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## Molecular mechanisms of antimigraine drugs: past, present, and future

**Abstract** Pharmacotherapeutic treatments for migraine have been documented for more than a century. Drugs that are effective in aborting an ongoing migraine attack exhibit a diversity of molecular mechanisms of action, but usually produce constriction of cranial arterial blood vessels, reversal of neurogenic inflammatory processes, and/or inhibition of sensory neuronal firing. This general understanding of drug action has led to the development of a unitary hypothesis for migraine pathophysiology, in which the onset of migraine is associated with activation of the trigemino-vascular system. Drugs which inhibit or reverse the activation of this system are effective acute treatments for migraine. Drugs useful in migraine prophylaxis have been discovered largely serendipitously, and display a fundamentally different pharmacology to the acutely effective agents. These drugs act at membrane receptors and ion channels, or by targeting intracellular biochemical pathways, and tend to reduce neuronal excitability in higher centers of the CNS. However, other than to suggest that this inhibits various migraine trigger events, it is not yet possible to delineate pre-

cisely how these drugs act to decrease the frequency and severity of migraine attacks. More recently, it has been observed that migraine is accompanied by sensory neuronal central sensitization that manifests as cutaneous allodynia in territory innervated by the trigeminal nerve. Although little is presently known about the ability of prophylactic drugs to modulate this process, it was recently shown that acute relief of migraine with triptan drugs is only reliably achieved when the drugs are given prior to the development of central sensitization. This important observation suggests that inhibition of migraine-related central sensitization could be an important new focus for future drug discovery, and may, for the first time, provide a rational target for the development of preventative medicines.

**Key words** Trigemino-vascular system • Migraine • Acute treatment • Prophylaxis • Pathophysiology

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## Introduction

The modern view of migraine, and of the molecular mechanisms of drugs that are used to treat this disorder, draws on a well-documented history of pharmacotherapy that goes back more than 100 years [1]. Perhaps because of this, coupled with the polysymptomatic nature of the disorder, drug treatments have evolved down several different paths. Numerous prophylactic regimens now exist, with apparently multiple mechanisms of action, that aim to reduce the frequency and severity of attacks in the frequent migraineur (>3 attacks monthly). These regimens are fundamentally different in purpose and pharmacology from those used acutely to abort attacks once they have started. Indeed, the molecular mechanisms of action for most acutely effective antimigraine drugs appear to be better understood, being spearheaded by well-established cyclo-oxygenase inhibitors on the one hand and the “triptan” serotonin 5-HT<sub>1B</sub> receptor agonists on the other. Finally, treatment regimens have also evolved that focus on treating the autonomic dysfunction (nausea, vomiting, sensory perception changes) that sometimes precedes or accompanies an attack [2].

Any attempt to understand the fundamental pathophysiology of disease has, as one aim, the design of even more effective and well-tolerated treatments. This requires an in-depth understanding of the pharmacology of drugs currently effective in the treatment-or aggravation-of the disorder. This brief overview highlights some of the significant advances that have been made in migraine pharmacotherapy in the last century and considers how this information is now being used to drive the discovery of the next generation of therapeutics and to obtain a more comprehensive understanding of the disordered biochemistry that underlies this debilitating condition.

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## Drugs used to treat nonpainful migraine symptoms

Numerous drugs have been used to alleviate the severe, throbbing head pain of a migraine attack, but in some individuals nausea, vomiting, and sensory disturbances can be equally disruptive. In some cases, these symptoms merit treatment in their own right, although more often they are treated simultaneously with the headache. Drugs that moderate nausea, and hence vomiting, include domperidone, a modulator of dopaminergic pathways, and metoclopramide, a mixed 5-HT<sub>3</sub> receptor antagonist/5-HT<sub>4</sub> receptor partial agonist. The primary therapeutic benefit from metoclopramide derives from its ability to accelerate the absorption of oral antimigraine drugs such as aspirin,

by exerting prokinetic effects in the upper gastrointestinal tract to overcome the effects of migraine-induced gastric stasis [2].

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## Drugs used to treat an ongoing attack

About two-thirds of migraineurs rely upon acute intervention to abort an ongoing or emerging migraine attack. Ergot was the first chemical substance documented to be effective in treating migraine acutely more than a century ago, although in the following decades, aspirin, cannabis, opium, and various ergot derivatives were also found to be effective drug treatments. For many years, aspirin and newer nonsteroidal anti-inflammatory drugs (NSAIDs) have been a mainstay of acute treatment, with opiate drugs such as butorphanol (Stadol) or systemically administered ergotamine or dihydroergotamine (DHE) reserved for severe or intractable migraine attacks. However, in the last decade, selective 5-HT<sub>1B</sub> receptor agonist drugs heralded by sumatriptan have assumed preeminence in the treatment of acute migraine attacks [3].

In general, drugs useful in acute treatment of migraine fall into three broad pharmacological categories: anti-inflammatory cyclo-oxygenase inhibitors, analgesic opiate mu receptor agonists, and vasoconstrictor serotonin 5-HT<sub>1B</sub> receptor drugs (ergot derivatives and triptans). The pharmacological diversity of these drugs indicates that the course of a migraine attack involves an inflammatory response, a neuronal component presumably responsible for the transmission of afferent nerve traffic, and a cranial vascular component. These apparently distinct facets of a migraine have resulted in the modern view that activation of a “trigeminovascular complex” (the trigeminovascular system) underlies an attack, and that any intervention which normalizes activity of this complex will provide relief from the primary symptoms of migraine (see below).

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## Drugs used to reduce attack frequency and severity

In frequent severe migraine (>3 attacks monthly), the therapeutic aim is to reduce attack frequency and/or severity using preventative medication. Most of the drugs currently used in this way have been discovered serendipitously, so that heavy off-label use of drugs designed to treat other indications is presently the norm. Various categories of drugs have found utility as migraine prophylactics, most notably certain  $\beta$ -blockers (propranolol, nadolol, atenolol, timolol, metoprolol) and a variety of

cation channel antagonists used to treat neuro-excitatory conditions (flunarizine, verapamil, topiramate, divalproate). However, drugs modulating monoaminergic transmission indirectly (SSRIs, tricyclic antidepressants, MAO inhibitors) or directly (methysergide) have also found widespread use, as have a number of treatments that in some way modulate cellular metabolism [ $Mg^{++}$ , riboflavin (Vit B<sub>2</sub>)] [4]. Most recently, botulinum toxin type A has been shown to reduce the frequency, severity, and disability associated with migraine headache, although the mechanism(s) are not well understood [5].

Clearly, drugs useful in migraine prophylaxis share few pharmacological mechanisms in common, and exhibit effects that are fundamentally different from drugs used to treat migraine acutely. At this time, it remains unclear how this tapestry of pharmacological effects results in a reduced frequency and severity of attacks. However, it seems intuitive that in some way they act to “stabilize” neuronal processes, or trigger events, that in some way underlie attack initiation.

### Pathophysiology of migraine

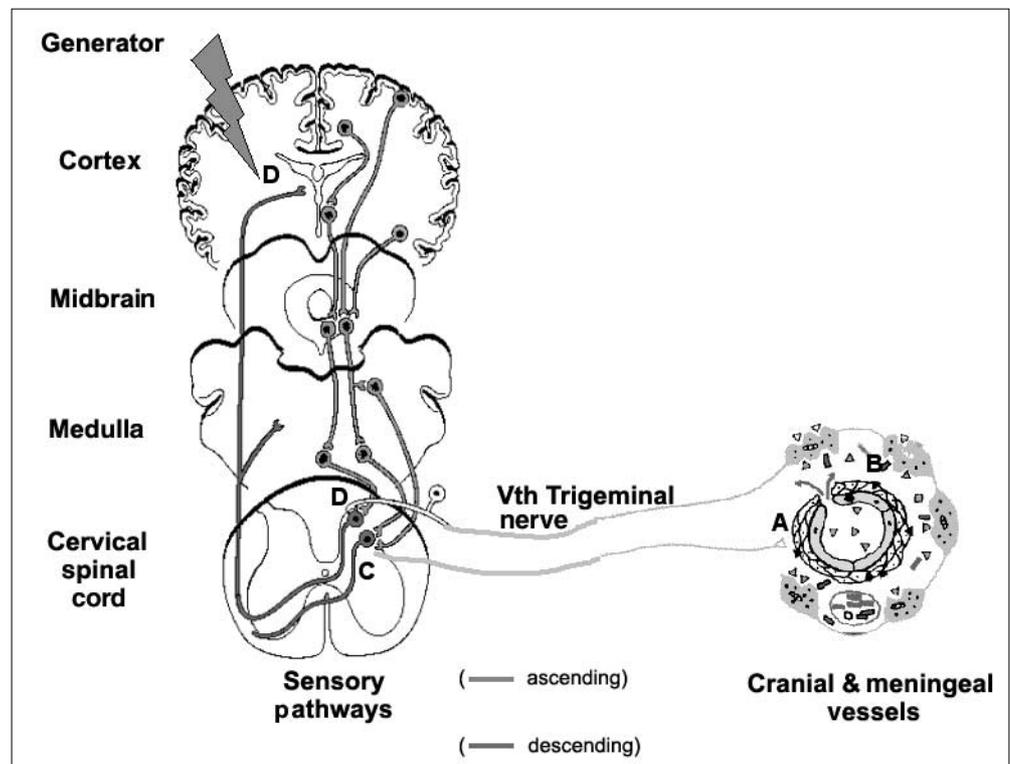
It is clear from the forgoing that multiple mechanisms of drug action are involved in either aborting an ongoing migraine or reducing the frequency and/or severity of

attack occurrence. Over the years, this diversity of drug effects has resulted in discrete biochemical, vascular, and neuronal theories of migraine pathogenesis. However, the cause of this debilitating condition most likely involves elements of each hypothesis which can be synthesized into a unitary scheme, in which migraine is triggered by activation of the trigemino-vascular system, and is effectively treated by drugs that turn off or dampen hyperactivity of this system [6].

Figure 1 illustrates the components of the trigemino-vascular system, and the points at which antimigraine drugs are believed to inhibit activation. Drugs effective in acute treatment act at one or more of three key components of the system:

1. Meningeal and cerebral arterial blood vessels: ergot derivatives and the triptan 5-HT<sub>1B</sub> receptor agonists all potently constrict these vessels, and are thought to reverse vessel dilation that accounts for the throbbing nature of migraine headache.
2. Perivascular trigeminal sensory afferent neurons: at the onset of an attack, antegrade activation of these neurons, which innervate the meningeal and cerebral arteries, results in the release of neuropeptides (CGRP and substance P) into the perivascular space to initiate a sterile inflammatory response in the blood vessel wall. Consequently, the vessels dilate and the sensory nerve terminals become sensitized to nociceptive stimuli. Acutely effective drugs either inhibit the

**Fig. 1** Elements of the trigemino-vascular system, illustrating points of antimigraine drug intervention. Drugs effective in acute treatment have been shown to produce constriction of meningeal and cerebral arteries (A), inhibition of neurogenic inflammation as well as the accompanying release of sensory neuropeptides (B), and/or inhibition of second-order sensory nerve processing within the caudal trigeminal nucleus (C). Drugs effective in preventative treatment have less well-defined sites of action, but probably act at higher centers in the brain to dampen neuronal excitability and inhibit migraine trigger events (D)



inflammatory process (NSAIDs) or inhibit sensory nerve activation directly (5-HT<sub>1B</sub> agonists, opiates, cannabinoids).

3. Ascending second-order sensory neurons in the trigeminal nucleus cordalis: centrally acting 5-HT<sub>1B</sub> receptor agonist drugs such as zolmitriptan and rizatriptan have been shown to inhibit the activation of second-order sensory neurons, presumably through prejunctional inhibition of transmitter release from the incoming primary afferents. It is likely that mu receptor agonists also produce this effect, and conceivable that NSAIDs likewise inhibit second-order afferents by reducing neurogenic inflammation within the dorsal horn of the spinal cord.

Dugs effective in migraine prophylaxis have a less well-defined interaction with the trigemino-vascular system. First, it is clear that these drugs do not produce cranial vascular effects, do not inhibit neurogenic inflammation, and do not appear to modulate directly activity in first- and second-order sensory afferent neurons. Instead, these drugs are thought to modulate systems within the CNS that are presumed to trigger a migraine by activating the trigemino-vascular system. While the primary molecular mechanisms of action for these drugs are understood, precisely how these effects modulate migraine trigger mechanisms remains obscure. However, the fact that these drugs require up to 6 weeks to become fully effective suggests that they induce adaptive changes in CNS pathways that are in some way involved in migraine initiation in susceptible individuals.

### Future of migraine pharmacotherapy

There remains a substantial need for safe, highly effective antimigraine drugs. However, the ability to design novel drugs that will address the current unmet therapeutic needs requires a better understanding of migraine pathophysiology. In this regard, the recent work of Burstein and colleagues [7, 8] offers some interesting insights. A combination of preclinical and clinical experiments suggests that central sensitization can develop during a migraine attack, and this manifests as a cutaneous allodynia with receptive fields that map dominantly to the trigeminal nerve. Interestingly, in patients in whom central sensitization has already developed, triptan drugs are much less effective [8]. However, triptans are effective if administered prior to the development of central sensitization. These exciting data suggest that early drug treatment should maximize clinical benefit with acutely effective drugs, especially members of the triptan class [8]. Perhaps more intriguing, they also provide a rational basis for studying the effect of drugs effective in preventative treatment. Many of the drugs presently used for migraine prophylaxis modulate neuronal activity directly or indirectly, therefore it is not unreasonable to suspect that they too may act by inhibiting the development of central sensitization. Should further experimental work confirm that this is an important component of existing prophylactic drug action, a novel, physiologically specific target for new preventative drugs will be suggested for the first time.

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