Review Article

Understanding migraine: Potential role of neurogenic inflammation

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Abstract

Neurogenic inflammation, a well-defined pathophysiologial process is characterized by the release of potent vasoactive neuropeptides, predominantly calcitonin gene-related peptide (CGRP), substance P (SP), and neurokinin A from activated peripheral nociceptive sensory nerve terminals (usually C and A delta-fibers). These peptides lead to a cascade of inflammatory tissue responses including arteriolar vasodilation, plasma protein extravasation, and degranulation of mast cells in their peripheral target tissue. Neurogenic inflammatory processes have long been implicated as a possible mechanism involved in the pathophysiology of various human diseases of the nervous system, respiratory system, gastrointestinal tract, urogenital tract, and skin. The recent development of several innovative experimental migraine models has provided evidence suggestive of the involvement of neuropeptides (SP, neurokinin A, and CGRP) in migraine headache. Antidromic stimulation of nociceptive fibers of the trigeminal nerve resulted in a neurogenic inflammatory response with marked increase in plasma protein extravasation from dural blood vessels by the release of various sensory neuropeptides. Several clinically effective abortive antimigraine medications, such as ergots and triptans, have been shown to attenuate the release of neuropeptide and neurogenic plasma protein extravasation. These findings provide support for the validity of using animal models to investigate mechanisms of neurogenic inflammation in migraine. These also further strengthen the notion of migraine being a neuroinflammatory disease. In the clinical context, there is a paucity of knowledge and awareness among physicians regarding the role of neurogenic inflammation in migraine. Improved understanding of the molecular biology, pharmacology, and pathophysiology of neurogenic inflammation may provide the practitioner the context-specific feedback to identify the novel and most effective therapeutic approach to treatment. With this objective, the present review summarizes the evidence supporting the involvement of neurogenic inflammation and neuropeptides in the pathophysiology and pharmacology of migraine headache as well as its potential significance in better tailoring therapeutic interventions in migraine or other neurological disorders. In addition, we have briefly highlighted the pathophysiological role of neurogenic inflammation in various other neurological disorders.

Key Words

Migraine, neurogenic inflammation, neuropeptides

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Introduction

Migraine is a common disabling neurovascular disorder, which affects approximately 10-15% of the general population.[1] Migraine attacks are characterized by recurrent, intense, throbbing, and unilateral head pain often associated with nausea, vomiting, photophobia, and phonophobia. The exact pathophysiological mechanism underlying migraine headache is still a major incompletely understood issue. For a long period, several theories posited migraine as a vascular disorder with headache attributed solely to dilatation and inflammation of extracranial arteries within pain-producing intracranial meningeal structures.[2] However, over the past decade, abundant evidence accumulated from animal and human data has shifted the focus from the

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blood vessels toward a more integrated theory that involves both vascular and neuronal components. In particular, it has become increasingly evident that the activation of meningeal afferents, neuropeptide release, and neurogenic inflammation plays a pivotal role in the generation of pain in migraine headache.[3,4] Inhibition of dural neurogenic inflammation with compounds that prevent or suppress the phenomena promoted by activation and sensitization of trigeminovascular neurons at the level of both their central and peripheral perivascular nerve endings has been proposed as one of the key therapeutic strategies for the treatment of migraine and other primary headaches. However, the underlying mechanism or mechanisms and the molecular targets that should be tackled by novel medicines are still uncertain and extending our knowledge of sensory pharmacology, neurogenic inflammatory roles of substance P (SP) and calcitonin gene-related peptide (CGRP), together with their relevant receptor system would bring insights into some fascinating aspects of human neurobiology and also herald a new era in the treatment of migraine.

Defining Neurogenic Inflammation

Over a century ago, Bayliss[5] first made the observation that stimulation of the dorsal root ganglia neurons resulted in signs of cutaneous vasodilation, leading to the notion that neurons subserve a dual sensory-efferent function and antidromic "impulses being propagated along sensory fibers in a direction opposite to that of normal conduction," activation of sensory fibers is an important mechanism mediating peripheral inflammatory protective responses. A large body of experimental evidence has since been accumulated, advocating similar views of the activation of primary afferent neurons (e.g., by disease processes or experimentally by electrical stimulation) or activation of polymodal nociceptive receptors (vanilloid-1 channel and proteinase activated receptor-2) expressed on the peripheral nerve terminal generate axon-reflexes that cause the "retrograde" release of proinflammatory neuropeptides. These neuropeptide mediators, in turn, interact with endothelial cells, mast cells, immune cells, and vascular smooth muscle, thus initiating a cascade of inflammatory responses characterized by erythema and hyperemia (secondary to local vasodilatation), local edema (secondary to plasma-protein extravasation), and hypersensitivity (secondary to alterations in the excitability of certain sensory neurons).[6] This phenomenon of both vasodilatation and increased vascular permeability is referred to as "neurogenic inflammation."

Neurogenic Inflammation and Migraine Pathophysiology

Role of neuropeptide modulators

Calcitonin gene-related peptide

CGRP, a 37-amino acid neuropeptide, is a principal sensory vasoactive neuropeptide with vasodilatory, immunomodulation, and inflammatory roles.[7] CGRP has two isoforms available:

1. Alpha-CGRP mainly present in sensory neurons and
2. Beta-CGRP preferentially expressed in enteric myentric and submucosal intrinsic neurons.[7]

CGRP-containing sensory nerve fibers are widely distributed with predominant expression in the cerebral vascular and neuronal tissues, including the trigeminal ganglion and trigeminal nucleus caudalis.[8] CGRP acts by binding three subtypes of 7-transmembrane spanning G-protein-coupled receptors, namely, CGRP-1, CGRP-2, CGRP-3. This receptor-effector coupling results in stimulation of adenyl cyclase and an increase in cyclic adenosine monophosphate (cAMP), thus producing potent vasodilatation via the direct (i.e., endothelium-independent) relaxation of vascular smooth muscle.[9] It has been established that nerve growth factor (NGF) and nitric oxide (NO) modulate the synthesis of CGRP and serotonergic control regulates the release of CGRP.[10] CGRP is often colocalized with SP in peripheral sensory neurons.[11] Various studies have indicated a putative interaction between SP and CGRP. CGRP has been shown to potentiate SP-induced plasma-protein extravasation in the rat skin.[12] Similarly, CGRP inhibits degradation and facilitates excitation induced by SP in the dorsal horn neurons,[13] thus proving synergism between two peptides. CGRP is implicated in several of the pathophysiological processes of migraine including dilation of cerebral and dural blood vessels, stimulation of nociceptive trigeminovascular pathway, and induction of mast cell degranulation.[14] In addition, CGRP has wide array of biological activities including glucose uptake and the stimulation of glycolysis in skeletal muscles, cardiac contractility, bone growth, and mammalian development.[15] Electric stimulation of the trigeminal nerve causes CGRP to be released from perivascular nerve endings in the external jugular vein in animals and man. In cats, stimulation of the superior sagittal sinus leads to increased cerebral blood flow, along with elevated levels of CGRP in the external jugular vein.[16] CGRP level has also been reported to be elevated in the headache phase of migraine,[14,17] thus supporting the concept of migraine as a neurovascular phenomenon and that CGRP is indeed the relevant mediator responsible for neurogenic vasodilatation and has an important role in migraine pathophysiology.

Substance-P/neurokinin A/neurokinin B

Undecapeptide SP, decapeptide neurokinin A, and decapeptide neurokinin B are three tachykinin-like peptides, expressed mainly in neuronal and glial cells of the human central and peripheral nervous system. These peptides act mainly as neurotransmitters in the central nervous system (CNS) and as mediators of non-noradrenergic, non-cholinergic transmitter (NANC) excitatory neurotransmission in the autonomic nerves.

SP and neurokinin A are encoded by the preprotachykinin A (PPT-A) gene while neurokinin B is encoded by preprotachykin B (PPT-B). These neuropeptides exert their biological activities mainly through binding with three specific G protein-coupled receptors, neurokinin 1 (NK1) for SP, neurokinin 2 for neurokinin A, and neurokinin 3 for neurokinin B.[18] This receptor-effector coupling leads to the activation of phospholipase C and thus, the generation of inositol triphosphate and diacylglycerol and thus the release of carbonic anhydrase II (Ca2)+ from internal stores.[18] Neurokinins exert a variety of biological activities including nociception, synaptic transmission (as excitatory neurotransmitters), neuroimmunomodulation, and neurogenic inflammation. In particular, SP is the best characterized of these peptides and has been shown to be functionally implicated in nociceptive (pain) responses and neurogenic inflammation.[19] SP is synthesized translation and transcription of messenger RNA (mRNA) molecule in the cell bodies of sensory nerve fibers

(dorsal root ganglia), from where it is transported to the dorsal horn of the spinal cord and peripherally to nerve terminals of sensory neurons. SP often coexists and is coreleased with other transmitter molecules, particularly CGRP[11] and glutamate,[20] in the trigeminal ganglion and trigeminal nucleus caudalis. It has been indicated that adrenal steroid hormones play a role in the synthesis of SP and that neurotrophic factors derived from glial cells and N-methyl-D-asparate (NMDA) receptors regulate the release of SP.[21] In response to prolonged noxious stimuli, SP and CGRP are released from trigeminal sensory nerve fibers around dural blood vessels, leading to endothelium dependent vasodilation, increased microvascular permeability, and subsequent plasma and protein extravasation, by acting directly on vascular smooth muscle or indirectly through release of histamine from the mast cells.[22] SP is the prime mediator causing plasma leakage at the site of inflammation via NK-1 receptors, whereas both CGRP and SP induce vasodilatation.[23] The involvement of SP in plasma leakage and neurogenic inflammation has been well-established by the ability of NK1 receptor antagonists and SP immunoneutralization to attenuate neurogenic exudative responses to a variety of stimuli.[24] A significant increase in plasma SP and CGRP levels is demonstrated during the headache phase of migraine. Recent neuroimaging studies provided strong evidence of dural neurogenic inflammation involvement in the pathogenesis of migraine headache.[24] On the basis of these observations, SP deserves further evaluation as a useful tool in determining therapeutic options for treating migraine headache.

Role of nonneuropeptide modulators

Serotonin

5-Serotonin [5-hydroxytryptamine (5-HT)], a biogenic amine is synthesized in serotonergic neurons in the CNS and enterochromaffin cells in the gastrointestinal tract.[25] Serotonin mediates a wide range of physiological functions, both centrally and peripherally, by interacting with a large and diverse range of postsynaptic 5-HT receptors. So far, 15 different serotonin receptors and receptor subtypes, 5-HT1 through 5-HT7 as well as eight other subtypes, have been identified and all are located in the cerebral cortex, posterior hypothalamus, and central gray matter.[25] In the CNS, 5-HT acts as a neurotransmitter and modulates a number of behavioral functions including control of appetite, sleep/wakefulness, memory and learning, thermoregulation, nociception, mood, stress, and behavior (including sexual and hallucinogenic behaviors). Abnormality in the 5-HT neuromodulation affects several behavioral traits and personality disorders such as impulsive aggression, manic depressive illness, anxiety and alcoholism, and neurological conditions such as migraine.[26] On the basis of its pain processing and modulation, and vasoactive properties, serotonin has long been implicated in the pathophysiology of migraine.[27] The serotonin -1B, -1D, and -1F receptors situated prejunctionally in the trigeminovascular system have been thought to be involved in pain transmission.[27] The serotonin -1B receptor and its mRNA are often colocalized with SP and CGRP in the human trigeminal ganglia and trigeminal nerves. Activation of receptor-1B by serotonin agonist sumatriptan leads to inhibition of CGRP gene transcription and prevents CGRP release, thus suggesting a possible role of receptor in modulating the release of vasoactive neuropeptides.[28] Sumitriptan attenuates plasma protein extravasation induced by electrical trigeminal ganglion stimulation by preventing release of CGRP.[29] Studies in knockout mice and guinea pigs revealed that 5-HT1D receptors on primary afferent fibers are coupled to inhibition of neuropeptide release, thus modulating the dural neurogenic inflammatory response.[30] Similarly, activation of the serotonin-1F receptor by a potent selective agonist also showed efficacy in inhibiting plasma protein extravasation in rats and guinea pigs.[31] Evidence suggests that increased 5-HT2B-receptor expression and activation are coupled to the production and release of NO.[32] NO, in turn, stimulates the release of neuropeptides, resulting in neurogenic vasodilation and plasma protein extravasation, the two key elements implicated in migraine pathogenesis.[33] Selective 5-HT2B receptor antagonists (LY-26697, LY-202146, and LY-272015) have been shown to inhibit m-chlorophenylpiperazine-induced dural plasma protein extravasation in guinea pigs.[34] Indirect data have also implicated a predominant role of the serotonin-7 receptor in the vasodilation component of a neurogenic dural inflammation model.[35] Taken together, these observations and studies support the potential role of serotonin receptors in dural neurogenic inflammation.

Nerve growth factor

NGF is a well-characterized neurotrophic factor, synthesized primarily in nociceptive neurons. NGF plays an essential role in the survival and differentiation of sensory and sympathetic nerve fibers, exerts a neuromodulatory role on sensory, nociceptive nerve physiology, and influences the generation of pain related to tissue inflammation.[36] NGF also differentially modulates transient receptor potential vanilloid-1 (TRPV1)-mediated neuropeptide secretion sensitivity. NGF induces its trophic action largely by binding to the high affinity tropomyosin receptor kinase A (TrkA) receptor that is selectively expressed by nociceptive sensory neurons, particularly those containing neuropeptides such as SP and CGRP.[37] Immunocytochemistry and molecular biological studies have shown the presence of the TrkA receptor for NGF in adult rat dorsal root ganglia, trigeminal ganglia, spinal cord, and nerve fibers innervating cranial blood vessels.[38] Several inflammatory models have suggested that NGF increases the expression of the proinflammatory neuropeptide, CGRP and enhances the production and release of neurpeptides, including SP and CGRP, in sensory neurons.[39] CGRP-encoding mRNA expression is markedly increased in the dorsal root ganglia neurons after injecting NGF into the rat hind paw.[40] Similarly, injection of NGF resulted in enhanced expression of the mRNA for CGRP in sensory neurons of the guinea pig trigeminal ganglion.[41] Recent studies have demonstrated significantly high levels of neurotrophins [brain-derived neurotrophic factor (BDNF) and NGF] in the cerebral spinal fluid (CSF) of patients suffering from chronic migraine and primary fibromyalgia syndrome (PFMS), suggesting potential involvement of BDNF and NGF in the pathophysiology of these disorders.[42] Therefore, these results suggest a possible link between NGF and the synthesis and release of dural neurogenic inflammatory neuropeptides in migraine.

Nitric oxide

NO is a ubiquitous and unique biological messenger molecule that is biosynthesized from the amino acid L-Arginine by a family of three distinct calmodulin-dependent NO synthase (NOS) enzymes: Neuronal NOS (nNOS), endothelial NOS

(eNOS), and inducible NOS (iNOS).[43] NO is produced prominently within endothelial cells, macrophages, and neuronal tissue. NO mediates a wide range of important biological processes such as endothelium-dependent vasodilation, inhibition of platelet aggregation, inflammation, immunoregulation, and neuronal transmission in the CNS and peripheral nervous system.[43] In the central system, NO is believed to be involved in the regulation of cerebral blood flow, blood flow-metabolism coupling, and neurotransmission. NO also appears to contribute to memory and learning, mediation of nociception, modulation of neuroendocrine functions, and behavioral activity.[44] Over the past decade, a great deal of evidence has accumulated from various clinical and animal experimental studies supporting the role of NO as a likely important molecular trigger mechanism underlying the primary vascular headaches such as migraine and cluster headache.[45] NO can induce the initial phase of migraine headache by inducing cerebral vasodilation via a direct action of the NO-cyclic guanosine monophosphate (cGMP) pathway and may trigger the delayed phase of headache by stimulating CGRP release and sensitizing the perivascular nociceptors and central nociceptive neurons in the trigeminovascular system. NO triggers perivascular neurogenic inflammation by facilitating the synthesis and release of immunoreactive CGRP and SP from dural nociceptive afferent fibers.[46] NO stimulates CGRP gene promotor activity in trigeminal neurons via signaling through a mitogen-activated protein (MAP) kinase pathway and T-type calcium channels, thus suggesting a modulatory role for endogenous NO during neurogenic inflammation.[47] Cotreatment with the serotonergic, antimigraine drug sumatriptan suppresses stimulatory effects of NO on CGRP promoter activity and release. Similarly, the application of nonselective and neuronal nitric oxide synthase (nNOS) inhibitors was able to partially attenuate neurogenic vasodilation.[48] Studies have demonstrated a significant increase in plasma nitrate concentrations in migraine and cluster headache patients.[49] Thus, these findings consistently indicate that NO production and neuropeptide release are functionally linked in severe vascular headaches.

Prostaglandins

Prostaglandins, potent mediators of inflammation and nociception, are derivatives of arachidonic acid (AA), a 20-carbon unsaturated fatty acid produced from membrane phospholipids.[50] Prostaglandins are produced following the sequential oxidation of AA, dihomo-gamma-linolenic acid (DGLA), or eicosapentaenoic acid (EPA) by the constitutive enzymes, cyclooxygenases [cyclooxygenase (COX)-1 and COX-2) and terminal prostaglandin synthases.[50] In the CNS, COX enzymes are present in neurons, astrocytes, and microglia, and can be induced with cytokines, growth factors, or other inflammatory stimuli. The COX-2 isoenzyme is predominantly expressed in the neurons of the caudal nucleus of the trigeminal. In recent studies, COX-2-derived prostaglandins have been shown to augment the stimulus-induced release of the neuroactive peptides, SP, and calcitonin gene-related peptide from the central and peripheral terminals of the embryonic rat sensory neurons grown in culture.[51] Similarly, electrical stimulation of the trigeminal ganglion resulted in significant release of CGRP and prostaglandin E2 from the dura mater.[52] Nonsteroidal anti-inflammatory analgesics, including aspirin and indomethacin, which impair prostaglandin biosynthesis through the irreversible blockade of COX, were shown to inhibit the neurogenically-induced plasma extravasation in rat dura mater.[53] The COX-2 inhibitor, parecoxib, significantly attenuated plasma protein extravasation in the rat dura mater, most likely by modulating the release of SP.[53] These studies provide some support for the possible role of the COX-prostaglandin system in neurogenic inflammation.

Gamma-aminobutyric acid

Gamma-aminobutyric acid (GABA) is the most important and widespread inhibitory neurotransmitter systems that modulate the neuronal excitability and nociceptive response in the brain and spinal cord.[54] GABA acts on inhibitory synapses in the brain by binding to two distinct transmembrane receptors subtypes:

1. The A receptor, a pentameric transmembrane chloride ion channel receptor and
2. The B receptor, a G-protein-coupled metabotropic receptor in the plasma membrane of both pre- and postsynaptic neurons.[54]

Over the past decades, several studies have suggested possible involvement of GABA in the pathophysiological events of migraine. Welch *et al*.[55] demonstrated increased levels of GABA in the cerebrospinal fluid (CSF) of patients during migraine attacks. Elevated levels of GABA were also found in the platelets of migraine patients.[55] The antiepileptic drug, sodium valproate, is useful in aborting migraine headache and may act by enhancing peripheral GABA activity at the GABA-A receptor.[56] Experimental studies in animal models of cephalic pain have shown that sodium valporate blocks dural plasma protein extravasation and attenuates nociceptive neurotransmission via GABA-A receptor-mediated mechanisms.[56] Similarly, allopregnanolone, a progesterone metabolite, was found to suppress neurogenic and SP-induced plasma extravasation within the rat meninges by modulating GABA-A receptor activity in the trigeminal nucleus caudalis.[57] This evidence indicates that GABAergic inhibitory mechanisms plays a role in migraine pathogenesis and that GABA-A receptor mediated antimigraine effects may be a result of modulation of dural neurogenic inflammation.

Capsaicin

Capsaicin, a pungent constituent in red chili peppers, has been found to play a key role in nociceptive transmission as well as in the generation of neurogenic inflammation. Capsaicin acts on a subset of primary sensory neurons via heat sensitive vanilloid type 1 (TRPV1) receptor to release proinflammatory neuropeptides such as CGRP and SP.[58] TRPV1 receptors are often colocalized with CGRP receptors in human trigeminal ganglion cells.[58] In several *in vivo* models of migraine, systemic administration of capsaicin resulted in CGRP-induced vasodilatation at the trigeminovascular junction.[59] The TRPV1 receptor antagonist, capsazepine, may inhibit capsaicin-induced dilation of dural blood vessels. Repeated application of capsaicin resulted in impairment of effector function of small diameter sensory afferent nerve fibers (initial excitation followed by long-lasting desensitization) by depleting neuronal neuropeptide content.[59] The TRPV1 receptor agonist, civamide, when given intranasally, diminished migraine headache pain as a result of decreased vasodilatation, plasma extravasation, and

histamine and serotonin release.[60] These interactions between TRPV1 receptor, neurogenic inflammation, and migraine attacks are suggestive of their role in migraine mechanism and could be further explored to develop promising therapeutic alternatives for migraine headache.

Neurogenic Inflammation and Other Neurological Disorders

Complex regional pain syndromes (CRPSs), also known as reflex sympathetic dystrophy or causalgia, are painful neuropathic disorders that develop following fracture or limb trauma with (Type I) or without (Type II) nerve injury. The clinical picture is characterized by sensory (spontaneous pain, allodynia and hyperalgesia), motor (paresis, tremor, dystonia), edema, sudomotor (alterations in transpiration, hair and nail growth) and vasomotor (changes in color or temperature) disturbances.[61] Despite several models that were proposed, the underlying pathophysiological mechanism of CRPS still remains obscure. The clinical picture of acute CRPS resembles classical signs of inflammation such as swelling, redness, warmth, and pain, thus suggesting that neurogenic inflammation may be a pathophysiologic mechanism in CRPS. Birklein *et al*. showed increased neuropeptide levels of CGRP in patients with CRPS with ongoing edema and vasodilation.[62] In one study, transcutaneous electrical stimulation provoked plasma protein extravasation and vasodilation only in the CRPS patients as compared to controls.[62] Similarly, in another study, application of exogenous SP-induced protein extravasation in the affected and unaffected contralateral limbs of patients with CRPS.[63] These proinflammatory responses appear to be a result of upregulation of NFκB activity by the neuropeptides involved in CRPS. Sciatic nerve transection experiments in rat have further shown that SP contributes to the vascular and nociceptive abnormalities observed in CRPS.[64] Systemic administration of NK1 receptor antagonist in rat models has shown inhibition of mechanical hyperalgesia and partial reversal of spontaneous extravasation, edema, and warmth in the hind paw.[64] Taken together, both clinical and experimental animal model studies substantiate the role of neurogenic inflammation in the pathomechanism of CRPS and development of antagonists or synthesis inhibitors could be beneficial in the treatment of this challenging neuropathic condition.

Fibromyalgia (FM) is a chronic, generalized neuromuscular pain disorder of unknown etiology. The clinical symptoms are characterized by widespread muscular pain, fatigue, multiple tender points, and multiple other somatic symptoms.[65] Till recently, CNS (central sensitization) was considered to be the major factor involved in the pathophysiology of FM. However, recent investigations in FM patients have suggested that peripheral nerve endings also play a pivotal role. An increased neurogenically-mediated axon reflex flare reaction to mechanical and chemical stimuli and a lower threshold of the capsaicin-induced flare were observed in FM patients.[66] This increased receptor activity may also contribute to the pain and tenderness experienced by these patients.[66] A recent study demonstrated high amounts of SP in the nerve endings of the trapezius muscle of FM patients, compared with controls.[67] In other studies, SP concentration was found to be three times higher in the CSF of FM patients, compared with controls.[68] These findings thus support the role of neurogenic inflammation in the development and perception of myofascial pain in FM patients.

Recent studies in rat animal models have identified that neuropeptides, specifically SP, play a role in edema formation and development of functional deficits following traumatic brain injury (TBI) and cerebral ischemia and stroke.[69] Levels of SP are increased following acute insults to the brain, indicative of neurogenic inflammation. Administration of a SP receptor antagonist as well as inhibition of SP release by capsaicin has also been shown to decrease cerebral edema resulting in improved motor and cognitive outcome.[69] Topical application of capsaicin has yielded promising results in alleviating peripheral neuropathic pain such as diabetic neuropathy and postherpetic neuralgia.[70] Capsaicin is thought to block pain signals by the depletion of SP. This implies that neurogenic inflammation is involved in forms of neuropathic pain in which C-fibers play a pathophysiological role and could be a potential treatment approach for these painful conditions.

Therapeutic Significance and Conclusion

Considerable data concerning the involvement of neurogenic inflammation in various neurological disorders have been accumulated over the past few years, boosting the scientific interest in the pharmacological modulation of neurogenic inflammation. The ability to develop selective receptor agonists, which block the deleterious neurogenic inflammatory feedback loop has opened up exciting therapeutic possibilities. The CGRP 1 receptor antagonist, BIBN 4096 BS, has been shown to inhibit the dilatation of cutaneous arterioles evoked by stimulation of afferent nerve fibers and found to be effective in aborting migraine headache.[71] Several peptide and nonpeptide NK-1 receptor agonists such as RPR-100893, LY-303870, L-758298, GR-205171, and FK-888 have been shown to inhibit plasma protein extravasation and vasodilation in the dura matter of animal models and have nociceptive (and antiemetic) properties.[72-74] However, the efficacy of these drug molecules in aborting migraine headache in humans is still under investigation. Various pilot trials have also shown the nonselective NO synthase inhibitor, L-N-monomethylarginine (L-NMMA), to be highly efficacious in treating both migraine attacks and chronic tension-type headache.[75] NO synthase inhibitors act by inhibiting NO production and neuropeptide release and pharmacological inhibition of several steps of the NO-signaling cascade may pave the way to new avenues in the pharmacological treatment of migraine. LY-334370, a selective serotonin-1F-receptor agonist, has been found to be efficacious in the abortive treatment of migraine.[76] LY334370 acts by inhibiting neurogenic inflammation. Further, new compounds such as 4991W93[77] and PNU-14263,[78] which are selective serotonin-1D-receptor agonists, and RO-470203,[79] an endothelin-receptor antagonist, must undergo clinical trials before these approaches can be established as worthwhile in the treatment of acute migraine. Botulinum toxin (BoNT) injections are becoming a well-recognized therapeutic modality for the treatment of migraine headache, chronic daily headache, myofascial pain, painful dystonia, trigeminal neuralgia, facial chronic pain, and pain related to spinal

cord pathology.[80] The peripheral antinociceptive and anti-inflammatory effect of BoNT-A may be a result of inhibition of the release of neuropeptides. Application of BoNT resulted in the reduction of release of CGRP from autonomic vascular nerve terminals.[81] In a double-blind study, subcutaneous administration of BoNT-A reduces capsaicin-induced pain and neurogenic vasodilatation.[82] These findings suggest a potential clinical benefit of BoNT-A in the treatment of painful neurogenic inflammatory disorders where the axon reflex plays a role. Recently, it has been suggested that the cholesterol-lowering statin medications might be useful in the treatment of diseases with prominent neurogenic inflammation.[83] Statins might act directly on sensory neurons to downregulate the expression of proinflammatory neuropeptides such as CGRP and SP.[84]

The prospect of treatment modalities involving the manipulation of neuroinflammatory response holds great promise but translating the ideas presented here into therapeutic benefit remains a major challenge. Better understanding of the molecular mechanisms involved in the neurogenic inflammatory pathway and its role in the pathogenesis of neurological disorders is needed. This would provide important insights and with them the hope of being able to offer clinicians new therapeutic targets and improved approaches in the treatment of migraine and related neurological disorders.

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Conflicts of interest
There are no conflicts of interest.

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