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Chemical Mediators of Migraine: Preclinical and Clinical Observations

Saurabh Gupta, PhD,

Glostrup Research Institute, Glostrup Hospital, Faculty of Health Science, University of Copenhagen, Glostrup, Denmark

Stephanie J. Nahas, MD, and

Thomas Jefferson University, Philadelphia, PA, USA

B. Lee Peterlin, DO

Johns Hopkins University, Bayview, Baltimore, MD, USA

Abstract

Migraine is a neurovascular disorder, and although the pathophysiology of migraine has not been fully delineated, much has been learned in the past 50 years. This knowledge has been accompanied by significant advancements in the way migraine is viewed as a disease process and in the development therapeutic options. In this review, we will focus on 4 mediators (nitric oxide, histamine, serotonin, and calcitonin gene-related peptide) which have significantly advanced our understanding of migraine as a disease entity. For each mediator we begin by reviewing the preclinical data linking it to migraine pathophysiology, first focusing on the vascular mechanisms, then the neuronal mechanisms. The preclinical data are then followed by a review of the clinical data which support each mediator's role in migraine and highlights the pharmacological agents which target these mediators for migraine therapy.

Keywords

migraine; 5-HT; CGRP; NO; histamine

INTRODUCTION

Migraine is a neurovascular disorder, and although the pathophysiology of migraine has not been fully delineated, much has been learned in the past 50 years. This knowledge has been accompanied by significant advancements in the way migraine is viewed as a disease process and in the development therapeutic options. In this review, we discuss the preclinical and clinical observations for 4 mediators which have significantly advanced our understanding of migraine as a disease entity and have been identified as targets toward which migraine-specific therapy is directed. These mediators are nitric oxide (NO),

histamine, serotonin (5-HT), and calcitonin gene-related peptide (CGRP). For each mediator we begin by reviewing the preclinical data linking it to migraine pathophysiology, first focusing on the vascular mechanisms, then the neuronal mechanisms. The preclinical data are then followed by a review of the clinical data which support each mediator's role in migraine and highlights the pharmacological agents which target these mediators for migraine therapy.

5-HT AND MIGRAINE

Serotonin, or 5-hydroxytryptamine (5-HT), was first isolated from human blood in 1948¹ and its structure was deciphered within the following year.² The pleiotropic effects of 5-HT are matched by its extensive distribution in the body and its multiple receptor subtypes. As a result, and depending on the nature of the 5-HT receptors involved, 5-HT elicits an array of physiological and pharmacological actions, many of which are opposing responses, such as hypotension or hypertension, vasodilatation or vasoconstriction, and bradycardia or tachycardia.³

Although there are at least 14 known 5-HT receptors, the best characterized include the 5-HT₁ (subdivided into 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, and 5-HT_{1F} subtypes), 5-HT₂ (sub-divided into 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} subtypes), 5-HT₃, 5-HT₄, 5-HT₅, 5-HT₆, and 5-HT₇ receptors.⁴ All of these receptors (with the exception of the 5-HT₃ receptors) are coupled to G_{i/o}, a protein that inhibits adenylyl cyclase activity.^{5,6} The 5-HT₁, and to some extent the 5-HT₂ receptors, are of prime interest in migraine.^{7,8}

The 5-HT receptors are widely expressed in the trigeminal vascular system (TVS). In the vasculature, messenger RNA (mRNA) and protein expression of the 5-HT_{1B} receptor (and to a lesser extent the 5-HT_{1D} receptor), have been detected in human cerebral arteries.⁹ Additionally, 5-HT_{1B} mRNA expression has also been detected in coronary arteries. In contrast to the 5-HT_{1B/1D} receptors, minimal mRNA transcripts of 5-HT_{1F} receptors have been detected in human cerebral arteries.¹⁰ At the neuronal level, all 3 receptors (5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1F}) have been identified in both the trigeminal ganglion (TG)^{9,11,12} and the trigeminal nucleus caudalis (TNC).^{13,14} Thus, 5-HT_{1B/1D/1F} receptor agonists, such as the triptans, are capable of acting at both at the vascular and neuronal levels.

To fully appreciate 5-HT's role in the genesis and treatment of migraine, and in view of its paradoxical pharmacology, which is guided by its differential distribution of its receptor subtypes, in the following sections we will discuss the preclinical and clinical data implicating 5-HT in migraine pathophysiology. The Table briefly describes the various preclinical models discussed in this review in the following sections.

Preclinical Studies

Vascular Actions of 5-HT and Its Receptors—The success of therapeutic interventions like methysergide, a 5-HT_{2B} receptor antagonist, and ergotamine, a 5-HT_{1A/1B/1D/1F/2A/2B} agonist, in migraine treatment spurred the early research at a pharmacological level. *In vitro* models, using segments of cranial blood vessels, which are innervated with 5-HT and its receptors, provided an optimum starting point. The spiral strips

of cranial arteries from cows, dogs, and humans showed concentration-dependent contractions to 5-HT and ergotamine.¹⁵ Importantly, Owman and co-workers¹⁶ discovered that there were significant differences in the reactivity of cranial and non-cranial blood vessels to 5-HT, thus presenting a pharmacological opportunity to target intracranial blood vessels selectively to elicit an antimigraine action. Within cranial arteries, contractile effects of 5-HT_{1B/1D} receptor agonists like sumatriptan were more pronounced in human meningeal artery segments compared to cerebral or temporal arteries, and these responses were much less pronounced in peripheral arteries.¹⁷ Additionally, the 5-HT_{1B/1D} receptor agonist zolmitriptan has been shown to contract the primate basilar artery 2–3 times more potently than its lesser lipophilic analog, sumatriptan.¹⁸ In contrast, the 5-HT_{1F} receptor agonists in various vascular models have shown no or a very limited potential to induce contractile responses.^{19–21}

While the contractile effects of the 5-HT₁ receptor agonists on cranial blood vessels substantiated the development of triptans, based on the vascular theory of migraine, it also highlighted the risk of similar effects on other vasculatures, especially that of the coronary arteries. Both sumatriptan and avitriptan (a triptan which has not been marketed) have been reported to constrict isolated human coronary arteries.²² However, therapeutic concentrations of both eletriptan and sumatriptan have been demonstrated to contract middle meningeal artery segments to a higher degree as compared to the very small contractile response produced in the coronary arteries.²³ Therefore, in individuals without cardiac disease, it is unlikely that therapeutic concentrations of triptans can precipitate myocardial ischemia by coronary constriction. However, caution needs to be exercised when prescribing triptans to individuals with cardiac conditions, as rare cases of myocardial infarction²⁴ and arrhythmia²⁵ have been associated with their use.

In agreement with the *in vitro* studies, *in vivo* models have also underscored the role of 5-HT in migraine. In porcine carotid arteriovenous anastomotic shunt models,^{26,27} sumatriptan dose-dependently decreased the total common carotid blood flow. This effect is likely to be mediated via constriction of the carotid vasculature,²⁸ and was demonstrated to be elicited by 5-HT_{1B} and not 5-HT_{1D} receptors.²⁹ Sumatriptan has also been shown to decrease TG stimulation-induced increased blood flow in the TNC.³⁰ Furthermore, triptans have also demonstrated their efficacy against neurogenic vasodilatation induced by transcranial electrical stimulation, but not by the vasodilation induced by exogenous CGRP in rats^{31,32} in a closed cranial window model. It should be noted that the dilations caused by transcranial electrical stimulation are predominantly mediated by CGRP stored in the perivascular nerves of meningeal artery.³³ Taken together, these studies point toward presynaptic actions of triptans on 5-HT_{1B/1D} to inhibit antidromic stimulation-induced CGRP release. A final mechanism proposed for the antimigraine action was based on success of the selective 5-HT_{1D} receptor agonist to inhibit plasma protein extravasation.³⁴ However, as this class of agonists proved ineffective as acute antimigraine agents, this pathway seems to have a limited contribution to antimigraine actions of the 5-HT_{1B/1D} agonists.³⁵

Neuronal Mechanisms of 5-HT and Its Receptors—In the past 2 decades there has been a paradigm shift in the theory of the pathogenesis of migraine, from one of being a predominantly vascular disease to a predominantly neuronal disease. The animal models

which measure the neuronal activity after the stimulation of meninges, superior sagittal sinus (SSS), or TG have been instrumental in this shift. SSS stimulation in cats has been demonstrated to induce increases in TNC activity, which is attenuated by naratriptan, and reversed by the 5-HT_{1B/1D} antagonist GR127935.³⁶ Lambert and co-workers similarly showed that eletriptan decreased the enhanced neuronal firing in the brain stem using a glyceryl trinitrate (GTN) provocation model in cats.³⁷ It has also been demonstrated that increased brainstem neuronal activity in the nucleus tractus solitarius and ventrolateral periaqueductal grey is attenuated after triptan treatment.^{38,39}

5-HT has also been implicated in cortical spreading depression (CSD). In rats subjected to 5-HT depletion, there was an increase in number of CSD waves generated as compared to the respective control.⁴⁰ As 5-HT_{1B/1D/1F} receptors have been co-localized with glutamate in TG neurons,⁴¹ these receptors are aptly placed to inhibit glutamate release. This observation becomes more significant in light of the findings that the minor allele of rs1835740 is associated with migraine with and without aura⁴² and that rs1835740 is located between astrocyte-elevated gene-1 and the gene encoding for plasma glutamate carboxypeptidase, both of which are associated with glutamate homeostasis.

Besides electrophysiological recordings, neuronal activity can also be indexed by expression of c-Fos, which is a non-specific marker for increased neuronal activity. It is important to note that the use of c-Fos as an index of antimigraine activity is influenced by differences in the species employed as well as stimulation paradigms, and the predictable validity of this parameter is not without limitations. However, several c-Fos studies have reported pertinent and interesting findings.

Dihydroergotamine⁴³ and sumatriptan⁴⁴ both are reported to decrease expression of c-Fos in the TNC after SSS stimulation in cats. Interestingly, in the same model, when a restricted analog of sumatriptan (without 5-HT_{1B} receptor-mediated vasoconstrictor actions) was administered, there was no significant attenuation in c-Fos expression in TNC, even after blood brain barrier (BBB) disruption.⁴⁵ This indicated that the 5-HT_{1B} receptor activity is an essential feature of triptans' antimigraine action. Additionally, 5-HT_{1F} agonists are also reported to suppress c-Fos expression^{21,46} and a 5-HT_{1F} receptor agonist was reported to be effective in the acute treatment of migraine.⁴⁷

Clinical Studies with 5-HT

Pre-Triptan Clinical Trials—As the first signaling molecule to be implicated in migraine pathogenesis, 5-HT can be credited for fueling the early migraine research. Soon after its discovery, Ostfeld and co-workers⁴⁸ reported that temporal perivascular administration of 5-HT induced attacks similar to “clinical migraine,” whereas i.v. injection of 5-HT was reported elsewhere to relieve spontaneous migraine attacks.⁴⁹ Kimball and Friedman⁵⁰ also showed that reserpine, a 5-HT depleter, can induce migraine which was relieved by 5-HT infusion. During a migraine attack, 5-HT turnover increases significantly in the plasma^{51,52} and saliva.⁵³ Additionally, increases in the levels of 5-hydroxyindoleacetic acid, a major metabolite of 5-HT, have also been reported in the cerebrospinal fluid of migraineurs during acute attacks.⁵⁴

In contrast, interictal levels of plasma serotonin have been shown to be low in migraineurs.^{4,55,56} In addition, a recent interictal neuroimaging study showed an increased availability of 5-HT transporters in the brainstem of migraineurs. Taken together, these findings suggest an imbalance of the brainstem serotonergic system with the hypothesis that migraine is a syndrome of chronically low serotonin, with migraine attacks triggered by a sudden raise in 5-HT release.^{57–59}

Triptan Trials—The basic science and translational research demonstrating the involvement of 5-HT and its receptors in migraine ultimately led to the development of the triptans, a class of drugs now considered the gold standard for acute abortive therapy of migraine. In the first clinical trial of GR43175, now known as sumatriptan, an i.v. infusion showed rapid and complete relief in 71% of attacks.⁶⁰ This study was subsequently followed by a series of clinical trials, which repeatedly demonstrated the efficacy of sumatriptan as well as of other triptan analogs. Although all the triptans exert their effect through the 5-HT_{1B/1D/1F} receptors, each triptan has a distinctive pharmacokinetic and receptor affinity profile that determines its efficacy and tolerability. When compared, most of the triptans demonstrate a similar therapeutic gain when administered at doses recommended by manufacturer,⁶¹ although s.c. sumatriptan has the highest therapeutic efficacy (For a full review of the efficacy and tolerability of all triptans, the reader is referred to previously published reviews as this is beyond the scope of the current manuscript. See Loder, Bigal et al, and Ramadan et al.^{61–63}).

Two non-triptan 5-HT receptor agonists have been shown to demonstrate efficacy in migraine. Alniditan, a non-triptan compound, is also a 5-HT_{1B/1D} agonist with minimal affinity toward 5-HT_{1F} receptors,⁶⁴ and has been found to be an effective antimigraine agent.⁶⁵ Additionally, an analog of alniditan, lasmiditan (COL-144/LY573144) has been proven to be efficacious in the abortive treatment of migraine in a randomized proof-of-concept trial.⁶⁶ On the other hand, early clinical trials with the 5-HT_{1F} agonist LY334370 showed significant therapeutic gains in acute migraine treatment and with mild to moderate associated adverse events.⁶⁷ However, the development of LY334270 was arrested at the proof of concept level because of compound-specific concerns in long-term exposure.

Observations of cerebral, carotid, and pial blood vessel changes during acute migraine attacks have provided valuable insights into the site and mechanism of action of 5-HT and triptans. The middle cerebral artery (MCA) on the side ipsilateral to head pain was reported to dilate by approximately 20% as compared to the unaffected side of migraineurs, and sumatriptan normalized the blood flow in the headache side with simultaneous relief from the symptoms.⁶⁸ GTN-induced migraine attacks led to a decrease in blood flow velocity in the MCA which normalized after triptan treatment.⁶⁹ Along with the MCA, sumatriptan is also reported to increase the blood flow in the internal carotid artery (indicating vasoconstriction), in responders and non-responders alike. Therefore, vasoconstriction is likely not to be the primary mode of action of 5-HT_{1B/1D} agonists in migraine pain relief.⁷⁰ Recently, Schoonman and co-workers⁷¹ innovated a technique to measure diameter changes in meningeal artery in migraineurs. Interestingly, they did not observe any dilation in the second phase of headache provoked by GTN infusion. In contrast, with an improved version of the same technique (although using a CGRP-provoked migraine model), dilation in the

meningeal artery *was* observed, normalized following sumatriptan treatment, and was concomitant with pain relief.⁷² Therefore, the debate whether meningeal arteries dilate during migraine attack, and so, contribute to nociception, is not settled yet. Further studies measuring the diameter of the human meningeal artery during a migraine attack, after migraine-specific treatment, and during the interictal phase are needed to correlate the predictability of vascular models to clinical observations.

The exact mode of action of triptans is still under scrutiny. In view of the localization of 5-HT receptors in TVS, and the preclinical observations and clinical data reviewed above, the following modes of action have been proposed: (1) inhibitory actions (eg, inhibition of glutamate/CGRP release) in the central nervous system, particularly in the TNC and even at higher brain centers like ventrolateral periaqueductal grey; (2) prejunctional trigeminovascular inhibition of release of signaling molecules like CGRP at the level of cranial extracerebral arteries; and (3) a direct vasoconstrictor action on meningeal and cerebral arteries. A similar mode of action can be attributed to 5-HT_{1F} receptors agonists, with the notable exception of a lack of vasoconstrictive activity.^{19,21}

CALCITONIN GENE-RELATED PEPTIDE AND MIGRAINE

Calcitonin gene-related peptide, the most potent endogenous vasodilator, is a 37 amino acid peptide discovered in 1980.⁷³ CGRP exists in 2 isoforms, h- α CGRP and h- β CGRP, differing only by 3 amino acids. In humans these isoforms have similar biological actions.^{74,75} However, α CGRP is localized in primary afferents throughout the body, whereas β CGRP expression is primarily restricted to the enteric autonomic sensory system.⁷⁶

Calcitonin gene-related peptide's c-terminal end determines receptor affinity. The n-terminal portion is responsible for signal transduction. Therefore, CGRP₈₋₃₇, which is an n-terminal fragment, acts as an antagonist for the CGRP receptors. CGRP transduces its action through a heteromer, CGRP₁ receptor, comprised of (1) the calcitonin receptor-like receptor (CLR); (2) a receptor component protein; and (3) an accessory protein known as receptor activity-modifying protein 1 (RAMP1).^{77,78} RAMP1 endows the receptor with the specificity for CGRP (other RAMP members, such as RAMP2 and RAMP3, form complexes with CLR, which result in the adrenomedullin receptors 1 and 2, respectively).⁷⁷ RAMP1 also promotes the expression of CLR receptors on the cell membrane, as well as determines the selectivity of CGRP antagonist in different species. Over-expression of human RAMP1 in mice has been demonstrated to accompany light avoidance behavior induced when CGRP was injected intracerebroventricularly.⁷⁹ This phenomenon appears to be similar to the photophobia which often is experienced during migraine attacks.⁷⁹

The CGRP receptor belongs to the family B of G protein-coupled receptor which activates adenylate cyclase and ultimately leads to increased intracellular cyclic adenosine monophosphate (cAMP). However, other transduction mechanisms have also been associated with the activation of CGRP receptors.⁸⁰⁻⁸² CGRP is present in perivascular afferents in cranial arteries which project into the brain stem, including the TNC via the TG.^{83,84} Stimulation of peripheral and central trigeminal processes leads to CGRP release.⁸⁵ Within the human TG 40% of neurons are CGRP-positive.⁸⁶ A similar distribution has also

been detected for the CGRP receptors throughout TVS, both postsynaptically and presynaptically, with the exception that receptor expression is absent in the sensory nerve ending.⁸⁷ The actions of postsynaptic CGRP receptors have been well described. However, the actions of presynaptic CGRP receptors have not yet been ascertained. Finally, CGRP has also been detected in other parts of brain which have been directly or indirectly implicated in the migraine syndrome, such as the anterior pituitary, cerebellum, hypothalamus, and periaqueductal grey.^{88–91}

Preclinical Studies

The development of CGRP receptor antagonists for abortive migraine therapy is a “fairy tale” of translational research, a textbook case of a bench to bedside story. Clinical observations of increased plasma CGRP levels in the craniovascular outflow in migraineurs, and its normalization after triptan treatment and headache resolution,⁹² were instrumental in provoking the interest in preclinical experimentation pertaining to CGRP and migraine.

Vascular Actions of CGRP and Its Receptors—Calcitonin gene-related peptide is richly localized in perivascular nerves in large cerebral arteries as well as in meningeal arteries. Early studies showed that the precontracted cranial artery segments from humans,⁹³ as well as from experimental animals,⁹⁴ were relaxed by CGRP in a concentration-dependent manner. Furthermore, CGRP_{8–37} antagonized these responses. These data thus established the role of CGRP receptors in the relaxation of intracerebral arterioles.⁹³

Development of olcegepant (BIBN4096BS), a potent CGRP receptor antagonist (K_i 14 pM), marked a breakthrough in CGRP research.⁹⁵ This antagonist was first studied in bovine and human isolated cranial arteries, where it inhibited CGRP-induced vasorelaxations in a concentration-dependent manner with a potency at least 10-fold higher than that of CGRP_{8–37}.⁹⁶ It is also important to note that the CGRP antagonists only blocked the vasorelaxations induced by CGRP and did not cause any contraction *per se* in either cranial arteries or coronary arteries,^{97,98} unlike triptans. Further studies showed that the vasodilator responses to CGRP were independent of the endothelium, and that all the components required for a functional CGRP receptor were present in human cranial arteries.^{98,99} Specifically, while the luminal application of CGRP in perfused MCAs had no effect, relaxation was observed after abluminal challenge.¹⁰⁰ Furthermore, this suggested that CGRP does not cross the BBB.

The cranial window model in rats,³³ cats,^{101,102} and piglets¹⁰³ confirmed CGRP's role in vasodilations in *in vivo* settings. Electrical stimulation-induced dilations in dural arteries were CGRP-dependent, but independent of substance P.³³ These findings validated the predictability of the model, as NK₁ (neurokinin 1 receptor, substance P receptor) antagonists have been found to be ineffective in the acute treatment of migraine,¹⁰⁴ in contrast to CGRP receptor antagonists.

Another signaling molecule which has been used extensively to study the endogenous CGRP release is capsaicin. Capsaicin is a transient receptor potential vanilloid type 1 agonist. Capsaicin-induced dilatations in the closed cranial window were attenuated by CGRP receptor antagonism, whereas NK₁ antagonists have been found to be ineffective.¹⁰⁵

Intracarotid modification of the model also established that CGRP does not dilate pial arteries, likely because CGRP receptors are secured by the BBB.¹⁰⁶ Additionally, in the porcine model of carotid arteriovenous anastomoses, olcegepant blocked the carotid vasodilatation produced by intracarotid infusions of either capsaicin¹⁰⁷ or CGRP,¹⁰⁸ without any effect of on carotid vasodynamics. Finally, CSD-induced dilatations in pial arteries are blocked by CGRP₈₋₃₇.^{109,110} Taken together, these data suggest CGRP-induced dilations contribute, at least in part, to the overall migraine cascade, and are a predictable parameter to evaluate efficacy of antimigraine agents.

Neuronal Mechanisms of CGRP and Its Receptors—In the past decades the focus of migraine research has moved from peripheral (vascular) actions of CGRP towards a greater understanding of its central actions, in areas like the TG, TNC, and higher pain centers in the brain. Increased neuronal activity in the TNC was reported after CGRP administration (i.v.), and in parallel to meningeal artery dilatation. Furthermore, this activity normalized following treatment with a 5-HT_{1B/1D} agonist.¹¹¹ In contrast, i.v. or topical administration of CGRP did not result in the activation or sensitization of the rat meningeal nociceptors, although there was a significant vasodilatation in the meningeal arteries.¹¹² Similarly, in a model of meningeal nociception, the increased neuronal activity was dose-dependently arrested by i.v. olcegepant, but not by its topical application.¹¹³ Furthermore, a slow infusion of NO donors over 2 hours results in a persistent increase in the neuronal activity in the rat TNC which can be inhibited by a high dose of olcegepant (900 µg/kg, i.v.; Figure).¹¹⁴ Finally, it is notable that olcegepant, when applied locally to the TNC, resulted in inhibition of activated neurons, whereas when CGRP was microinjected in TNC, it enhanced glutamatergic activation of central neurons.¹¹⁵ These studies suggest that the locus of action of olcegepant may be in the TNC directly, a central site secured from systemic blood supply by the BBB.

Even the c-Fos expression in a rodent migraine model is strongly connected to CGRP-centric interventions. Capsaicin intracisternal injection increased the expression of c-Fos in TNC in guinea pigs, and this response was inhibited by valproic acid, an established antimigraine drug.^{116,117} When CGRP-knockout mice were challenged with capsaicin, there was a significantly decreased expression of c-Fos compared to the wild-type mice.¹¹⁸ Furthermore, when capsaicin was injected unilaterally in the face of rat, olcegepant pretreatment decreased neuronal activation in the TNC, but not in the TG,¹¹⁹ indicating a central site of action. Finally, electrical stimulation of the TG led to an enhanced CGRP immune reaction, which was attenuated by triptans^{120,121} in parallel with a decrease in c-Fos expression in the TNC. Therefore, triptans may decrease CGRP mobilization in the TG.

Interestingly, in cultured TG neuronal cells, activation of CGRP receptors enhanced CGRP mRNA levels and augmented CGRP promoter activity.¹²² Furthermore, CGRP challenge to the cultured TG neurons induced increased transcription and enhanced trafficking of P2X₃, a receptor for the pain mediator adenosine triphosphate.¹²³ Therefore, increased CGRP can enhance the sensitivity of the TVS to adenosine triphosphate, causing central sensitization,¹²³ manifesting eventually as allodynia.

Several preclinical studies have relied on the measurements of CGRP levels to study the activation of trigeminovascular system. SSS activation in cats has been reported to increase CGRP levels, with these levels normalizing to control values, after treatment with sumatriptan⁹² and avitriptan, but not by CP122,288 (a conformationally restricted analog of sumatriptan).¹²⁴ It is noteworthy that while CP122,288 blocked protein plasma extravasation, avitriptan did not. In contrast, avitriptan was shown to be efficacious in treating migraine, while CP122,288 was not.¹²⁴ Finally, studies of CGRP levels have been carried out with the use of a hemisected skull model to evaluate CGRP release from the dura mater of rats. Using this model, it has been demonstrated that there is an increased CGRP release following NO donor or capsaicin challenge.^{125–127} Furthermore, sumatriptan is reported to decrease CGRP release in the hemisected skull model.¹²⁸ Thus, changes in CGRP levels may be used as one of the indices of antimigraine efficacy in animal models.

Clinical Studies with CGRP

In 1988, Goadsby and colleagues¹²⁹ notably reported that CGRP levels were increased in the external jugular vein of patients undergoing thermocoagulation for the treatment of trigeminal neuralgia. Since that discovery, although conflicting findings have been reported in regards to CGRP blood levels, the bulk of the data suggests CGRP is elevated in the plasma and saliva both interictally and ictally in migraineurs. Goadsby et al reported increased ictal CGRP levels in the external jugular vein of migraine patients, which normalized after sumatriptan treatment, with simultaneous alleviation of headache in 2 studies.^{92,130}

Follow-up studies of antecubital levels have also reported an increase in CGRP levels ictally.¹³¹ Additionally, interictal antecubital levels of CGRP in migraineurs have been reported to be elevated in 2 studies.^{132,133} Finally, in addition to plasma levels of CGRP, reports suggest that the salivary levels of CGRP are also elevated during acute migraine attacks and are decreased after the treatment with sumatriptan¹³⁴ and rizatriptan.¹³⁵

Given these studies, it is tempting to suggest that CGRP may be a biomarker for migraine. However, it is not clear if that is the case as several studies have reported no change in the CGRP levels in migraineurs. Specifically, Friberg et al reported that CGRP plasma levels were not elevated in patients with migraine with aura.¹³⁶ More recently, Tvedskov et al reported no increase in the CGRP levels in the venous jugular blood of migraineurs without aura ictally, as did Gupta et al while evaluating plasma from migraineurs interictally.^{137,138} Additionally, in human migraine provocation studies, either with sildenafil¹³⁹ or GTN,¹⁴⁰ no change in plasma CGRP was found. Therefore, the potential role of CGRP as a biomarker of migraine remains uncertain.¹⁴¹ It is possible that inconsistency in the CGRP levels may represent a manifestation of the variability in migraine experience, such as in regards to disease severity and duration.

Although CGRP's role as a biomarker for migraine is uncertain, its role in the pathophysiology of migraine has been largely confirmed by the success of 2 different CGRP receptor antagonists, or "gepants," for the acute abortive therapy of migraine: olcegepant and telcagepant.^{142,143} These drugs represent a significant advancement from the triptan era,

as they have not been associated with any significant changes in cardiovascular or craniovascular parameters.¹⁴⁴

The first “gepant” developed, olcegepant, is a dipeptide derivative and potent CGRP antagonist. Importantly, olcegepant treatment prevented CGRP-provoked headaches in healthy subjects.¹⁴⁵ Because of the limited oral bioavailability of olcegepant, telcagepant was developed.

Clinical usage of the CGRP receptor antagonists has also led to insights into the mechanisms and sites of action of these “gepants.” In the development phase of olcegepant, blockade of vascular responses was deemed paramount, but a number of observations have highlighted the critical importance of the central neuronal actions over the vascular mechanisms. In this respect it is important to recognize that relatively low doses of telcagepant were required to block the vascular response of capsaicin in humans ($EC_{90} = 900 \text{ nM}$)¹⁴⁶ whereas a 150- to 300-mg dose of telcagepant is required to achieve therapeutic efficacy, which translates into 2- to 4-fold higher concentrations than required to block the vascular response.¹⁴⁷ Similarly, a high dose of olcegepant (900 $\mu\text{g/kg}$, i.v.) was required to block GTN-induced increased neuronal activity¹¹⁴ whereas only $5.4 \pm 1.6 \mu\text{g/kg}$ of olcegepant is required to block the vascular effects of CGRP in rats.¹⁴⁸ This again translates into an approximately 4-fold higher dose of olcegepant required to block neuronal signals as compared to that of CGRP-induced vasodilatation. Therefore, it is hypothesized that the higher doses will pass the BBB and block CGRP receptor in the CNS. It is noteworthy that telcagepant is a P-glycoprotein substrate and thus has a very limited BBB permeability, approximately 1%.¹⁴⁹ CGRP itself is a heavy peptide (3789.4 MW), and thus it is believed that it cannot cross BBB. However, a recent study has shown that exogenous CGRP can be taken up in rat dura mater most probably in nerve endings.¹²⁶ If similar mechanisms are present in the human cranial vasculature, it will have implications on sites of action of CGRP receptor antagonists, and may also account in a part for reported variability in CGRP levels during the migraine attack.

Telcagepant’s efficacy has been well established by 3 successful randomized, placebo-controlled, double-blind, multi-centered trials.^{142,150,151} Over 350 patients were treated with 300 mg of telcagepant in a study by Connor et al, and CGRP receptor antagonist was shown to be more effective than placebo for pain freedom (24% 381 of patients vs 11% of 365) and pain relief (56% vs 33%). In the second study,¹⁴² similar results were seen with a 2-hour pain-free response of 61% of those treated with telcagepant ($n = 123$) as compared to 46% after placebo treatment ($n = 115$). In a third study, the efficacy of telcagepant 300 mg and zolmitriptan 5 mg were shown to be similar¹⁵¹ with 27% of 331 patients becoming pain-free at 2 hours for telcagepant and 31% of 342 for zolmitriptan. However, as compared to zolmitriptan, telcagepant had a better side effect profile.¹⁵¹ Additionally, the data support that even patients who did not report a good response to triptans have been shown to be responsive to telcagepant.¹⁵² The most common side effects of telcagepant reported in these studies were fatigue, dizziness, and upper abdominal pain.¹⁵⁰

Given the animal and human data, there is sufficient evidence that CGRP has a role in migraine. Future research is needed to determine whether CGRP-induced increases in the

craniovascular outflow is a feature of all forms of migraine, and if so, whether this increase is a cause or consequence of trigeminal activation. Finally, further exploration into the mechanisms and sites of action of CGRP receptor antagonists is likewise warranted.

NITRIC OXIDE AND HEADACHE

The soluble gas nitric oxide (NO) is formed endogenously from L-arginine by nitric oxide synthase (NOS). Three types exist: neuronal (nNOS), endothelial (eNOS), and inducible (iNOS).¹⁵³ It also forms after administration of nitric oxide donors, such as GTN (also known as nitroglycerin). Its main biological action is vasodilation, which occurs after binding to guanylyl cyclase in vascular smooth muscle cells, forming cyclic guanosine monophosphate, which in turn forms phosphorylated protein kinase G. This cascade ultimately leads to phosphorylation of ion channels and decreased calcium levels, causing relaxation and effecting vasodilation.¹⁵⁴

Since the mid 1990s, NO has been implicated in the neuroinflammatory cascade of migraine headache.¹⁵⁵ Although the full mechanism for the role of NO is not known, it is hypothesized that in acute migraine attacks, NO is released by neurons (along with other chemical mediators), leading to vasodilation and the subsequent development of headache.¹⁵⁶ Exogenously administered NO (through NO donors such as GTN) often causes an immediate tension-type headache in normal individuals. In patients with primary tension-type, migraine, or cluster headache disorder, a second delayed headache often occurs, and typically resembles the primary type of headache the patient experiences spontaneously. One exception is that patients who have migraine with aura tend not to develop aura with GTN-provoked headaches.¹⁵⁷ Thus, NO has also been implicated in the mechanisms of other primary headaches. In addition, GTN-induced attacks have been demonstrated to respond to typical acute headache treatments.^{158–160}

Given the vasoactive properties of NO and the reproducibility of NO-induced headache, much basic and clinical research has been devoted to better understanding headache, particularly migraine. New treatments are being sought which can target this aspect of migraine. In this section, we will discuss how some of these discoveries have come about, the implications for our understanding of migraine pathophysiology, and the direction of future therapeutic options.

Preclinical Studies: Vascular Aspects of NO

While some early data regarding the role of NO in the regulation of cerebral blood flow have been conflicting,¹⁶¹ recent studies have furthered our understanding of the complex vasculoneuronal mechanisms relevant to migraine pathophysiology and treatment. It is generally accepted that NO causes vasodilation through the cyclic guanosine monophosphate cascade, and in rats, GTN has been reported to promote dural vasodilation;^{162,163} this is blocked partially by indomethacin and sumatriptan.¹⁶³ There is evidence that NO also releases CGRP from rat dural afferents, which in part mediates an increase in meningeal blood flow.¹⁶⁴ In guinea pigs, non-selective NOS inhibition has been reported to block protein plasma extravasation induced by metachlorophenylpiperazine, implicating a role for NO in neurogenic inflammation.¹⁶⁵ A non-selective NOS inhibitor

was reported to reduce basal flow and to blunt the increase in blood flow seen after electrical stimulation in rat dural arteries.¹⁶⁶ Later, it was reported that in rats, dural vasodilation induced by electrical stimulation is partially blocked by non-selective NOS and nNOS inhibitors, CGRP-induced dural vasodilation is partially blocked by non-selective NOS and eNOS inhibitors, and iNOS inhibition has no effect on dural vasodilation induced by either stimulus.¹⁶⁷

Preclinical Studies: Neuronal Aspects of NO

NO has been shown to be involved in central nociception and to increase pain responses in animal models. In rats, infusion of a non-selective NOS inhibitor decreased the spontaneous firing rate of dural afferent neurons in the spinal trigeminal nucleus.¹⁶⁸ In rat and primate models, spinal cord NO has been shown to maintain, and nNOS inhibition to reduce, central sensitization.^{169–173} NO has been shown to be released during CSD,¹⁷⁴ in association with a corresponding but delayed increase in nNOS-positive cells hours to days later.^{175,176} However, evidence is conflicting as to whether and how NO mediates changes in cerebral blood flow during CSD.¹⁶¹

Clinical Studies with NO

Triggering Migraine with NO—In 1846, when GTN was first synthesized by Ascanio Sobrero, he quickly recognized its headache-inducing properties. After taking a taste of the substance, he developed a severe headache.¹⁵⁴ Over a century passed before GTN was evaluated formally in the study of headache pathophysiology, and recognized to participate in the delayed headache and migrainous features associated with NO.¹⁵⁹ In recent decades, the GTN model has become valued for its importance and potential in elucidating migraine mechanisms and seeking new treatments.

The utility of the GTN model has been discussed extensively in animals and humans, both for the understanding of pathophysiology and for the screening and testing of therapeutic drugs.^{159,161,177} While animal models are largely unreliable or unvalidated, it has been demonstrated more clearly and reliably in humans that NO donors trigger attacks that are responsive to treatment as one would predict.

In recent studies in migraineurs, GTN-induced migraine has been aborted or averted successfully by several acute antimigraine drugs of differing mechanisms, including prednisolone,¹⁵⁹ sodium valproate,¹⁶⁰ and sumatriptan.¹⁷⁸ In contrast, the CGRP-antagonist olcegepant failed to prevent GTN-induced migraine, suggesting that CGRP may exert its migraine-inducing effect upstream from NO in the migraine pathophysiology cascade.¹⁷⁹

What happens to blood flow and vessel diameter in GTN-induced migraine? One study showed immediate but transient vasodilation in middle meningeal, external and internal carotid, middle cerebral, basilar, and posterior cerebral arteries. Vessel diameter returned to baseline during the headache phase. Blood flow remained constant in basilar and internal carotid arteries.⁷¹ This demonstration of dissociation adds to the evidence against previous beliefs that vasodilation is key to the headache phase of migraine.

NO Biology and Physiology—Other effects of NO have been studied in migraineurs and healthy volunteers which may further our understanding of the role of NO in migraine. Flow-mediated dilation in the brachial artery is a process mediated by endothelium-derived NO. Migraineurs, particularly those with aura, had higher flow-mediated dilation values than controls, suggesting either an increased release of NO (metabolites were not measured), or an arterial supersensitivity to it.¹⁸⁰ The latter explanation was favored by the authors, given that it has been shown that migraine with typical aura patients' cerebral arteries are hyper-reactive to chemical stimuli.¹⁸¹ This hypothesis would be consistent with the observation that migraineurs have a lowered threshold for developing migraine after exposure to NO donors.

Recently, it has been demonstrated that GTN alters the nociceptive blink reflex and visual-evoked potentials (VEP) in healthy subjects in a manner very similar to that displayed by migraineurs during attacks: (1) both reflex and pain thresholds of nociceptive blink reflex were lowered; (2) reflex latency was shorter with increased response area under the curve; (3) VEP amplitudes were increased; and (4) VEP habituation was replaced by potentiation.¹⁸²

Genetics—Genetic studies have not yet provided significant conclusions as to the role of NO in headache. One study showed that allele distributions in the human iNOS gene for both migraineurs and controls were not significantly different.¹⁸³ Homozygosity for a variant of eNOS was shown to be an independent risk factor for migraine with typical aura in 1 study,¹⁸⁴ but no association of eNOS polymorphisms and migraine could be demonstrated in 4 others.^{185–188} Two different genetic variants of nNOS were examined for association with migraine, but none was found in a large case control study.¹⁸⁹ Associations between cluster headache and 5 different polymorphisms in NOS genes (accounting for all 3 forms of the NOS enzyme) also were sought but not discovered.¹⁹⁰ Curiously, neither familial hemiplegic migraine type 1 nor type 2 show the same hypersensitivity to NO that migraineurs with and without aura share.^{191,192}

Treatment Implications—Nitric oxide synthase inhibitors present potential attractive alternatives for migraine prophylaxis. Although non-selective NOS inhibitors are effective in treating acute migraine,^{193–195} they cause significant hypertension, precluding clinical utility. Selective iNOS inhibitors do not affect blood pressure and may be effective. Only 1 negative trial utilizing selective iNOS inhibitors has been published to date;¹⁹⁶ it was suspected that the unfavorable pharmacokinetic and pharmacodynamic profile of the compound may have been the major reason for its inefficacy. Other selective NOS inhibitors (1 nNOS and 1 iNOS) are currently in phase II clinical trials.¹⁷⁷

How else might our knowledge of NO in headache pathophysiology be helpful in discovering new treatment approaches? When workers manufacturing dynamite (GTN combined with Kieselguhr) first began work, they would develop NO-induced headaches. Many would habituate quickly,¹⁹⁷ but this habituation would also disappear quickly, leading to what was nicknamed “Monday disease” (return of NO-induced headaches following the weekend off). Workers learned to avoid this by taking some dynamite home with them over the weekend to rub on their skin periodically.¹⁵⁴

It is possible that repeated exposure to NO donors at low doses could desensitize migraineurs (similar to what occurred with the early dynamite workers), and at least in theory could present a potential prophylactic approach. Although there is evidence supporting that humans do become more tolerant over time to NO donors, like GTN and isosorbide mononitrate,¹⁹⁸ continuous administration of NO donors to induce tolerance has not yet been attempted to prevent spontaneous headache attacks.

HISTAMINE AND HEADACHE

Histamine is another key component of the neuroinflammatory process. With trigeminovascular activation and plasma protein extravasation, mast cells degranulate and release histamine. In the nervous system, histamine acts mainly on H1 and H3 receptors.¹⁹⁹ H1 receptors mediate inflammation, whereas H3 receptors are much more sensitive to histamine and serve as negative feedback to inhibit further excessive release of histamine by C-fibers.²⁰⁰

Like NO, histamine triggers both immediate and delayed headaches, more frequently and intensely in migraineurs, with attacks that resemble the pattern of NO-induced headaches.²⁰¹ As with GTN, histamine has been utilized as model for scientific study of headache mechanisms. Given the similarities in human responses to GTN and histamine, a common mediator in headache generation is suspected to exist. Ongoing exploration of histamine effects may lead to alternative treatments for headache.

Preclinical Studies

Intracranial and extracranial large arteries are reported to be dilated in monkey after histamine exposure.²⁰² This has been proposed to be mediated by NO, as activation of cerebral endothelial H1 receptors reportedly leads to NO formation in conjunction with vasodilation.²⁰³ Electrically stimulated dural vasodilation in rats has been reported to be inhibited by high doses of an H1 antagonist but not by an H2 antagonist.²⁰⁴ While neither H1 nor H2 antagonists have been shown to block NO-induced meningeal vasodilation,¹⁶³ they have been reported to block histamine-induced meningeal vasodilation,²⁰⁴ supporting a hypothesis that NO may mediate this phenomenon.

Clinical Studies with Histamine

Histamine-Related Biology—Histamine triggers a headache with similar temporal profile and clinical characteristics as NO, and this headache is completely prevented by the H1 receptor antagonist mepyramine.²⁰⁵ However, GTN-induced headaches are unaffected by mepyramine.²⁰⁶ As NO was hypothesized to be the common mediator of histamine- and GTN-induced headaches, healthy volunteers were subjected to histamine infusion after pretreatment with placebo or the non-selective NOS inhibitor L-nitromonomethylarginine (L-NMMA). While L-NMMA blunted the effect of histamine on ophthalmic artery and ocular circulation, there was no effect on the generation of headache or related symptoms or on mean blood flow velocities in MCA.²⁰⁷ Similar findings were observed in a later study involving migraineurs, which also examined middle cerebral, temporal, and radial arteries, and described craniospecificity for vasodilating effect of histamine and for arterial effects of

NOS inhibition.¹⁹³ It may be that both NO and histamine merely act as a switch to the same entry portal into the complex cascade of events underlying migraine.

In the realm of genetics and migraine, it was hypothesized that an association between migraine and polymorphisms of the gene encoding histamine N-methyltransferase, the enzyme which degrades histamine in the CNS, might exist. However, a recent study has failed to demonstrate this.²⁰⁸

Treatment Implications—In the past few decades, modulation of histamine has been employed successfully in the treatment of migraine and cluster headache. For migraine, the H3-mediated negative feedback loop has been exploited by intermittent very low doses of s.c. histamine. In theory, low concentrations in the body will lead to preferential stimulation of the more sensitive H3 receptors while leaving H1 receptors relatively untouched, thus activating the negative feedback loop and reducing the potential for C-fibers to become activated to play their part in the neuroinflammatory cascade. One group demonstrated in different double-blind studies that a series of escalating twice weekly s.c. doses for 12 weeks (1–10 ng in 1 ng increments, then the cycle repeated) was superior to placebo²⁰⁹ and equal to topiramate,²¹⁰ divalproex sodium,²¹¹ and botulinum toxin type A²¹² in measures of efficacy of migraine prophylaxis, including headache frequency, intensity, and duration; acute medication intake; and migraine-related disability. Another group reported benefit of IV histamine infusion escalated from 0.5 mg/day to 4 mg/day over 21 days, although this was a single-center open-label retrospective study.²¹³

The histamine catabolite N α -methylhistamine also possesses a selective affinity for H3 receptors. In a double-blind, placebo-controlled study, twice weekly s.c. doses of 1–3 ng was shown to be effective.²¹⁴

Single-center open-label retrospective studies have also purported histamine (used as a gradually escalating continuous low-dose infusion) to be a successful treatment for chronic cluster headache.^{215,216} Since procuring histamine and its catabolite for these purposes is often impractical, and the latter requires long stays in hospital, these treatments are rarely utilized in the USA.

CONCLUSION

Significant advancements in the way migraine is viewed as a disease process and in the therapeutic options available for the treatment of migraine have occurred over the past 50 years. In this review, we highlighted the importance of nitric oxide, histamine, serotonin, and CGRP. These 4 mediators have significantly advanced our understanding of migraine as a disease entity, have become drug targets for migraine specific therapy, and have been implicated in the mechanism of drugs which are efficacious for migraine therapy. While vascular and neuronal mechanisms have been implicated for all, future research will continue to advance our understanding of these mechanisms and migraine as a disease state.

Abbreviations

5-HT	5-hydroxytryptamine
BBB	blood brain barrier
cAMP	3'-5'-cyclic adenosine monophosphate
CGRP	calcitonin gene-related peptide
CLR	calcitonin receptor-like receptor
CNS	central nervous system
CSD	cortical spreading depression
eNOS	endothelial nitric oxide synthase
GTN	glyceryl trinitrate
HNMT	histamine N-methyltransferase
iNOS	inducible nitric oxide synthase
L-NMMA	L-nitromonomethylarginine
MCA	middle cerebral artery
MMA	middle meningeal artery
mRNA	messenger RNA
NK₁	neurokinin 1
nNOS	neuronal nitric oxide synthase
NO	nitric oxide
NOS	nitric oxide synthase
RAMP	receptor activity-modifying protein
SSS	superior sagittal sinus
TG	trigeminal ganglia
TNC	trigeminal nucleus caudalis
TVS	trigeminal vascular system
VEP	visual-evoked potentials
VSMC	vascular smooth muscle cells

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Figure.

Ongoing activity of 2 spinal trigeminal neurons after infusion of the NO donor sodium nitroprusside (SNP). The lower panel shows decrease in activity after a 5 min infusion of olcegepant (BIBN4096BS).¹¹⁴ Reproduced with permission.

Table**Summary of the Most Commonly Used Preclinical Models in Migraine Research**

Preclinical Models	Principle/Phenomenon	Comments
Isolated cranial arteries ²¹⁷	Vascular theory ²¹⁸	Optimal for receptor characterization and predictive model
Isolated coronary arteries ²¹⁹	Side effect profiling of putative vasoconstrictors and surrogate assay ²²⁰	Optimal for receptor characterization
Extracranial external carotid vasodilatation ²²¹	Vascular theory	Predictive model
Arteriovenous anastomotic shunt model using radioactive microsphere ^{222,223}	Vascular theory and dilation of arteriovenous anastomoses ²²⁴	Predictive model
Intravital microscopy on closed cranial window ³³	Vascular theory	Predictive model; release of endogenous signaling molecules can be studied by electrical or chemical stimulation
CSD-based models; chemical, electrical stimulation of cortex ²²⁵	CSD represents the aura phase of migraine ^{226,227}	Based on a well-described clinical phenomenon but do not represent migraine without aura
Plasma protein extravasation model ²²⁸	Neurogenic inflammation of migraine ^{229,230}	Not a predictive model
Superior sagittal sinus stimulation to record activity in TNC ⁴³	SSS stimulation induces pain. Neurogenic theory ²³¹	Predictive, measure of neuronal activity as an index for pain
c-Fos expression in brain after various stimulation, eg, GTN infusion ²³²	c-Fos is a marker for brain activation/pain ²³³	One of the closest markers for pain perception
Hemisected skull model, where brain tissue is removed and skull lined with the dura is used for study ²³⁴	CGRP release from dura mater	Allow the assessment whether experimental intervention affects CGRP release

CGRP = calcitonin gene-related peptide; CSD = cortical spreading depression; GTN = glyceryl trinitrate; SSS = superior sagittal sinus; TNC = trigeminal nucleus caudalis.