Chapter 60

Potential New Drugs for Acute and Prophylactic Treatment of Migraines

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INTRODUCTION

Headache is the most common reason for neurologic referral (10), and the majority of disabling headache has migraine as its biological basis. Migraine is certainly common (74), often very disabling (81), and increasingly recognized as a fundamentally neurologic disorder (49). Although many patients are now adequately treated with the therapies developed in the 1990s, there is still a substantial group of patients who continue to suffer and require better treatment (71). Here we try to capture possible approaches to both acute and preventive treatment of migraine that have emerged from laboratory science in the last decade. We have recently written on promising targets in other primary headaches (39). Here we cover targets for which there are clinical data to make some balance; elsewhere we cover targets promising because of effects on trigeminovascular nociceptive traffic, but without clinical data, such as the nociceptin (ORL-1) receptor, cannabinoid receptor, orexin receptors, and transient receptor potential (TRPV1 or VR-1) family receptor mechanisms, have been presented (38).

SEROTONIN RECEPTORS

Although there are a range of acute and preventive therapies for migraine (71), serotonin 5-$HT_{1B/1D}$ receptor agonists, triptans (36), stand out in terms of clinical and neuroscientific impact. The triptans are safe (18) and effective in migraine (27,28). However, the development of triptans left a so-called smoking gun by constricting vessels; did this mean migraine was after all a vascular disease, and could future developments disentangle the clinically undesirable, albeit small vascular risk penalty of triptans, and develop purely neurally acting medicines? Can the useful effects of 5-HT receptor agonism be dissected from the vascular complications?

5-HT_{1F} Receptor Agonists

The potent specific $5HT_{1F}$ agonist LY334370 was developed (94) and shown to block neurogenic plasma protein extravasation in the rat dura mater (63). Activation of 5-HT_{1F} receptors does not seem to have vascular effects (14,100). LY334370 is effective in acute migraine, albeit at doses with some central nervous system side effects and no cardiovascular problems (50). Unfortunately development was stopped because of a nonhuman toxicity problem. $5HT_{1F}$ receptors are found in the trigeminal nucleus (11,30,90,134) and trigeminal ganglion (7). 5-HT_{1F} receptor activation is inhibitory in the trigeminal nucleus in rat (82) and cat, albeit in cat seeming less potent than $5HT_{1B}$ or $5HT_{1D}$ receptor activation (41). Using electron microscopic methods, presynaptic 5-HT_{1F} receptors in the trigeminal nucleus of the cat have been reported (77). There is a good expectation that 5-HT_{1F} receptor agonists would be both nonvascular and probably useful in migraine (98) and cluster headaches.

5-HT_{1D} Receptors

$5HT_{1D}$ receptor agonists are potent inhibitors of neurogenic dural plasma protein extravasation (133) and have no vascular effects. Peptidergic nociceptors express these receptors (95) in a manner that is activation dependent (2). Specific potent $5HT_{1D}$ agonists have been developed by taking advantage of similarities between human and nonhuman primate $5HT_{1B}$ and $5HT_{1D}$ receptors (96). The compound that went into clinical studies, PNU 142633, was ineffective (51), although it was a relatively weak agonist when compared to sumatriptan in in vitro studies (97), and was poorly brain penetrant. This compound was developed using gorilla receptors (81). It must, therefore, be asked whether this was the correct compound to test the 5-HT_{1D} hypothesis. Interestingly, there were no complaints of adverse events of a cardiovascular nature in the placebo

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group, with cardiovascular adverse events, including chest pain, in the PNU 142633-treated group (29). Preclinical studies are able to dissect out a potent 5-HT_{1D} receptor–mediated inhibition of the trigeminocervical complex (41), so that this mechanism remains both plausible and not fully tested.

CALCITONIN GENE-RELATED PEPTIDE RECEPTORS

The trigeminal innervation of the cranial circulation contains a number of neuropeptides, of which the most important for migraine seems to be calcitonin gene-related peptide (CGRP) (23). Stimulation of the trigeminal ganglion in cat and humans results in elevations in CGRP and substance P levels in the cranial circulation (46). However, during acute attacks of migraine (31,47), cluster headache (25,43), and paroxysmal hemicrania (45), CGRP is elevated but substance P is not. Similarly, nitroglycerin-induced migraine, which is very similar to the spontaneous attack (1,125), also exhibits increased levels of CGRP in plasma (64). Triptans inhibit CGRP release in the superior sagittal sinus of the rat (9) and in the spinal cord of the cat (5). Triptans inhibit release of CGRP into the cranial circulation of experimental animals when it is evoked by trigeminal ganglion activation (42,44). Similarly, stimulation of the superior sagittal sinus in cat leads to cranial release of CGRP (135), which can be blocked by triptans, but not by specific inhibits of neurogenic dural plasma protein extravasation (67,68). Interestingly, triptans also influence the CGRP promoter (21), and regulate CGRP secretion from neurons in culture (20). All of these data would predict that a CGRP receptor antagonist would have antimigraine effects and not need have vascular actions.

Successful treatment of acute migraine (42) or cluster headache (25,43) with sumatriptan normalizes cranial CGRP levels. Moreover, local microiontophoresis of the CGRP-receptor antagonist BIBN4096BS (19,85) inhibits trigeminocervical neurons (121). This potent CGRP-receptor antagonist has been shown to be effective in the treatment of acute migraine (86) and is devoid of vasoconstrictor actions in humans (92,93). CGRP antagonists may have a preventive as well as acute attack effects that merits consideration and eventual study. They hold great promise for both migraine and cluster headaches.

GLUTAMATE EXCITATORY AMINO ACID RECEPTOR ANTAGONISTS

Glutamate is the major excitatory neurotransmitter and plays an important role in conveying sensory and nociceptive information in the brain and spinal cord. It acts through both ionotropic (ion channel–type) and G-protein–coupled (metabotrophic) receptor families. Glutamatelike immunoreactivity has been seen in tooth pulp neurons that project to the trigeminal nucleus caudalis in the rat (13); glutaminase immunoreactivity is most dense in the nucleus caudalis when compared with other parts of the trigeminal nucleus of the rat (76). Each of *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid (AMPA), kainite, and metabotropic glutamate receptors have been identified in the superficial laminae of the trigeminal nucleus caudalis of the rat (124). Ionotropic receptor channel blockers, such as MK-801 acting at the NMDA receptor, and GYKI-52466, acting at the AMPA receptor, have been found to block trigeminovascular nociceptive transmission in the trigeminocervical nucleus (12,40,122). Similarly, both NMDA and non-NMDA ionotropic receptor blockades reduces fos protein expression in trigeminal nucleus caudalis associated with intracisternal capsaicin injection (83,84). Last, glutamate receptors are involved in transmission of trigeminovascular nociceptive information in the ventrobasal thalamus (115). This glutamate-mediated thalamocortical transmission, which must be crucial in the appreciation of head pain, can be modified by β-adrenoceptor antagonists effective in migraine, such as propranolol, by a β_1-mechanism (99,114).

Consistent with these preclinical data there are small trials that suggest glutamate blockade as a strategy to treat migraine. A mixed AMPA/kainate receptor antagonist, LY293558, when given by intravenous injection, was shown to be effective and well tolerated in acute migraine (105). Interestingly, ketamine, which acts at the glutamate NMDA receptor, reduced aura symptoms in patients with familial hemiplegic migraine in an open-label study (65). Taken together these data speak to a high likelihood that glutamate receptor antagonists would have effects in both migraine and cluster headaches.

NITRIC OXIDE MECHANISMS AS TARGETS FOR MEDICINE DEVELOPMENT

Much has been written of nitric oxide (NO) and migraine, and this review cannot hope to do this area justice (87,126,127). Moreover, NO donors are clearly effective triggers of acute cluster headache (24). Some important mechanistic data in migraine are cited here because they bear on the issue of nonvascular therapeutic development. It has been considered that nitroglycerin triggers migraine, or indeed cluster headache, by a necessary dilation of cranial vessels (62). However, three recent observations suggest that dilation is an epiphenomenon. First, nitroglycerin triggers premonitory

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symptoms in many patients (1). These were no different to those reported in spontaneous attacks (35) and occurred well after any vascular change would have been present. Second, downstream activation of the cyclic guanosine monophosphate pathway by sildenafil can induce migraine without any change in middle cerebral artery diameter (70). Third, dilation of the internal carotid artery after nitroglycerin administration in cluster headache patients is dissociated in time from the onset of the attack (79). Taken together these observations suggest that although NO mechanisms may play a role in some part of the pathophysiology of these disorders, it need not be a vascular effect. A role, for example, of inducible NO synthase has been suggested (102), or in inhibition of trigeminocervical complex fos expression with NO synthase blockade has also been reported (58). Both examples provide a nonvascular approach, although potentially with rather different NO synthase subtype targets. The available data, therefore, suggest that NO-based developments may find clinical utility in both migraine and cluster headaches.

ADENOSINE A_1 RECEPTORS

There is a substantial literature to suggest that the purine, adenosine, may have some role in nociception (107,108). Based on studies comparing the rank order of potency of adenosine analogs (109), or on the use of selective adenosine agonists and antagonists (119), it is likely that the antinociceptive effects of adenosine are mediated via the A_1 receptor (109). Adenosine may contribute to the antinociceptive effects of morphine (16) and serotonin (15). The adenosine A_1 receptor protein has been localized in human trigeminal ganglia (110), which suggests a potential ability of adenosine A_1 receptor agonists to inhibit the trigeminal nerve.

It has been shown that two highly selective adenosine A_1 receptor agonists, GR79236 (52) and GR190178 (113), can inhibit trigeminovascular activation, both in the trigeminal nucleus and by inhibition of release of CGRP in the cranial circulation (48). The effect within the trigeminal nucleus reflects a central action, and inhibition of CGRP release is likely to be attributable to an action at adenosine A_1 receptors on peripheral terminals of the trigeminal nerve (48). Both effects are in keeping with the concept of adenosine A_1 receptors being located prejunctionally on primary afferent neurons and causing inhibition of transmitter release, as has been described in other systems (106). Adenosine A_1 receptor agonists, such as GR79236 have no effect on resting meningeal artery diameter in rats (57). Moreover, GR79236 can inhibit the nociceptive trigeminal blink reflex (66) at doses in humans (34) that are both trigeminally inhibitory and without vascular effects in experimental animals. Humphrey et al. (60) reported a successful proof-of-concept study with an adenosine A_1 receptor agonist some years ago during a presentation at an International Headache Congress (New York, USA 2001), although the full details of the study have not yet been published. Such a result again demonstrates that a neurally based strategy is possible, although for this target other systemic pharmacodynamic effects may preclude its further development.

SOMATOSTATIN RECEPTOR AGONISTS

Effective in Cluster Headache But Not in Migraine

Somatostatin, an endogenously occurring 14-amino acid peptide, has been shown to inhibit the release of numerous vasoactive peptides, including CGRP (56) and vasoactive intestinal polypeptide (26). Neurons containing somatostatin are found in the regions of the central and peripheral nervous systems involved in nociception, such as peripheral sensory fibers, dorsal horn of the spinal cord, trigeminal nucleus caudalis, periaqueductal gray, and the hypothalamus (61,69,111). Somatostatin mediates its actions by binding to high-affinity membrane receptors. Five somatostatin receptors (sst_{1-5}) have been cloned (59), with octreotide acting predominantly on sst_2 and sst_5 (91).

Two studies have evaluated the abortive effect of somatostatin in migraine. In the first study, intravenous somatostatin (25 μg/min for 20 minutes) was compared to treatment with ergotamine (250 μg intramuscularly), or placebo in a double-blind trial comprising 72 attacks in 8 patients (117). Infusion of somatostatin reduced the maximal pain intensity and the duration of pain significantly compared to placebo, and to a degree comparable to intramuscular ergotamine. In another randomized, double-blind study subcutaneous somatostatin was compared with ergotamine (33). Five patients were treated for three attacks by each of the drugs. Subcutaneous somatostatin and ergotamine were equally beneficial as regards effects on maximal pain intensity and the pain area, but somatostatin was less effective in reducing the duration of pain. Given the distribution and effects of somatostatin in preclinical models we embarked on two placebo-controlled, double-blind crossover studies to test the principle of somatostatin receptor agonism in migraine and cluster headache. We used octreotide, a somatostatin analog with a half-life of approximately 1.5 hours (54), because somatostatin needs to be infused and octreotide can be given subcutaneously as an outpatient.

For the first study, patients with migraine with and without aura as classified by the International Headache Society (55) were recruited to a double-blind placebo-controlled crossover study. They were instructed to treat two attacks of at least moderate pain severity, with at

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least a 7-day interval, using subcutaneous 100 μg octreotide or matching placebo. The primary endpoint was the headache response, defined as severe or moderate pain becomes mild or nil, at 2 hours. The study was powered to detect a 30% difference at an α of 0.05 and a β of 0.8. Fifty-one patients were recruited, of whom 42 provided efficacy data on an attack treated with octreotide, and 41 with placebo. The 2-hour headache response rates were 20% for placebo and 14% for octreotide, and the 2-hour pain free rates were 7% and 2%, respectively. The study concluded that subcutaneous octreotide 100 μg is not effective in the acute treatment of migraine when compared to placebo (73).

For the second study, patients with episodic and chronic cluster headache, as defined by the International Headache Society, were recruited to a double-blind placebo-controlled crossover study. They were instructed to treat two attacks of at least moderate pain severity, with at least a 24-hour break, using subcutaneous octreotide 100 μg or matching placebo. The primary endpoint was the headache response, defined as very severe, severe, or moderate pain becomes mild or nil, at 30 minutes. Fifty-seven patients were recruited, 46 of whom provided efficacy data on attacks treated with octreotide and 45 with placebo. The headache response rate with subcutaneous octreotide was 52%; with placebo was 36%. Modeling the treatment outcome as a binomial where response was determined by treatment, and considering period effect, gender, and cluster headache type as other variables of interest, subcutaneous octreotide 100 μg was significantly superior to placebo ($P < .01$) (78).

The studies suggest an interesting difference between migraine, where octreotide was not effective, and cluster headache where it had a modest but clear effect. Many issues arise, including whether more suitable, probably more brain-penetrant substances would have a better outcome and how the treatments would perform with repeated use. Certainly the data demonstrate a nonvasoconstrictor, effective acute therapy for cluster headache, which has generic important implications for medicine development for the condition.

CORTICAL SPREADING DEPRESSION INHIBITORS

The clinical features of migraine aura (103) and the key features of cortical spreading depression (CSD) have much in common (72). It seems likely that CSD is the animal homolog of migraine aura in humans (53). Some animal studies indicate that CSD activates the trigeminal system via unmyelinated A-δ and C-fibers innervating the meninges, and results in migraine pain (6), although the question of whether human aura is pain producing is a hotly contested question (37). Certainly for prolonged aura, a treatment that would prevent its development or arrest its progression would be a major development for afflicted patients.

Tonabersat is a CSD inhibitor that has entered clinical trials in migraine. Other potential CSD inhibitors include (i) σ-receptor (σR1) agonists such as dextromethorphan, carbetapentane, and 4-IBP; (ii) non-AMPA/KA receptor modulators such as CP-101,606 (a NR_{2B} antagonist) and ZD9379 (a glycine-site antagonist); (ii) K-current modulators such as compound-2 (KCNQ2 opener); (iv) chloride-channel enhancers such as BTS72664; and (v) connexin hemi-channel modulators that might block astrocytic calcium waves implicated in CSD.

Tonabersat (SB-220453) inhibits CSD, CSD-induced NO release, and cerebral vasodilation (101,120). Tonabersat does not constrict isolated human blood vessels (75), but does inhibit trigeminally induced craniovascular effects (89). Remarkably, topiramate, a proven preventive agent in migraine (8,17,118), also inhibits CSD in cat and rat (3). Tonabersat is inactive in the human NO model of migraine (129), as is propranolol (131), although valproate showed some activity in that model (130). Topiramate inhibits trigeminal neurons activated by nociceptive intracranial afferents (123), and thus CSD inhibition may be a model system to contribute to the development of preventive medicines.

INHIBITION OF VOLTAGE-GATED CHANNELS

Broadly speaking, inhibition of voltage-gated channels, particularly Ca^{2+} channels, has become at attractive target in migraine after the description of mutations in the *CACNA1A* gene in about half of patients with familial hemiplegic migraine (88). In some responses, this option links back to CSD (see above) with recent observations of changes in thresholds for CSD initiation in knockin mice with P/Q Ca^{2+} channel mutations (132). Topiramate (112) and flunarizine (32) clearly interact with Ca^{2+} flux, although it must be said immediately that they have other actions. Indeed, topiramate acts on cellular mechanisms of phosphorylation thereby (i) blocking voltage-dependent sodium channels (Na_v); (ii) potentiating GABA activity; and (iii) inhibiting non-NMDA receptor activation, in addition to (iv) blocking L- and N-channel calcium channels. Gabapentin and pregabalin are two gabapentinoids that suppress neuronal excitability by (i) modulating the non–pore-forming $\alpha_2\delta$ subunit of the calcium channel and consequently regulating intracellular calcium influx; and (ii) influencing glutamate and GABA function, perhaps through a complex interaction with the amino acid transporters GAT and BGT. Admittedly, the clinical data for the action of gabapentin in migraine are tenuous. There is good preclinical evidence for the existence of each of the

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L-, P/Q-, and N-type voltage-gated Ca^{2+} channels in the trigeminocervical complex neurons (22,116). They seem to play a role in CGRP release in dura mater (4) and thus provide a link and plausibility to their targeting in migraine therapeutics.

DRUGS THAT ACT ON BRAIN ENERGY METABOLISM

Magnesium, riboflavin (vitamin B_2), and coenzyme Q10 (CoQ10) act on brain energy metabolic pathways and accordingly influence neuronal excitability. For example, magnesium plays a role in the oxidative stress response by modulating the sensitivity of mitochondria to undergo permeability transition. Also, magnesium influences the conductance and gating of multiple ion channels including the NMDA receptor channel. Magnesium can initiate and propagate CSD. Finally, magnesium regulates the sodium pump (Na/K ATPase), which plays a pivotal role in the astrocytic uptake and clearance of glutamate. The clinical data on the role of magnesium supplementation have been conflicting. A recent study suggested that CoQ10 may be effective in migraine (104).

ANGIOTENSIN SYSTEM MODULATORS

Angiotensin participates in various physiologic functions, some of which may be relevant to migraine. For example, angiotensin II constricts blood vessels, increases sympathetic discharge, and causes the release of catecholamine from the adrenal medulla. Angiotensin II may also modulate potassium channels and calcium activity in cells, and increases the expression of inducible NO synthase (128). Acting through the angiotensin II type 1 receptors (AT_1) in the brain, angiotensin modulates cerebral blood flow and helps in regulating autonomic and neuroendocrine functions. AT_1 receptors are presynaptic inhibitors of GABA release. Furthermore, AT_1, glutamate, and GABA receptors are colocalized on medullary neurons of the rostroventromedial nuclei, which suggests that they may participate in nociceptive modulation.

Candesartan is an AT_1 inhibitor that may possess antimigraine activities by enhancing GABA inhibitory tone and, perhaps, by reducing glutamate release. The results of a recent randomized crossover clinical trial indicate that candesartan is effective in migraine prevention (128). This proof-of-principle trial calls for further exploration of these targets in migraine.

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