain signals to the brain.

TRIGEMINOVASCULAR PATHOPHYSIOLOGY OF HEADACHE PAIN

Although the central processes involved in the initiation of a migraine attack are relatively poorly understood, considerably more is known about the factors involved in the pathophysiology of migraine headache pain. The brain has a sparse sensory innervation and, like other viscera, it is the capsule structures (meninges) that are the most significant pain producing intracranial tissues.21,22,23 Primarily the ophthalmic division of the trigeminal nerve (V cranial nerve) innervates the meninges. The trigeminal nerves arise from pseudo-unipolar neurones in the trigeminal ganglia and project to the intracranial extracerebral blood vessels in the meninges (peripheral terminals) and behind the blood brain barrier into the trigeminal nuclei in the brain stem and upper cervical spinal cord (central terminals). These fibres therefore provide a pathway for pain signal transmission from meningeal blood vessels into the brain where headache pain is registered. This system has been described collectively as the ‘trigeminovascular’ system.

Our understanding of the pathophysiological mechanisms involved in migraine pain has been enhanced by increased knowledge of the serotonin receptor distribution within the trigeminovascular system and their functional pharmacology. This has been driven by the introduction of highly effective acute anti-migraine drug therapies and in particular, the selective serotonin receptor agonists that have become collectively known as the triptans. The 5-HT1B/D, 5-HT1F and 5-HT1E agonists currently available for clinical use are sumatriptan (Imitrex®), rizatriptan (Maxalt®) naratriptan (Amerge®) and zolmitriptan (Zomig®) with eletriptan a fifth entrant currently in the late stages of the regulatory approval process.
MIGRAINE TREATMENT STRATEGIES

There are several possible anti-migraine approaches that could be followed based on the scheme for migraine pathophysiology that has been proposed above.

For example, migraine prophylactic agents could inhibit the central processes involved in the initiation of a migraine attack or prevent meningeal vasodilatation and so stop the occurrence of migraine pain. Indeed, it has been speculated that the key mode of action of sodium valproate is to enhance activity within central inhibitory pathways by promoting the release of the neurotransmitter GABA through a blocking action at terminal ion channels. Calcium channel antagonists such as verapamil and flunarizine reduce neuronal activation directly by blocking voltage gated calcium channels. The serotonin antagonist antimigraine agents (e.g. pizotifen, methysergide) have been suggested to block the initial meningeal vasodilator step in the migraine pathogenesis pathway through blocking 5-HT<sub>1B</sub> receptors that have been proposed to mediate a nitric oxide dependent vasodilatation. Indeed, there have been strong arguments for a pivotal role for nitric oxide (NO) in mediating the vasodilator and inflammatory effects of vasoactive neuropeptides and in the sensitization of perivascular sensory nerves. In support of this hypothesis, it has been observed that migraineurs are supersensitive to NO-donors such as glyceryl trinitrate and there is preliminary evidence that NO-synthase inhibitors may be effective anti-migraine agents.

The mode of action of the adrenergic β-blockers (propranolol, metoprolol, nadolol) and brain penetrant serotonin antagonists is also likely to be central by inhibition of the monoaminergic nuclei (raphe nuclei (5-HT) and locus coeruleus (NE)) that become activated at the onset of an attack, thereby preventing disturbances in vascular control systems. Older agents such as amitriptyline also work centrally but it is difficult to discern the critical mechanism involved in their actions because of their rich receptor and ion channel pharmacology. It is clear, however, that all these prophylactic strategies are of little value once a migraine attack has progressed to the point at which the trigeminovascular system has become activated. At this time then, a different therapeutic approach is needed to reverse migraine headache pain.

KEY STEPS IN MIGRAINE HEADACHE PAIN

Current theories suggest that after an initial CNS dysfunction, there are three key processes in the generation of migraine headache pain. These mechanisms have been carefully studied in the clinic and with experimental models. The first key process is thought to involve meningeal blood vessel dilation. As the arteries swell, they activate perivascular sensory trigeminal nerves causing pain impulses to be transmitted to the caudal brain stem nuclei. Activation of these nerve terminals triggers the second key process in migraine – a release of vasoactive neuropeptides. These substances worsen and perpetuate vasodilatation, setting up a vicious cycle that increases meningeal blood vessel diameter further, thereby increasing nerve activation and intensifying headache pain. The most notable of these peptides is substance P, neurokinin A and calcitonin gene-related peptide (CGRP). Substance P primarily increases blood vessel permeability (with transient dilation), neurokinin A has longer lasting effects on permeability and blood vessel calibre whereas CGRP produces a profound and long lasting vasodilatation but has no effects on blood vessel permeability. Indeed, the vasodilator effects of CGRP potentiate the permeability effects of the neurokinins. Their effects are mediated primarily by endothelial neurokinin 1 (NK<sub>1</sub>) receptors and nitric oxide release (substance P) and by actions directly on vascular smooth muscle (CGRP). The third key event involves the relay of pain impulses from the activated peripheral sensory nerves to second order sensory neurones within trigeminal nuclei in the caudal brain stem and upper cervical spinal cord (trigeminocervical complex). It has been hypothesized that these central sensory neurones may become sensitized during migraine. This sensitization may be responsible for the intensification of headache pain as an attack progresses and for an increased sensitivity to convergent sensory stimuli from extracranial tissues. The trigeminal sensitization process may underlie the facial sensory disturbances that are sometimes associated with migraine and perhaps also underpins its transformation in some individuals to a more chronic condition. The trigeminal nuclei are then responsible for relaying incoming pain signals to higher cortical centres where migraine pain is registered. Symptoms commonly associated with a migraine attack such as nausea, photophobia and phonophobia are produced when other associated central nuclei and pathways are activated.

An ideal acute anti-migraine therapy would target these three key processes occurring in the trigeminovascular system that give rise to headache pain. It is noteworthy that acute antimigraine agents that target the trigeminovascular system have little or no therapeutic value as prophylactics since this system is not in play until headache pain has started.

5-HT<sub>1B</sub> RECEPTOR SUBTYPE DISTRIBUTION IN TRIGEMINOVASCULAR PATHWAYS

Vasoconstrictor 5-HT<sub>1B</sub> receptors. Detailed molecular biology mapping of mRNA and immunohistochemistry for receptor protein have shown conclusive evidence for substantial populations of 5-HT<sub>1B</sub> receptors on human meningeal blood vessels. These receptors are localized on the smooth muscle and mediate vasoconstriction. The 5-HT<sub>1B</sub> receptors are thus ideally placed to reverse the dilation of meningeal vessels that is thought to occur during a migraine attack. Evidence for 5-HT<sub>1B</sub> receptors has also been found on human coronary arteries making it important to establish the relative contribution of this subtype to the contractile responses in coronary arteries as well as in the target meningeal blood vessels (see discussion below).

Vasodilator 5-HT<sub>1B</sub> and 5-HT<sub>7</sub> receptors. It is fascinating to see that evidence is now emerging for 5-HT<sub>1B</sub> and 5-HT<sub>7</sub> receptors on vascular endothelium which could mediate vasodilatation. These receptors could be involved in the pathogenesis of migraine by initiating the meningeal vasodilatation that activates the trigeminovascular system. It is therefore possible that a 5-HT<sub>7</sub> antagonist could be a migraine prophylactic agent. These vasodilator endothelial 5-HT receptors could also have a role in migraine headache recurrence with the serotonin agonist anti-migraine agents. Thus endothelial 5-HT<sub>1B</sub> and 5-HT<sub>7</sub> receptors could remain preferentially activated as plasma concentrations fall with time after dosing when 5-HT<sub>1B</sub>-mediated vasoconstrictor effects diminish. It is interesting to
speculate that 5-HT\textsubscript{1B} and 5-HT\textsubscript{1D} receptors could be the link to the vasculature for the early observations (decrease in platelet 5-HT and increased urinary 5-HT metabolite 5-HIAA) that suggested serotonergic activation as a key early process in the initiation of a migraine attack.

**Trigeminal inhibitory 5-HT\textsubscript{1B} and 5-HT\textsubscript{1D} receptors.** Studies on the localization of 5-HT\textsubscript{1B} and 5-HT\textsubscript{1D} receptors in human trigeminal ganglia and trigeminal nerves have produced a series of interesting findings. Mapping studies in ganglia have been inconclusive, showing mRNA evidence either for both subtypes\textsuperscript{38} or purely for 5-HT\textsubscript{1D} receptor expression.\textsuperscript{39,40} Immunohistochemical receptor protein mapping has shown that 5-HT\textsubscript{1B} and 5-HT\textsubscript{1D} receptors are present on cell bodies in human trigeminal ganglia. However, only 5-HT\textsubscript{1D} receptors were detected in trigeminal nerves projecting peripherally to the dural vasculature and centrally to the brain stem trigeminal nucleus.\textsuperscript{36} Activation of such prejunctional receptors on nerve terminals is known to modulate neurotransmitter release. The 5-HT\textsubscript{1D} receptors are thus ideally placed peripherally, to inhibit activated trigeminal nerves and promote normalization of blood vessel calibre by preventing vasoactive neuropeptide release and centrally, to interrupt pain signal transmission from the blood vessels to second order sensory neurones in the brain stem.

Interestingly, 5-HT\textsubscript{1F} receptors were also localized within the solitary tract nucleus in the brain stem\textsuperscript{36} which receives trigeminal inputs and is involved in the autonomic regulation of nausea and vomiting – two effects often clinically important in migraine.

A trigeminal location has recently been described for 5-HT\textsubscript{1F} receptors\textsuperscript{41} where its prejunctional pharmacological effects are thought likely to be similar to those of the 5-HT\textsubscript{1D} receptor (inhibition of sensory nerve activation and peptide release in the periphery and interruption of nociceptive transmission within central trigeminal nuclei). However, 5-HT\textsubscript{1F} receptors are also relatively abundant throughout the brain raising the possibility that its activation centrally may have other effects in addition to trigeminal inhibition.\textsuperscript{42} 5-HT\textsubscript{1F} mRNA has also been demonstrated in human blood vessels although there appears to be no expression of functional receptors since 5-HT\textsubscript{1F} agonists appear devoid of vascular effects.\textsuperscript{33}

**5-HT RECEPTOR PROFILE OF ACUTE ANTI-MIGRAINE DRUGS**

The serotonin receptor family is currently grouped into seven subfamilies (5-HT\textsubscript{1} to 5-HT\textsubscript{7}) and fourteen receptor subtypes that have different anatomical locations.\textsuperscript{44} The most common sites of action for effective serotonergic agonist acute migraine drugs (ergots and the 5-HT\textsubscript{1B/1D} agonists) appear to be through vasoconstrictor 5-HT\textsubscript{1B} receptors on the meningeal vasculature and inhibitory 5-HT\textsubscript{1D} Receptors on trigeminal nerve terminals.

Older anti-migraine compounds such as the ergot alkaloids have strong affinity for the anti-migraine 5-HT\textsubscript{1B} and 5-HT\textsubscript{1D} receptors but they also retain high affinity for other serotonin, adrenergic and dopaminergic receptor subtypes (see Table\textsuperscript{45,46}) that can potentially mediate unwanted nausea, dysphoria, asthenia and vascular effects. The triptan agents are a significant progression since they target only the anti-migraine 5-HT\textsubscript{1B} and 5-HT\textsubscript{1D} receptors and have reduced or eliminated unwanted activity at most other monoamine receptor subtypes, thereby improving therapeutic tolerability. The main limitations with the

**ANTI-MIGRAINE MECHANISMS OF ACTION FOR THE 5-HT\textsubscript{1B/1D} AGONISTS**

The figure shows diagrammatically the key sites of action for the 5-HT\textsubscript{1B/1D} agonist antimigraine agents. First is a vascular mechanism of action. The 5-HT\textsubscript{1B/1D} agonists selectively constrict pain-producing intracranial extracerebral blood vessels by a direct action at 5-HT\textsubscript{1B} receptors on the vascular smooth muscle.\textsuperscript{48} This effect reverses the vasodilatation and so reduces trigeminal sensory nerve activation during migraine. The 5-HT\textsubscript{1B/1D} agonists have good selectivity for the target blood vessels over others (e.g. coronary) that could mediate adverse effects (see below).

Second is a neurogenic mechanism of action probably at 5-HT\textsubscript{1D} receptors.\textsuperscript{49,50} The 5-HT\textsubscript{1B/1D} agonists inhibit peripheral trigeminal nerves and prevent neuropeptide release from the activated peripheral terminals thereby removing the influence of potent vasodilator peptides, particularly CGRP. This action breaks the dilator cycle of events that could intensify pain transmission and thereby promotes normalization of meningeal blood vessel calibre.

Third is a central mechanism of action probably at 5-HT\textsubscript{1D} receptors within brain stem sensory trigeminal nuclei. Brain penetrant 5-HT\textsubscript{1B/1D} agonists inhibit neurotransmitter release from the central terminals of activated trigeminal nerves.\textsuperscript{51,52} This action interrupts pain transmission from cranial structures that would otherwise pass through these central pain relay stations. Preclinical studies show that this action appears to be specific for trigeminal sensory divisions since 5-HT\textsubscript{1B/1D} agonists did not reduce pain transmission in the lumbar spinal dorsal horn\textsuperscript{53} – an observation that could explain why this class of compounds are not general analgesics. More recent studies have revealed that centrally acting 5-HT\textsubscript{1B/1D} agonists can also prevent dural vasodilatation-evoked sensitization of caudal trigeminal neurones,\textsuperscript{44} a phenomenon that could underlie their effectiveness in reducing extracranial facial sensory disturbances during migraine. As an aside, it is interesting to note that opiates and non-steroidal anti-inflammatory agents also inhibit this sensitization process and this may underlie their utility in migraine.

The relative importance of each of these mechanisms to migraine headache relief has been a subject of much discussion but it should be remembered that all could occur simultaneously. It is therefore likely that they act in a complementary manner to
reduce the intense trigeminal input that occurs during a migraine attack and so all contribute to the relief of migraine headache pain and associated symptoms.

**Central actions of the 5-HT\textsubscript{1B/1D} agonists**

There have been many debates on the importance of differences in the lipophilicity of the triptan agents and the effect that this has on oral absorption and brain penetration to the central terminals of the trigeminal nerves. It is, however, worth noting that all the 5-HT\textsubscript{1B/1D} agonists currently in clinical use are very poorly brain penetrant when compared to agents like diazepam. It has been argued that the speed of absorption and access to the central sites could influence how fast the anti-migraine clinical response is achieved, but it is also likely that these factors will underlie the consistency of response and therefore the drug’s overall effectiveness. There is one caveat to this argument and that is that the brain penetrability of the triptan agents have been determined experimentally in normal systems where the blood-brain barrier is intact. It has been speculated, but as yet unproven, that the blood-brain barrier may be open during migraine attack. It is not known whether this occurs early or late in an attack, but if it does, then clearly once it happens then all compounds will have equal access to central sites and differences between the various agents will disappear.

**Table: Pharmacological activity of dihydroergotamine, ergotamine and rizatriptan at monoaminergic receptors except where specified.**

<table>
<thead>
<tr>
<th></th>
<th>5-HT\textsubscript{1A}</th>
<th>5-HT\textsubscript{1B}</th>
<th>5-HT\textsubscript{1D}</th>
<th>5-HT\textsubscript{1E}</th>
<th>5-HT\textsubscript{1F}</th>
<th>5-HT\textsubscript{2A}</th>
<th>5-HT\textsubscript{2C}</th>
<th>5-HT\textsubscript{3}</th>
<th>5-HT\textsubscript{4}</th>
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</thead>
<tbody>
<tr>
<td>DHE</td>
<td>0.4</td>
<td>0.7</td>
<td>0.5</td>
<td>1100</td>
<td>180</td>
<td>9.0</td>
<td>1.3</td>
<td>&gt;3700</td>
<td>60</td>
</tr>
<tr>
<td>Ergot</td>
<td>0.3</td>
<td>1.0</td>
<td>0.8</td>
<td>840</td>
<td>170</td>
<td>n.d.</td>
<td>n.d.</td>
<td>&gt;3700</td>
<td>65</td>
</tr>
<tr>
<td>Rizatriptan</td>
<td>300</td>
<td>7.2</td>
<td>2.3</td>
<td>87</td>
<td>138</td>
<td>7200</td>
<td>7300</td>
<td>4100</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

**Top rows are 5-HT receptors, 5-HT\textsubscript{3} (rat) receptors and 5-HT\textsubscript{4} (guinea pig) receptors. Second row are alpha (α 1 rat liver, α 2 human prostate) and cloned beta adrenergic receptors and cloned dopamine D receptors. Data for rizatriptan at cloned 5-HT\textsubscript{1} receptor subtypes were modified from Pauwels et al.\textsuperscript{47} All values are affinity IC\textsubscript{50} nM. n.d. – not determined.**
migraine-associated nausea and vomiting. The 5-HT$_{1B/1D}$ agonists have been shown to decrease nausea and vomiting and this is likely to be an indirect effect of reducing trigeminal input to the NTS. Fast drug penetration to central sites may bring additional benefits for the triptan agents by giving access to 5-HT$_{1D}$ receptors in the solitary tract nucleus. It is therefore noteworthy that the more brain penetrant 5-HT$_{1B/1D}$ agonists such as rizatriptan have some of the fastest effects against migraine associated nausea. However, it is important to remember that any benefit here could be offset by simultaneous activity at the more brain penetrant 5-HT$_{1B/1D}$ agonists such as rizatriptan have some of the fastest effects against migraine associated nausea. However, it is important to remember that any benefit here could be offset by simultaneous activity at 5-HT$_{1A}$ receptors, since these may be pro-nauseant. The window between activity at 5-HT$_{1D}$ and 5-HT$_{1A}$ receptors should therefore be maximized for the greatest anti-nausea therapeutic gain. Remember that recent preclinical studies suggest that agonist actions at central 5-HT$_{1A}$ receptors are unlikely to contribute to the anti-noceceptive effects of the 5-HT$_{1B/1D}$ agonists in trigeminal nuclei, in contrast to their analgesic effects in spinal dorsal horn.

**ALL TRIPAN 5-HT$_{1B/1D}$ RECEPTOR AGONISTS ARE PARTIAL AGONISTS IN HUMAN CORONARY ARTERIES**

The demonstration that 5-HT$_{1B}$ receptors are present in the coronary arteries has given rise to concern over the potential for adverse cardiac events with the ergots and the 5-HT$_{1B/1D}$ agonists and has resulted in this class of drugs being contraindicated for use in cardiovascular risk patients. Adverse cardiac events are, however, rare with all the 5-HT$_{1B/1D}$ agonists for two reasons. First, the 5-HT$_{1B}$ receptor reserve appears to be lower in the coronary than the meningeal arteries. Second, collectively all the triptan 5-HT$_{1B/1D}$ receptor selective agonists lack activity at 5-HT$_{2A}$ receptors which mediate most of the serotonergic contraction in coronary vessels. Taken together, these factors confer craniovascular selectivity and cardiovascular safety for the triptan class. At therapeutic concentrations there are no marked differences between the triptan 5-HT$_{1B/1D}$ selective agonists in their contractile effects on human coronary arteries in vitro. It is noteworthy that all the agents in the triptan class are partial agonists in human coronary blood vessels in vitro as their maximum effects are only a small fraction of the response that can be evoked by the endogenous ligand serotonin. Any small differences between the responses to the various triptan agents reflects their relative therapeutic potency and occur at high concentrations that are supramaximal clinically and therefore irrelevant to their therapeutic use against migraine.

There has been much discussion comparing the potential cardiovascular safety of the various triptan compounds but the arguments have often confused the safety and tolerability aspects of their profiles. Although there may be differences in the tolerability profiles of the 5-HT$_{1B/1D}$ agonists, their potential coronary safety profiles, as judged by pharmacological studies, appear basically indistinguishable at this time.

**NOVEL APPROACHES TO ACUTE MIGRAINE THERAPY**

Several recent drug development projects have been directed towards blockade of the prejunctional effects i.e. release of vasoactive peptides from activated trigeminal nerves, in the hope of discovering acute anti-migraine agents that lack the postjunctional vasoconstrictor effects of the 5-HT$_{1B/1D}$ agonists. The substance P NK$_{1}$ receptor antagonists (LY303870, RP100,893 GR205,171 and L-758,298) have failed in clinical trials for acute migraine treatment and, although disappointing, this finding is of interest with regard to the migraine pathogenesis theory. Experimental studies show that neurogenic extravasation/inflammation in the meninges is mediated by neurokinins acting at NK$_{1}$ receptors on the vascular endothelium. If this neurogenic extravasation occurs in migraine, then it should have been completely blocked by these agents. These data suggest that theories encompassing a role for ongoing neurogenic dural extravasation in the headache pain phase of migraine may have to be re-evaluated perhaps by examining the activity of these agents as prophylactics. Attention has now been directed towards CGRP-induced meningeal vasodilatation as a primary factor in producing migraine headache pain. Increased CGRP levels are perhaps one of the most reliable biochemical markers in migraine and cluster headache and levels are normalized concomitant with successful therapy. CGRP antagonists have been shown experimentally to block meningeal artery vasodilatation, suggesting that they may have anti-migraine activity. Non-peptide, CGRP antagonists are thought to be in early clinical trials.

These antagonist approaches involve postjunctional blockade of only one of the vasoactive substances that are released when the trigeminal nerves are activated and, since many substances are released, this strategy runs the risk that the other unblocked components can still be active in the migraine process. A more complete approach is to target prejunctional receptors on the trigeminal nerve terminals to prevent the release of all vasoactive substances at the same time. Immunohistochemical and mRNA studies in human tissues have shown that it is the 5-HT$_{1D}$ receptor that is selectively located on the perivascular and central terminals of trigeminal fibres. As a result it has been suggested that a 5-HT$_{1D}$ selective agonist (effectively a sensory neuropeptide-release inhibitor) would be an attractive drug target since it could potentially modulate transmission in the trigeminal pathways but lack the 5-HT$_{1B}$ mediated vasoconstrictor activity of current triptan anti-migraine agents. Recent reports also suggest that 5-HT$_{1D}$ receptors may modulate glutamatergic transmission in the cerebral cortex in vitro and if this occurs in the medullary dorsal horn, then it may be important in the central anti-noceceptive actions of the 5-HT$_{1B/1D}$ agonists and 5-HT$_{1D}$ receptor selective agonists. The 5-HT$_{1D}$ receptor selective agonist PNU 142,633 recently completed have entered Phase II clinical trials and the data showed no evidence for acute efficacy against migraine (R. McCall, personal communication, IBC Migraine Conference Philadelphia, May 1999). This finding was disappointing since the rationale for the development of these compounds appears sound. The reason for the failure is probably that PNU 142,633 lacked sufficient efficacy at 5-HT$_{1B}$ receptors (approximately one third the efficacy of sumatriptan at gorilla cloned 5-HT$_{1D}$ receptors) and so was unable to shut down the activated sensory nerves during migraine. It should be remembered that the actions of the serotonin agonists to inhibit neurotransmitter peptide release will be frequency dependent such that the harder the nerves are firing the harder it is to inhibit them. The 5-HT$_{1D}$ hypothesis thus remains untested and requires re-evaluation with a compound with equally full efficacy at 5-
HT\textsubscript{ID} receptors as the currently used ‘triptan’ agents but lacking activity at 5-HT\textsubscript{1B} receptors.

Several of the current triptan agents have affinity for 5-HT\textsubscript{1F} receptor sites and it has been proposed that this may contribute to their anti-migraine efficacy.\textsuperscript{64} The development of 5-HT\textsubscript{1F} receptor selective agonists has been underpinned by the same lines of argument that were used for the 5-HT\textsubscript{1D} selective strategy, since functional 5-HT\textsubscript{1G} receptors appear to be present on peripheral trigeminal nerve terminals but absent from blood vessels. The most advanced compound in this class is LY334370.\textsuperscript{65} This compound has been recently withdrawn from phase III clinical trials, due to animal toxicity. Preliminary phase II data on the efficacy of LY 334370 were recently presented at the International Headache Society in Barcelona and looked promising with anti-migraine efficacy being demonstrated at 60 and 200 mg doses.\textsuperscript{66} It remains to be established whether this is due to activity solely at 5-HT\textsubscript{1G} receptors, as the plasma concentrations after 200 mg of LY334370 were quite high,\textsuperscript{67} raising the possibility that selectivity may have been compromised. Further studies with this class are clearly warranted.

Further clinical trials to determine the effectiveness of 5-HT\textsubscript{1D} or the 5-HT\textsubscript{1F} receptor selective agonists as anti-migraine agents will help settle the long-running debate on the relative importance of vasoconstriction and trigeminal inhibition to the anti-migraine effects of the “triptan” 5-HT\textsubscript{1B/1D} agonists. The success of these strategies is likely to be critically dependent upon adequate brain penetration to central trigeminal sites to interrupt trigeminal pain signal transmission. It will be most interesting if only one of these approaches shows anti-migraine efficacy, since this will redefine the anti-migraine neuropharmacology of the trigeminovascular system and perhaps reveal other neural components as novel therapeutic targets. Future anti-migraine strategies will undoubtedly examine the relationship of P/Q calcium ion channel mutations to brain dysfunction and perhaps target this as a migraine prophylactic strategy. In addition, the findings of ‘wind up’ in the trigeminal dorsal horn that can be driven by meningeal dilation and inflammation suggests that drugs that target this sensitization process may have a role in anti-migraine therapy.

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