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Review Article

Migraine: nonvascular/neurally acting drugs as novel treatment strategies*

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CONTENTS

Abstract

Migraine is a common, highly disabling disorder of the brain. It is generally considered to be an inherited disorder so that therapy largely centers on reducing the disability due to the problem through either effective treatment of the acute attack or preventive treatments to reduce headache frequency and severity. The triptan era produced the crucial development of 5-$HT_{1B/1D}$ receptor agonists, which are extremely effective for many patients. The two immediate and substantial unmet needs in migraine therapeutics are effective, nonvasoconstrictor acute attack medicines and effective preventives with minimal side effects. A range of options seems possible based on current science and early proof-of-principle studies. These include 5-HT_{1F} receptor agonists, calcitonin gene-related peptide (CGRP) receptor antagonists, vanilloid TRPV1 receptor antagonists and agents that modify the nitric oxide synthesis cascade. On the preventive side, gap junction blockers are being actively studied, as is botulinum toxin. The future for the development of antimigraine treatments is bright, as are the prospects for better therapeutic outcomes for patients.

Introduction

Migraine is a common (3) and disabling (4) disorder of the brain (5, 6) that has been estimated to cost the European Community more than 27 billion euros per year (7) and the U.S. some USD 19.6 billion (8). Migraine is substantially an inherited disorder (9), so that cure is some way off and therapeutic interventions are currently the best option to minimize disability (10). Recent textbooks provide descriptions of the disorder and its management (10, 11). Based on our current understanding of the disorder (12), agents that modulate trigeminovascular nociceptive traffic may have a role in migraine treatment. In this review I will concentrate on approaches where proof-of-concept studies are completed or have commenced. Approaches with a good scientific rationale but no clinical data have recently been covered elsewhere (13), as have device-based strategies (1). Before reviewing new strategies, I will place the new treatments in the context of what is now available.

Migraine therapies can be considered as acute attack treatments or preventives. Although they are listed as separate entities, there is considerable use of these medicines together based on unproven synergies (14). The widespread use of triptans, 5-HT_1 receptor agonists (15), as abortive antimigraine treatments is supported by substantial controlled-trial literature (16) and clinical experience (11). The most recent development in this area involves combinations of triptans with nonsteroidal antiinflammatory drugs (NSAIDS) or acetaminophen (Table I).

It is generally accepted that triptans influence the trigeminovascular system by a combination of cranial vasoconstriction (17), inhibition of peripheral trigeminovascular nerves (18) and inhibition of second-order trigeminovascular traffic in the trigeminal nucleus (15). This latter site of action has attracted greater interest as sensitization as an explanation for allodynia in migraine (19) has been explored (20), and with the aim of developing nonvasoconstrictor treatments for migraine (13). It also seems possible that triptans can alter trigeminovascular traffic by an action at third-order neurons in the ven-

**Some parts of this review are modified from previous work of the author (1, 2).*

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Table I: Current therapies for migraine by class.*

Indication	Class	Examples
Acute attack therapies	Analgesics**	Acetaminophen (paracetamol)
		Aspirin
		NSAIDs
	Antimigraine agents§	Ergot derivatives
		5-$HT_{1B/1D}$ receptor agonists
		Sumatriptan†
		Almotriptan
		Eletriptan
		Frovatriptan
		Naratriptan
		Rizatriptan‡
		Zolmitriptan
Preventive therapies	Amine modulators	β-Blockers
		Pizotifen
		Methysergide
		Tricylic antidepressants
		MAO inhibitors
	Neuromodulators	Depakote (valproate)
		Topiramate
		Gabapentin
	Calcium channel blockers	Flunarizine
	Metabolic enhancers	Riboflavin
		Coenzyme Q10
	Other	Lisinopril
		Candesartan

*Class distinctions and listings here are somewhat arbitrary because it is unclear how these treatments work. Agents included are based on controlled trials and expert consensus (144), and the list is not exhaustive (10).
**Analgesics are often given with antiemetic prokinetics such as metoclopramide or domperidone.
§These agents are also effective when given by injection or spray in cluster headache (145).
†Some studies suggest that its effect may be enhanced by naproxen (146, 147).
‡A study of the combination of rizatriptan and acetaminophen is in progress (148).

troposteromedial thalamus (21), or by altering the behavior of modulatory neurons in the ventrolateral periaqueductal grey (22).

How preventive therapies work is much less clear, although in principle there is no reason why they would not work on similar structures. There is now evidence that β-blockers can modulate thalamic trigeminovascular nociceptive traffic (23), and the preventive topiramate is able to alter second-order trigeminocervical activation (24). Recently, it has been suggested that inhibition of cortical spreading depression is a common mechanism of action (25). Given that most patients do not have aura, and that there is no preventive therapy with controlled data to suggest that it works better in migraine with aura compared to migraine without aura, this seems a clinically implausible mechanism.

Nonvasoconstrictor 5-HT receptor agonists

Triptans act as agonists at 5-HT_{1B} and 5-HT_{1D} receptors, and in some cases also activate 5-HT_{1F} receptors (15). Given that 5-HT_{1B} receptors mediate the vasoconstrictor actions of triptans (26), drug development has been directed at the neural 5-HT targets, 5-HT_{1D} and 5-HT_{1F} receptors.

5-HT_{1F} receptor agonists

The potent and specific 5-HT_{1F} agonist LY-334370 was developed (27) and shown to block neurogenic plasma protein extravasation in the guinea pig dura mater (28). Activation of 5-HT_{1F} receptors does not appear to lead to vasoconstriction (29-31). LY-334370 is effective in acute migraine, albeit at doses with some central nervous system (CNS) side effects but no cardiovascular disturbances (32). Unfortunately, development was stopped because of animal toxicity.

5-HT_{1F} receptors are found in the trigeminal nucleus (33-36) and trigeminal ganglia (37). 5-HT_{1F} receptor activation is inhibitory in the trigeminal nucleus in rats (38) and cats, although in cats it is apparently less potent than 5-HT_{1B} or 5-HT_{1D} receptor activation (39). Using electron microscopic methods, presynaptic 5-HT_{1F} receptors were found in the trigeminal nucleus of cats (40). Thus, it is expected that 5-HT_{1F} receptor agonists would be nonvascular and useful in migraine. This hypothesis is currently

being tested with COL-144 (LY-573144) (41), a potent and specific 5-HT_{1F} receptor agonist.

5-HT_{1D} receptor agonists

5-HT_{1D} receptor agonists are potent inhibitors of neurogenic dural plasma protein extravasation (42) and have no vascular effects. Peptidergic nociceptors express these receptors (43) in a manner that is activation-dependent (44). Specific and potent 5-HT_{1D} agonists have been developed using nonhuman primate 5-HT_{1B} and 5-HT_{1D} receptor expression (45). PNU-142633, developed using gorilla receptors (46), was a relatively weak agonist when compared to sumatriptan in *in vitro* studies (47) and showed poor brain penetration. PNU-142633 reached clinical studies but proved ineffective (48). There were no complaints of cardiovascular adverse events in the placebo group, whereas cardiovascular adverse events such as chest pain occurred in the PNU-142633-treated group (49). However, as preclinical studies demonstrated a potent 5-HT_{1D} receptor-mediated inhibition of the trigeminocervical complex (39), this mechanism remains plausible, and the lack of efficacy of PNU-142633 may have been due to insufficient brain penetration.

Calcitonin gene-related peptide (CGRP) receptor antagonists

The trigeminal innervation of the cranial circulation contains a number of neuropeptides, of which the most important for migraine appears to be calcitonin gene-related peptide (CGRP) (50, 51). Stimulation of the trigeminal ganglia in cats and humans results in elevations in CGRP and substance P levels in the cranial circulation (52). Similarly, CGRP is elevated during acute attacks of migraine (53, 54) and cluster headache (55, 56), at least in severe and prolonged cases. However, CGRP may not be a useful marker for all migraine attacks, since in less severe attacks, perhaps sampled earlier in the course, levels are not clearly elevated (57).

Interestingly, although CGRP is elevated, substance P is not. Neurokinin NK_1 (substance P) receptor antagonists are not effective in either acute attacks or in the prevention of migraine in controlled trials (58). Nitroglycerin-induced migraine, which is very similar to spontaneous attacks (59, 60), is also associated with increased plasma levels of CGRP (61).

Triptans inhibit CGRP release in the superior sagittal sinus of rats (62) and the spinal cord of cats (63). Triptans also inhibit the release of CGRP into the cranial circulation of experimental animals evoked by trigeminal ganglion activation (64, 65). Similarly, stimulation of the superior sagittal sinus in cats leads to cranial release of CGRP (66), which can be blocked by triptans but not by specific inhibitors of neurogenic dural plasma protein extravasation (67, 68). Interestingly, triptans also influence the CGRP promoter (69) and regulate CGRP secretion from neurons in culture (70). Moreover, nitric oxide (NO) donors can trigger CGRP release from the trigeminal ganglia via T-type calcium channels (71). These data indicate that a CGRP receptor antagonist may also have nonvascular antimigraine effects.

The successful treatment of acute migraine (65) or cluster headache (55, 56) with sumatriptan normalizes cranial CGRP levels (51). Moreover, local microiontophoresis of BIBN-4096BS, a potent CGRP blocker (72-74), inhibits trigeminocervical neurons *in vivo* (75). BIBN-4096BS was shown to be effective in the treatment of acute migraine (76) and is devoid of vasoconstrictor actions in humans (77). The response rate in a clinical trial of 66% compared to the placebo response rate of 27% was less than that for injected sumatriptan (78). At least one other nonpeptide CGRP antagonist has been reported (79). Other strategies to block the effects of CGRP include so-called RNA-Spiegelmers, or single-stranded mirror-image oligonucleotides highly resistant to nuclease degradation and which bind to CGRP (80-82), or monoclonal antibodies directed to CGRP. Such anti-CGRP strategies may have preventive effects in addition to efficacy against acute attacks, and further study is warranted.

Vanilloid receptor TRPV1 antagonists

Capsaicin is the pungent ingredient in hot chilli peppers that activates the vanilloid receptor (TRPV1, previously called VR1) (83). TRPV1 receptors are located on small- and medium-sized neurons that are either unmyelinated C-fibers or thinly myelinated Aδ-fibers (84). TRPV1 receptors are found on neurons in the trigeminal and dorsal root ganglia (85, 86). Intravenous capsaicin promotes the release of the proinflammatory neuropeptides substance P and neurokinin A (NKA) from trigeminal neurons and causes dural extravasation in the rat (87). TRPV1 immunoreactivity has been found in 16% of total neuronal cell bodies in human trigeminal ganglia, a small proportion of which show co-localization with CGRP (88). The TRPV1 receptor is thus considered a target for the development of antimigraine compounds.

Electrical stimulation, CGRP and capsaicin bolus injections each produce a reproducible dural vessel dilatation measured by intravitral microscopy in rats. The capsaicin-induced dilatation can be inhibited by the TRPV1 antagonist capsazepine to a moderate degree (89). Capsaicin-induced dilatation is also inhibited by the CGRP receptor blocker $CGRP_{8-37}$ (89), which was previously shown to inhibit both CGRP- and electrically induced dilatation of dural blood vessels (90-93). Interestingly, anandamide interacts with TRPV1 mechanisms in the dura mater to produce vasodilatation (94). However, relatively few trigeminal ganglion cells produce TRPV1 receptors, perhaps only about 16% (88), and the dural vascular effects of anandamide appeared to be small in comparison to, for example, CGRP. It would seem crucial to determine whether, or indeed the extent to which, manipulation of TRPV1 receptors can inhibit trigeminal neurons centrally. The potent TRPV1 antagonist SB-705498 (95) is currently undergoing a phase II study in acute migraine.

Nitric oxide (NO) as a target for antimigraine drug development

The role of NO in migraine has been extensively evaluated (96-98), as has the role of NO in many biological systems (99). It is thought that nitroglycerin triggers migraine by dilating cranial vessels (100). However, two recent observations suggest that dilatation is an epiphenomenon. First, nitroglycerin triggers premonitory symptoms in many patients (60) which are no different from those reported in spontaneous attacks (101) and occur well after any vascular change would have occurred. Second, downstream activation of the cGMP pathway by sildenafil can induce migraine without any change in middle cerebral artery diameter (102). Taken together, these observations suggest that while NO may play a role in the pathophysiology of migraine, it may not exert a vascular effect. For example, a role for inducible NO synthase (iNOS) has been suggested (103), and blockade of NOS has been reported to inhibit trigeminocervical complex *fos* expression (104). Indeed, iNOS inhibition with GW-274150 results in analgesic properties in rat models (105). A more complete analysis of the preclinical rationale for NOS inhibition in terms of trigeminovascular nociception was recently published (106).

NOS inhibition using a nonselective inhibitor has been shown in a small study to abort acute migraine (107), although this study suffered from the design flaw of not having entirely contemporaneous controls. GW-274150 is a potent, selective iNOS inhibitor with good oral bioavailability (108). Again, there are no data on its ability to inhibit nociceptive trigeminovascular transmission in the trigeminocervical complex, although given its mechanism this would appear unlikely. The compound has entered an acute attack trial and a preventive trial (109, 110).

Inhibitors of cortical spreading depression (CSD)

Cortical spreading depression (CSD) is a neuroelectric phenomenon first described in the rabbit cortex (111, 112), which is thought to underlie migraine aura (113, 114). Tonabersat (SB-220453) is a CSD inhibitor that has entered clinical trials for migraine. Tonabersat inhibits CSD, CSD-induced NO release and cerebral vasodilatation (115, 116). Tonabersat does not constrict isolated human blood vessels (117), but does inhibit trigeminally induced craniovascular effects (118). Whether this compound proves useful in clinical trials is currently being determined (119). Remarkably, topiramate, an agent proven effective in preventing migraine (120-122), also inhibits CSD in cats and rats (123). Tonabersat is inactive in the human NO model of migraine (124), as is propranolol (125), whereas valproate showed some activity in this model (126). Topiramate inhibits trigeminal neurons activated by nociceptive intracranial afferents (24) and antimigraine agents block CSD upon chronic intake (25), indicating that CSD inhibition may be a promising target for antimigraine drug development.

Botulinum toxin

The injection of botulinum toxin into cranial structures for the treatment of headache disorders has been widely studied. Botulinum toxin type A inhibits the release of acetylcholine at motor nerve terminals (127), which led to its use in the treatment of movement disorders such as dystonia (128), and to its cosmetic use for forehead and other facial wrinkles. Open-label trials for the cosmetic indications suggested that it was useful in headache prevention. Subsequent basic experimental studies revealed antinociceptive properties in some standard models, such as formalin-induced pain in rats (129), and provided a rationale for its development for headache prevention (130). Given the remarkable unreliability of translating open-label studies to controlled clinical trials in headache, the data presented below are from controlled trials only.

Botulinum toxin has been studied in chronic tension-type headache, where controlled studies have consistently failed (131, 132). Studies of migraine have been difficult to interpret, although generally negative results have been obtained. The first controlled study was positive for the lower dose (25 units) and negative for the higher dose (75 units) compared to placebo (133). Four subsequent placebo-controlled studies in a total of 843 patients were negative (134-137). One small study gave a positive outcome (138); it is unclear what was different about this latter study. Overall, botulinum toxin appears to be ineffective in episodic migraine. Two large studies in a total of 1,057 patients with chronic daily headache have been reported. Both were negative for the primary endpoint of days with headache (139, 140). Subgroup analysis suggested that headache frequency was reduced in patients who were not on other preventive therapies (141). Botulinum toxin remains in clinical trials for chronic migraine, and time will tell if it is effective as a preventive treatment.

A promising development may be clinical phenotyping of the pain that patients experience since an exploratory analysis of patients treated with botulinum toxin suggests that those with a headache that feels “exploding” do not respond and those whose headaches feel tightening or imploding do (142). It would be most interesting if such a distinction were the explanation for the clinical observations of so many (143).

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