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Seeking the best care for acute migraine

Abstract In recent years, we have seen exciting advances in the knowledge of mechanisms that underlie migraine. These have thus promoted investigations into new drugs for the management of acute migraine. The major goal in migraine research is to identify and study non-vascular targets for migraine therapy. The 5-HT_{1F} neuronal receptor is apparently not involved in the vascular effects of triptans. Clinical evaluation of LY33470, a potent agonist of 5-HT_{1F} receptors, has demonstrated that the drug is effective in ending a migraine attack. These results suggest that 5-HT_{1F} receptor agonists may represent new antimigraine drugs without cerebrovascular or cardiovascular effects. From the plasma extravasation model of migraine, potential therapeutic targets were identified, although in testing no effects were observed: endothelin and substance P antagonists and the specific serotonin agonist CP 122,288, potent inhibitors of neurogenic inflammation, were ineffective in the treatment of a migraine attack. Since a causative role of CGRP in migraine has been postulated, novel antimigraine drugs include CGRP antagonists. Molecules with highly selective

antagonistic action on human CGRP receptors of cerebral circulation have been discovered. These CGRP antagonists are in preclinical and clinical trials and the results are awaited with great interest. In addition, a small pilot study found civamide, a capsaicin derivative which causes CGRP depletion from trigeminal sensory fibers, to be effective in the migraine attack. Both NMDA and non-NMDA receptors for glutamate and related excitatory aminoacids are found on trigeminal neurons; therefore excitatory aminoacid receptor antagonists may provide therapeutic action in migraine. Recently, a glutamate receptor antagonist (LY293558) that had not shown vascular effects in animal models demonstrated an antimigraine effect. More specific compounds are also warranted in confirming nitric oxide inhibition as a therapeutic approach in migraine. Thus, it is likely that in the near future emerging therapies will increasingly meet patients' and physicians' goals.

Key words Migraine • Triptan • 5-HT_{1F} receptor • CGRP receptor antagonist • Glutamate receptor antagonist • Civamide

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Introduction

What causes migraine? What does it mean to have a migraine?

The last decade has experienced remarkable advances in the knowledge of pathogenetic and clinical aspects of migraine, thus heralding a new age in the management of acute migraine.

Triptans

The most important change has been the identification of a class of compounds, commonly known as triptans, that are agonists of the serotonin receptor subtype 5-HT_{1B/1D} [1]. Triptans have improved the lives of migraine patients, but are triptans the best care for migraine attacks? Besides not being effective in all patients, current triptans have a vascular therapeutic component with the potential to cause small coronary artery contraction.

All triptans are effective, well tolerated and relatively safe when used correctly and in the absence of coronary and cerebro-artery disease and uncontrolled hypertension. However, no triptan is without potential risk of vasocorony or other vasospastic reactions [2]. The risk of coronary constriction is minimal since clinical data indicate that vascular 5-HT_{1B} receptors mediate only 25% of the overall vasoconstrictive potential of the coronary arteries [3]. However, because of this minimal risk, patients must be carefully evaluated for risk factors for cerebrovascular or coronary artery disease, prior to treatment, to reduce the likelihood that a patient with unrecognized vascular disease may be inadvertently exposed to these drugs.

Therefore, the major goal in migraine research is to design newer triptans without vascular activity. Since vascular side effects of triptans are presumed to be mediated by 5-HT_{1B} receptors, a non-vascular drug with an improved therapeutic index may be discovered by targeting neuronal 5-HT_{1D} and 5-HT_{1F} receptor subtypes. In fact, studies on human cerebral arteries demonstrated that the triptan-induced contraction in brain vessels is mediated exclusively by the 5-HT_{1B} receptor, which is also present in a majority of human coronary arteries [4]. Selective 5-HT_{1D} and 5-HT_{1F} agonists may represent new drugs devoid of cerebrovascular and cardiovascular effects, thus offering a safer strategy for the treatment of migraine.

The hypothesis that a 5-HT_{1D} subtype-selective agonist may inhibit the trigeminal nerve without causing vasoconstriction was initially encouraged by the discovery that messenger RNA for 5-HT_{1D} receptors, but not 5-HT_{1B} receptors, was present in post mortem human trigeminal ganglia [5]. The development of the PNU-142633 compound, a highly selective agonist for the human 5-HT_{1D} receptor, showed that these agonists may not be a safer, nor a more effective strategy for antimigraine therapy. Despite its good tolerability [6], demonstrated in a double-blind, randomized trial of 34 migraine patients, a single oral 50-mg dose of the drug did not alleviate migraine headache. The results seem to answer the current debate on whether actions at both receptors subtypes stimulated by triptans are necessary for therapeutic benefit and whether activation of the 5-HT_{1D} receptor alone may not be adequate for antimigraine efficacy.

Additionally, in patients treated with PNU-142633, cardiovascular adverse events (e.g. chest pain, mild arterioventricular block and mild QTc prolongation) have emerged, thus indicating that 5-HT_{1D} receptors or other unidentified 5-HT receptors may contribute to some of the cardiovascular effects of current triptan therapy [6, 7].

Triptans have high affinity for neuronal 5-HT_{1F} receptors. This observation suggests that, in addition to 5-HT_{1B/1D} receptor agonists, 5-HT_{1F} receptor agonists may also be useful in the treatment of migraine. Binding sites for 5-HT_{1F} have been widely identified in the human brain, in particular at the higher brain centers involved in pain perception [8]. The 5-HT_{1F} receptor agonists block dural plasma extravasation in guinea pig without significant contraction activity on human cerebral and coronary vascular beds [4].

The Eli Lilly compound LY334370, a potent agonist of 5-HT_{1F} receptors with an approximately 100-fold selectivity over 5-HT_{1B} and 5-HT_{1D} receptors, was recently taken into clinical development as an antimigraine agent [9]. Three single, oral doses (20, 60 or 200 mg) of LY334370 or placebo were administered in 99 patients with migraine in a double-blind, parallel group study. The 200-mg dose seemed to be the most effective in ending the attacks. The drug produced a pain-free rate at 2 hours higher than that of most triptans. The adverse event profile indicates that the drug produces a much higher incidence of asthenia, dizziness, somnolence and paresthesia than did other triptans; these adverse reactions strongly suggest a central mechanism of antimigraine action [9].

Experimental evidence in animals suggests that LY334370 blocks transmission of nociceptive impulses from the pain-producing cranial vessels to the central nervous system by inhibiting the activation of the second-order neurons in the trigeminal nucleus caudalis [10]. If further extensive clinical studies confirm these results, it may be possible to carry out triptan therapy without cardiovascular consequences.

Neuropeptide receptor antagonists

Neurogenic inflammation within the meninges may be a cause of pain in migraine and has been used as a model to characterize the pharmacology of antimigraine compounds. Most of the evidence collected in patients indicates that drugs preventing neurogenic inflammation in animal models fail to be effective in migraine and that substances effective in migraine are relatively ineffective in the model of neurogenic extravasation. In fact, the endothelin antagonist bosentan blocks neurogenic inflammation, but is ineffective in aborting migraine attacks [11]. In addition, two substance P antagonists, RPR100893-201 and lanepitant (a neurokinin-1 antagonist), all potent inhibitors of neurogenic

inflammation, were ineffective in acute migraine [12]. Moreover, the specific serotonin agonist CP122,288, an inhibitor of neurogenic inflammation 100-fold more potent than sumatriptan, was ineffective in migraine attacks in two studies. The drug was not clinically effective at doses and plasma concentrations in excess of those required to inhibit neurogenic plasma extravasation in animals [13].

Data obtained in migraine patients seem to indicate that painful neurogenic inflammation in the meningeal (dural) vasculature, mediated principally by substance P release, is not a key component of migraine attack. Moreover, by using fluorescein or indocyanine angiography, no increased endothelial permeability or leakage of indocyanine was found in human retinal or choroidal vessels during headache attacks or in the headache-free interval in patients suffering from migraine and cluster headache [14].

Clinical data emphasize the importance of calcitonin gene-related peptide (CGRP) release in migraine and the search for suitable antagonists of the receptors for this neuropeptide. Recently, small molecules with a highly selective action on human CGRP receptors have been disclosed [15].

CGRP does not seem to cause neurogenic inflammation, which depends on the release of substance P, whereas the peptide causes neurogenic vasodilatation, which may be important in the generation of migraine pain. Cerebral blood vessels are more sensitive to CGRP than to blood vessels in other parts of the body. It may therefore be possible to apply a CGRP antagonist in a dose that would be relatively selective for cerebral circulation. The effects of the CGRP receptor antagonist BIBN4096BS have been characterized in SK-N-MC cells and isolated human cerebral, meningeal and coronary arteries [16]. The potent, selective, small molecule antagonist BIBN4096BS is under investigation for the treatment of migraine and the results are awaited with great interest.

Civamide, a capsaicin derivative

A study with civamide [17] supports the suggestion that inhibition of CGRP action may be an important mechanism of antimigraine compounds. A pilot study with a single dose of intranasal civamide (20 or 150 µg) was performed in 34 migraine patients; migraine head pain improved and low headache recurrence was observed in the majority of the patients [17].

These results suggest that intranasal civamide may be effective in the treatment of acute migraine and that larger, vehicle-controlled studies are warranted to confirm these data. Civamide, a synthetic stereoisomer of capsaicin, is potent in depleting neuropeptides, such as substance P and CGRP, from the trigeminovascular system. Civamide

seems to act by inducing a relative depletion of available neuropeptides, CGRP in particular, for release by the trigeminal neurons, consequently preventing the resultant vasodilatation of dural vessels and pain associated with migraine headache.

Excitatory aminoacid receptor antagonists

The involvement of both *N*-methyl-D-aspartate (NMDA) and non-NMDA excitatory amino acid receptors in the transmission of nociceptive information in the trigemino-vascular system have been demonstrated in animal after the activation of a pain-producing intracranial structure [18]. This study also demonstrated that blockade of glutamatergic transmission at either NMDA or non-NMDA receptors results in the inhibition of transmission within the trigeminal nucleus caudalis [18].

Therefore, since head pain signals are likely to traverse the trigeminal nucleus, agents that block NMDA and non-NMDA receptors may provide antimigraine effects. Recently, a small phase II study has demonstrated that LY293558, an AMPA/KA receptor antagonist, is clinically effective in migraine [19]. In a placebo-controlled study, 44 patients were treated intravenously with 1.2 mg/kg LY293558 or subcutaneously with 6 mg sumatriptan or placebo. The drug under study was superior to placebo and also more effective and better tolerated than sumatriptan. No patients treated with LY293558 reported chest or throat symptoms [19].

Since preclinical studies have given no evidence of vasoconstriction due to LY293558, this non-vasoactive compound may play a major role in migraine therapy.

Recently, the NMDA receptor antagonist ketamine (25 mg intranasally) was found to be effective in aborting severe aura in 5 of 11 patients with familiar hemiplegic migraine [20]. Migraine aura is probably caused by cortical spreading depression or a similar phenomenon. In experimental animals, cortical spreading depression is mediated through excitatory amino acids and can be blocked by the glutamate NMDA receptors antagonist [21]. Since no treatment for migraine aura has been described previously, the therapeutic response to ketamine suggests that NMDA receptor antagonists may be useful in the management of acute migraine with aura.

Nitric oxide and NO synthase inhibitors

Since a large part of the scientific evidence suggests a key role for nitric oxide (NO) in migraine headache, this molecule is a major possible target for migraine therapy [22]. In

this context, some years ago, a new approach to migraine treatment was attempted by using intravenous infusion of a NO synthase (NOS) inhibitor during attacks.

In a double-blind study, the effects of the non-specific NOS inhibitor *L*-NGmethylarginine hydrochloride (546C88) or placebo on spontaneous migraine attacks were studied in a group of 18 patients. The drug was administered intravenously over 15 min for a single migraine attack. Two hours after infusion, there was significant headache relief and improvement in clinical disability of patients in the active treatment group when compared with the placebo group [23].

Due to the non-specific nature of the systemic effects of this compound, which are however likely to limit its clinical usefulness, more specific compounds are warranted in confirming NOS inhibition as a new therapeutic approach in migraine.

Conclusions

In the last few years the increased knowledge on the physiology and pharmacology of the trigeminovascular system have offered new drug targets which have given suggestive and promising clinical results for non-vascular therapy of acute migraine. The therapeutic effect of the 5-HT_{1F} agonist and glutamatergic receptor antagonist support the concept that migraine attack is due to a process that resides and is promoted by the brain. Other targets for the development of new drugs are still in the preclinical phase. In the near future the emerging therapies may overcome the limitations of currently available medication, so acute migraine treatment may meet more and more patient and physician goals.

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