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Sphenopalatine ganglion neuromodulation in migraine: What is the rationale?

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Abstract

Objective: The objective of this article is to review the prospect of treating migraine with sphenopalatine ganglion (SPG) neurostimulation.

Background: Fuelled by preliminary studies showing a beneficial effect in cluster headache patients, the potential of treating migraine with neurostimulation has gained increasing interest within recent years, as current treatment strategies often fail to provide adequate relief from this debilitating headache.

Common migraine symptoms include lacrimation, nasal congestion, and conjunctival injection, all parasympathetic manifestations. In addition, studies have suggested that parasympathetic activity may also contribute to the pain of migraineurs.

The SPG is the largest extracranial parasympathetic ganglion of the head, innervating the meninges, lacrimal gland, nasal mucosa, and conjunctiva, all structures involved in migraine with cephalic autonomic symptoms.

Conclusion: We propose two possible mechanisms of action: 1) interrupting the post-ganglionic parasympathetic outflow to inhibit the pain and cephalic autonomic symptoms, and 2) modulating the sensory processing in the trigeminal nucleus caudalis. To further explore SPG stimulation in migraineurs as regards therapeutic potential and mode of action, randomized clinical trials are warranted.

Keywords

Sphenopalatine ganglion, migraine, trigeminovascular pathway, trigemino-parasympathetic reflex, neurostimulation, neuromodulation

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Introduction

Migraine is a common neurological syndrome, rated as one of the most severe disabling disorders by the World Health Organization (1). It is managed pharmacologically with acute and preventive drug therapies. However, current treatment strategies are often suboptimal in terms of inadequate efficacy and substantial side effects (2). New treatment modalities are therefore warranted to better fulfill the therapeutic needs of migraineurs, especially patients suffering from severe and frequent migraine.

There is a growing interest in neuromodulation as a treatment for primary headache disorders. Applying electrical stimulation to relieve pain syndromes is no new approach, but within recent years devices and stimulation protocols have become more accurate and less invasive. While neuromodulation was previously limited to drug-refractory patients, it is now increasingly applied as an alternative to acute and prophylactic therapy (2), raising the question whether it can serve as a valid option in the treatment of migraine.

In addition to the diagnostic criteria specified by the International Headache Society (1), migraine can be associated with cranial autonomic symptoms (CAS) of lacrimation, conjunctival injection, eyelid edema, nasal congestion, and forehead/facial sweating (3,4) in 27% to 73% of cases depending on criteria

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and study design (3–6). This correlation is not limited to adults but also includes migraineurs under the age of 18 years, with a recent study showing 62% of children and adolescents complaining of migraine-associated CAS (7). The presence of CAS in migraineurs suggests activation of the trigemino-autonomic reflex resulting in increased parasympathetic outflow (8), as in the trigeminal autonomic cephalalgias (including cluster headache (CH), chronic paroxysmal hemicranias and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT)). In the latter headache group, clinicians have long attempted to treat attacks and associated symptoms by targeting the sphenopalatine ganglion (SPG), a procedure first introduced at the beginning of the 20th century by Sluder to treat so-called Sluder's neuralgia, a type of trigeminal autonomic cephalalgia (9). Besides pharmacological blocks, SPG interventions have since included surgical or radiofrequency ablations, radiosurgical targeting or lesions (10–13). As the SPG is the major source of parasympathetic innervation not only to the face but also to the cranial cavity, SPG activation could also be a likely contributor to migraine pathophysiology.

A multicenter study (Pathway M1: Sphenopalatine Ganglion Stimulation for the Treatment of Chronic or High Frequency, High-Disability Migraine Headache) is currently under way, a randomized, controlled, interventional, prospective study to evaluate the use of an implanted SPG neurostimulator for the treatment of migraine headache pain, migraine headache symptoms and migraine frequency in high-disability migraineurs (clinicaltrial.gov: NCT01540799). Inclusion criteria comprise subjects reporting at least 75% of migraine attacks to be fixed unilateral, preferably with associated CAS.

This review will focus on the SPG as a possible target for treating migraine. We will describe the pathophysiology of migraine, concentrating on a parasympathetic dysfunction and the possible role of a hypothalamo-parasympathetico-trigeminal triangle. In addition, we will discuss the possible rationale for potential therapeutic effects of SPG neurostimulation in migraine.

Methods

Search strategy and selection criteria

We searched PubMed for publications on SPG's influence on migraine, ultimately selecting articles from the period 1908–2013. The keywords were "sphenopalatine ganglion," "migraine," "trigeminovascular pathway," "trigeminal-parasympathetic reflex," "neuromodulation," and "neurostimulation." The search was limited to English language publications and resulting articles were reviewed based on their abstracts to include only pertinent publications, dealing specifically with CAS in migraineurs, anatomical and functional connections between the SPG, cerebral vessels, trigeminovascular system and hypothalamus, and possible therapeutic prospects of SPG neurostimulation.

Anatomo-functional characteristics of the SPG and the trigemino-parasympathetic reflex

The SPG is the largest extracranial parasympathetic ganglion (Figure 1), with sensory and sympathetic fibers also projecting through the ganglion, however, without synapsing. The parasympathetic fibers originate in the superior salivatory nucleus (SSN) of the pons and supply extra- and intracerebral arteries (14–16), the lacrimal gland (17,18), nasal mucosa (19,20), conjunctiva (20), and Müller's muscle in the upper eyelid (21). Sympathetic fibers originate in the internal carotid plexus to innervate the lacrimal gland, nasal, and palatine mucosa (22). The sensory root originates in the maxillary nerve, supplying the nose, palate, tonsil, and gingiva (22).

Physiologically, low-frequency electrical stimulation of the SPG (10–20 Hz) in animal studies has revealed dilation of intra- and extracranial arteries, increased cerebral blood flow (CBF), and plasma protein extravasation (PPE) in the dura mater (Table 1). PPE is mediated by sensory neurons that contain potent vasodilator neurotransmitters such as calcitonin gene-related peptide (CGRP), substance P (SP), and neurokinin A (NA) (23). As PPE may activate meningeal nociceptors to induce the headache of migraine via neurogenic inflammation (23,24) and dilation of intra- and extracranial arteries is related to migraine attacks (25–27), these effects of SPG stimulation contribute to the pathophysiologic understanding of migraine while introducing the prospect of targeting the ganglion with high-frequency stimulation (100 Hz) for treatment purposes.

The trigemino-parasympathetic reflex consists of a brainstem connection between trigeminal afferents and parasympathetic efferents of the facial nerve that synapse in the SPG (8,34,35). The reflex has been broadly demonstrated in animal and human studies, showing that trigeminal ganglion stimulation leads to intra- and extracranial vasodilation (36–38), increased regional CBF (39,40), and increased facial temperature, a response that is abolished by lesioning the facial nerve (41). Furthermore, painful stimulation of the ophthalmic nerve innervation area results in internal carotid

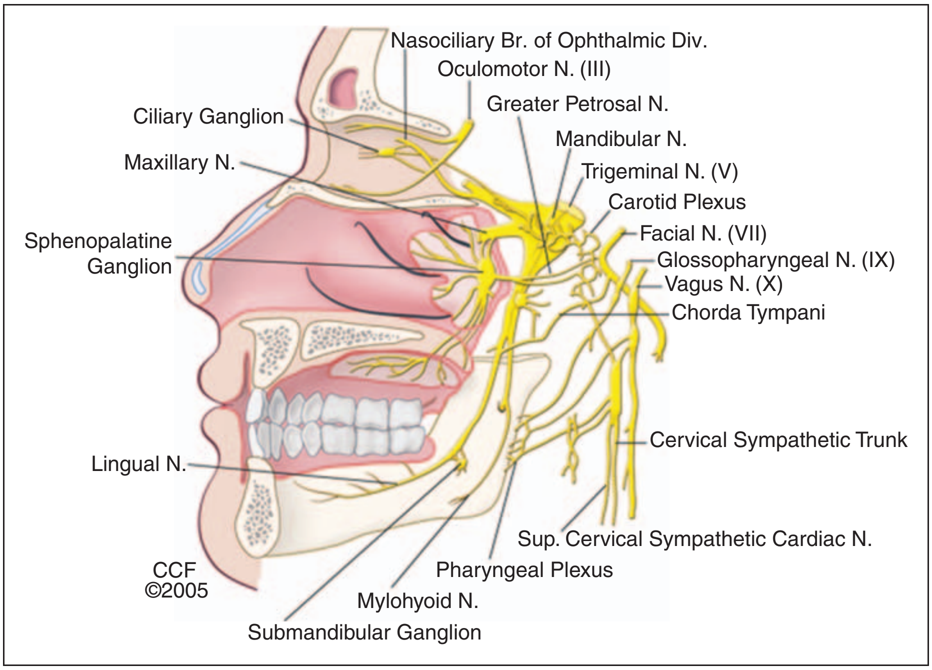

Figure 1. Anatomy of the sphenopalatine ganglion (SPG) and associated structures. The SPG is triangular shaped, located in the pterygopalatine fossa, and suspended from the maxillary nerve via the two pterygopalatine nerves. Posteriorly, it is connected to the Vidian nerve formed by the greater petrosal and the deep petrosal nerves. Efferent branches from the ganglion include the superior posterior lateral nasal, nasopalatine, greater and lesser palatine, and pharyngeal nerves. Caudally the ganglion is in direct connection with the greater and lesser palatine nerves.
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artery dilation, CAS, as well as increased ipsilateral blood flow and lacrimal response, of which the latter two effects are also inhibited by facialis lesioning (38,42–44).

Migraine and the parasympathetic nervous system

Involvement of the autonomic nervous system (ANS) in migraine is considered likely given the symptoms commonly associated with attacks; nausea, emesis, conjunctival injection, lacrimation, nasal congestion, rhinorrhea, salivation, diarrhea, and polyuria (45). Though an alleged autonomic dysfunction has been dealt with widely, migraine pathophysiology is complex, and results have advocated both hypo- and hyperfunction of the sympathetic and parasympathetic systems (Table 2) (46–54).

Involvement of specifically the parasympathetic nervous system is considered plausible as 1) CAS such as lacrimation, rhinorrhea, and eyelid edema are parasympathetic manifestations (55), 2) levels of vasoactive intestinal polypeptide (VIP) are elevated in cranial venous blood during attacks in patients with symptoms of lacrimation and rhinorrhea (56), 3) meningeal blood vessels receive dense parasympathetic innervation, 4) preganglionic parasympathetic neurons in SSN increase their activity after activation of meningeal nociceptors (57,58), and 5) intranasal application of lidocaine, which may block the SPG, is shown to abort migraine within 15 minutes in 36% of patients in a studied population (11). These latter results should be taken with caution as the effect may be due to blockade of the trigeminovascular afferents passing near the ganglion rather than blockade of the parasympathetic fibers (45). However, Yarnitsky et al. (59) interestingly suggested that SPG might not only play a role in mediating the CAS of migraine but may also contribute to the pain. This is based on their observations that patients with parasympathetic symptoms were more likely to experience pain relief by lidocaine than patients without parasympathetic symptoms, with a pain reduction of 53% and 15%, respectively.

Avnon et al. (46) studied the trigemino-parasympathetic reflex in migraineurs interictally by instilling soapy eye drops to activate the afferent limb, then measuring subsequent cutaneous vascular and systemic cardiovascular responses as a marker of parasympathetic activity. The authors concluded that autonomic dysfunction in migraine exhibits laterality with parasympathetic hyperfunction in left-sided migraineurs. This concept of asymmetric cerebral function has been suggested previously in studies on the autonomic control of the heart, where the left hemisphere

Table 1. Results of low frequency sphenopalatine ganglion (SPG) stimulation in animal studies.

Reference	Animal	Methods	Stimulation frequency	Stimulation duration	Outcome
Goadsby, 1990 (28)	Cat	Unilateral SPG stimulation	10 Hz	*Short stimulation:* 7–10 minutes *Long stimulation:* 45 minutes, both consisting of 250 μs duration, 500 μs separation	Increased regional CBF in ipsilateral cortex, with no changes in cerebral glucose utilization
Delépine and Aubineau, 1997 (29)	Rat	SPG stimulation after pretreatment with either atropine or capsaicin. Effect of carbachol infusion studied	20 Hz	Trains of rectangular pulses, one second on, one second off, 10 minutes' duration.	PPE in dura mater on the stimulated side. PPE is induced by carbachol infusion, reduced by capsaicin pre-treatment, and abolished by atropine pretreatment
Yarnitsky et al., 2005 (30)	Dog	Unilateral SPG stimulation seven days after induced SAH	10 Hz	Two sets of three 90-second stimulations separated by 60-second off time, administered 30 minutes apart	Dilation of ipsilateral extracranial and intracranial ICA, MCA, and ACA arteries
Bar-Shir et al., 2010 (31)	Rat	SPG stimulation 18 $\pm$ 2 hours after MCA occlusion	10 Hz	Two 60-second pulses separated by 12 seconds off time, applied every 15 minutes for three hours	Improved ischemic tissue condition and increased levels of N-acetyl-aspartate AA in treated animals
Takahashi et al., 2011 (32)	Monkey	Unilateral SPG stimulation seven days after induced SAH	10 Hz	Two sets of three 90-second stimulations separated by 60-second intervals, administered 30 minutes apart	Dilation of ipsilateral extracranial and intracranial ICA, MCA and ACA and increase of ipsilateral CBF.
Levi et al., 2012 (33)	Rat	Unilateral SPG stimulation either 15 minutes or 24 hours after induced focal cerebral ischemia	10 Hz	*Acute experiments:* 12 trains of two sets of 60-second stimulation separated by 12-second interval, followed by 13.6 minutes off time. *Chronic experiments:* three hours per day, four consecutive days	Dilation of pial vessels and increased CBF in healthy and photothrombotic brains and reduced blood brain-barrier permeability

CBF: cerebral blood flow; SAH: subarachnoid hemorrhage; PPE: plasma protein extravasation; ICA: internal carotid artery; MCA: middle cerebral artery; ACA: anterior cerebral artery.

Table 2. Studies reporting autonomic nervous system dysfunction interictally in patients with migraine, with and without aura.

	Reference	Test type	Reported ictal ANS dysfunction	Presence of aura	Conclusion
Testing cranial autonomic function	Avnon et al., 2004 (46)	Trigemino-parasympathetic reflex	±	±	Parasympathetic hyperfunction
	Drummond et al., 1997 (47)	Trigemino-parasympathetic reflex	N/A	±	Parasympathetic hypofunction
	Micieli et al., 1989 (48)	Pupillometry	±	±	Sympathetic hyperfunction or parasympathetic hypofunction
Testing systemic autonomic function	Havanka-Kanniainen et al., 1986 (49)	Cardiovascular tests	+	±	Sympathetic and parasympathetic hypofunction
	Pogacnik et al., 1993 (50)	Cardiovascular tests[a]	+	±	Sympathetic hypofunction
	Yakinci et al., 1999 (51)[c]	Cardiovascular tests	N/A	–	Sympathetic and parasympathetic hyperfunction
	Mosek et al., 1999 (52)	Cardiovascular tests, sudomotor axon-reflex test	N/A	±	Sympathetic hypofunction
	Sanya et al., 2005 (53)	Baroreflex	N/A[b]	±	Parasympathetic hypofunction

ANS: autonomic nervous system. aCardiovascular tests include: Valsalva maneuver, deep breathing test, handgrip test, orthostatic test, cold pressor test, head-up tilt test. bN/A: not applicable, i.e. not specified. cIncluding only children with migraine.

was found to predominantly affect parasympathetic function while the right hemisphere affects sympathetic function (60–63).

Collectively, these data suggest that ANS plays an important role in migraine pathogenesis, where the SPG in particular may mediate parasympathetic hyperactivity considering the efferent fibers, neurotransmitter, and innervation organs of the ganglion (14–16,18–20).

SPG and the migraine pathway: A rationale for aborting migraine with SPG stimulation

Studies on the effectiveness of SPG stimulation in migraine treatment are still pending. However, assuming a pivotal role of SPG in the pathogenesis and phenotype of migraine based on above considerations, how may we expect stimulation of the ganglion to abort an attack? We propose two hypotheses.

SPG modulates parasympathetic postganglionic outflow

Burstein and Jakubowski (57) have proposed that common migraine triggers (such as stress and awakening) may activate brain areas that all project to the SSN. The SSN then stimulates the release of parasympathetic neurotransmitters VIP, nitric oxide, and acetyl choline from meningeal terminals of SPG neurons (58). This cascade of parasympathetic activation results in dilation of intracranial blood vessels, PPE, and local release of inflammatory molecules to activate meningeal nociceptors, and thereby induce the migraine headache (23,57). Based on this theory of a common descending pathway that activates meningeal nociceptors, SPG neuromodulation may abort an attack by interrupting the centrally initiated cascade of parasympathetic outflow, possibly by depleting stored neurotransmitter. Inhibiting the activation of the trigeminal afferents may also cancel out triggering of the trigemino-autonomic reflex, thus hindering CAS presentation. Interestingly, Akerman et al. (64) have shown that low-frequency stimulation of the SSN in cats leads to firing of trigeminovascular neurons in the trigeminocervical complex as well as increased blood flow to the lacrimal sac, mediated by increased parasympathetic output. This response emphasizes the prospect that high-frequency SPG stimulation may decrease parasympathetic output, thereby inhibiting the excitatory action on trigeminal nociceptors to alleviate migraine pain and associated autonomic symptoms.

Tepper et al. (65) applied SPG stimulation to treat intractable migraine ($n = 11$), where two patients experienced complete abolition of the headache and three experienced pain reduction. While these results may not be conclusive as to the beneficial potential of this treatment, the authors conclude that lack of headache relief appears linked to suboptimal lead placement, poor physiological response, and diagnosis of medication-overuse headache. Ansarinia et al. (66) achieved more promising results in the treatment of acute CH, where complete resolution was obtained in 11 out of 18 attacks, and > 50% relief in an additional four attacks. Most recently, Schoenen et al. (67) published results of the randomized, sham-controlled pathway CH-1 study of SPG stimulation for chronic CH (CCH) treatment. This study included in total 28 eligible patients; 67.1% of attacks were relieved in 64% of patients and 43% had a ≥ 50% reduction in attack frequency. Acute pain relief as well as reduction in attack frequency were reported in 7% of patients. The authors concluded that SPG stimulation is an effective novel therapy for CCH sufferers, with a bimodal benefit: acute pain relief and attack prevention. The acute pain relief may arise because of SPG stimulation acting on the trigeminal nociceptive system via an inhibitory information block from the SPG to the target organs of CH (66). The prophylactic effect, however, may stem from antidromic hypothalamic modulation, the hypothalamus being a main contributor to the pathophysiology of CH (68–70). Anatomically, hypothalamus modulation through SPG stimulation is feasible as the ganglion receives parasympathetic fibers from the SSN, which in turn receives input from the hypothalamus.

SPG modulates sensory processing in trigeminal nucleus caudalis (TNC)

Could SPG stimulation result in pain relief due to modulation of sensory processing in the TNC rather than blockade of SPG parasympathetic output? While SPG stimulation has shown to produce mild residual facial pain in the maxillary distribution area (66), migraine headache is experienced in the innervation area of the ophthalmic nerve. Therefore, any pain relief due to sensory processing would presumably stem from a central modulation based on the convergence of trigeminal afferents in the TNC (71), an antinociceptive mechanism similar to that of ONS (72), as occipital nerve fibers also converge centrally with afferents from the first trigeminal branch.

In the parallel discussion of how occipital nerve stimulation (ONS) may be effective in treating CH patients, Magis et al. (69,73) suggest that ONS works by inducing slow neuromodulatory changes in central pain processing structures, rather than by sensory processing in the TNC. A positron-emission tomography (PET) study performed in CH patients treated with ONS showed that hypermetabolism in the pain-associated areas (e.g. cingulate gyrus and midbrain) prior to treatment normalized over three to six months with ONS, while hypermetabolism in the hypothalamus remained unchanged (70). These results suggest that ONS acts symptomatically rather than causally, as the study did not prove ONS to alter the activity of the hypothalamus. If we assume that the same mode of action applies to migraineurs, SPG stimulation might act symptomatically because of neuromodulatory changes in central pain processing structures, while not affecting the actual pathophysiology of migraine.

Assuming that our hypothesis of migraine pain alleviation through sensory modulation in TNC is viable, we cannot entirely exclude the consideration that trigeminal neurostimulation in itself may be equally effective, thus not necessarily implicating the SPG. In support of this, a recent randomized controlled trial shows that supraorbital transcutaneous stimulation is effective in preventing migraine (74). Finally, because of the close spatial connection between the SPG and surrounding structures, focal stimulation of the SPG may prove challenging. Therefore, parasympathetic and sensory fibers in the ganglion are possibly targeted simultaneously during SPG stimulation, and our proposed hypotheses of parasympathetic respective sensory modulation may not be mutually exclusive, but rather additive.

Methodological limitations of existing studies on autonomic dysfunction in migraine

There is currently no scientific consensus on the degree and character of autonomic dysfunction in migraineurs. The results of applied studies are largely contradictory (Table 2), even when comparing studies employing identical tests, indicating that objective verification of ANS dysfunction is complex.

Studies have largely investigated patients exhibiting the large spectrum of autonomic features (including nausea, vomiting, diarrhea, etc) rather than CAS specifically, leading to the question whether these tests have actually investigated the factor relevant to our focus, i.e. cranial autonomic dysfunction as migraine pain and CAS precipitator? Only two studies employ tests that specifically examine the cranial autonomic function, i.e. the trigemino-parasympathetic reflex and pupillometry test. Cardiovascular tests are more widely applied, but is cardiovascular dysfunction necessarily indicative of overall autonomic dysfunction, or indeed cranial dysfunction?

We need a refined test battery to specifically investigate cranial autonomic function in migraineurs to fully assess the possible role of SPG stimulation in migraine treatment. Also, more optimal patient stratification is warranted to provide detailed information on the degree of autonomic dysfunction and to increase the specificity of applied tests.

Future perspective

Based on anatomic and physiological considerations, parasympathetic nervous system involvement in migraine pathophysiology is probable. Therefore, interrupting the autonomic pathway that possibly both generates the pain of migraine and mediates CAS via the trigemino-parasympathetic reflex may serve to inhibit the initiation and presentation of this debilitating primary headache.

We suggest a possible role for SPG stimulation in the treatment of migraine, considering the central role of SPG in mediating parasympathetic outflow to structures of the cranium involved in migraine with CAS, particularly the cranial vessels, meninges, lacrimal gland, nasal mucosa, and conjunctiva. We hypothesize that SPG stimulation may work by either of two mechanisms to terminate migraine; 1) interrupting parasympathetic outflow of the ganglion by interfering with preganglionic SSN to SPG efferents or postganglionic outflow, or 2) modulating the sensory processing in TNC, perhaps by way of slow neuromodulatory changes to the pain processing structures of the brain stem. Admittedly, since attack-associated autonomic symptoms are more dramatic in the trigeminal autonomic cephalalgias than in migraine and because outcome in the proof-of-concept study of SPG stimulation during migraine attacks by Tepper et al. (65) was less favorable than that observed with the same method in CH attacks, one might expect migraineurs to benefit less from SPG stimulation than CH patients. However, we should be cautious in drawing any firm conclusions based on studies with small sample sizes. Also, there may be a tendency to overlook autonomic symptoms in migraineurs as they are often not spontaneously reported by the patients.

CAS presentation is not a prerequisite for SPG stimulation, as we anticipate analgesia attributed to the effects of neuromodulation. Such pain relief has been suggested to stem from activation of afferent Aβ fibers and gate control in the spinal cord (75) or from a descending supraspinal control from the periaqueductal gray matter and rostroventromedial medulla (76).

Additional clinical trials are needed to fully uncover whether optimal treatment is achieved by stimulating uni- or bilaterally. Prominent symptom and pain laterality may indicate unilateral stimulation, while side-shift occurrence (68,77) may advocate for bilateral stimulation.

A possible role of the hypothalamus in migraine onset is supported by the premonitory symptoms experienced prior to attack onset, the nature of typical migraine triggers (including stress regulation, sleep, food intake, and hormonal changes) and the neuronal connection between hypothalamus and SSN (57,78,79). Moreover, in a recent imaging study hypothalamic activation was demonstrated during the premonitory phase of migraine attacks (80). Could SPG stimulation then work antidromically to modulate hypothalamic output, thereby preventing the autonomic cascade that initiates migraine? At present, there are no data supporting a hypothalamic effect of SPG stimulation. However, this thesis may be worth investigating further, seeing as the application of neuromodulation to affect upstream components is no new therapeutic concept. Namely, vagus nerve stimulation is widely recognized as an effective treatment of intractable epilepsy, approved by the United States Food and Drug Administration (FDA) in 1997 (81–83).

Overall, more refined studies on autonomic dysfunction in migraineurs will aid in assessing the therapeutic relevance of SPG neurostimulation. Also, future randomized clinical trials using SPG stimulation to treat migraine are warranted to conclude on its true promise as treatment modality as well as to uncover how exactly a beneficial effect is exerted.

Clinical implications

- Migraine symptoms including parasympathetic manifestations of lacrimation, nasal congestion, conjunctival injection, and parasympathetic activity may also contribute to the pain of migraineurs.
- The sphenopalatine ganglion (SPG) is the largest extracranial parasympathetic ganglion of the head, innervating structures involved in migraine with cephalic autonomic symptoms.
- Because of the association between innervation organs of the SPG and the clinical presentation of migraine, we suggest the prospect of treating migraine with SPG neurostimulation.
- Two possible mechanisms of action are: 1) interrupting the post-ganglionic parasympathetic outflow to inhibit the pain and cephalic autonomic symptoms, and 2) modulating the sensory processing in the trigeminal nucleus caudalis.

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Conflicts of interest

Dr Messoud Ashina is a principal investigator in the ongoing Pathway M-1 trial: Sphenopalatine Ganglion Stimulation for the Treatment of Chronic or High Frequency, High Disability Migraine Headache (ClinicalTrials.gov Identifier: NCT01540799). The remaining authors have nothing to declare.

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