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Parasympathetic Cholinergic and Neuropeptide Mechanisms of Migraine

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Abstract

Context: Migraine mechanisms remain largely uncovered for various reasons including a very high complexity of the neurophysiological mechanisms implicated in this disorder and a plethora of endogenous biologically active compounds involved in the pathological process. The functional role of parasympathetic innervation of meninges and cholinergic mechanisms of migraine are among little explored issues despite multiple evidence indirectly indicating the role of acetylcholine (ACh) and its analogues in migraine and other types of headache. In the current short review, we discuss morphological, functional, and clinical issues related to the role of ACh and its analogues such as carbachol and nicotine in this most common neurological disorder.

Evidence Acquisition: In the present work, studies published from 1953 to 2016 were investigated. Literature was searched with following keywords: acetylcholine (ACh), carbachol, nicotine, parasympathetic, mast cells, vasoactive intestinal polypeptide (VIP), and pituitary adenylate cyclase-activating polypeptide (PACAP).

Results: Parasympathetic fibers originated from SPG and trigeminal nerves can interact at the level of meninges which is considered to be the origin site of migraine pain. Here, in dura mater, ACh, VIP, and PACAP released by parasympathetic afferents can both affect mast cells provoking its degranulation and additional release of neurotransmitters, or they can directly affect trigeminal nerves inducing nociception.

Conclusions: In summary, cholinergic mechanisms in migraine and other types of headache remain little elucidated and future studies should clarify the role of parasympathetic nerves and molecular mechanisms of cholinergic modulation within the nociceptive system.

Keywords: Migraine, Headache, Cholinergic, Trigeminal Pain, Mast Cells, Nicotine

1. Context

The pathophysiology of migraine pain, especially of severe migraine, remains largely unknown despite high prevalence of this neurological disorder. In the current review, we present data on the parasympathetic innervation of meninges, cholinergic, and neuropeptide modulation of nociception, the control of mast cells implicated in early stages of migraine attack, the local cranial parasympathetic effects and general role of parasympathetic nerves in migraine, and the effect of smoking in development of headaches. These data extend our knowledge on little explored aspects of migraine pathology and can serve as a background for development of new type medicines in the complex therapy of this common neurological disorder.

2. Evidence Acquisition

Various reliable databases, such as PubMed and Web of Science, were searched for literature. The search was conducted using following keywords: migraine, acetylcholine, carbachol, nicotine, parasympathetic, mast cells, degranulation, VIP (vasoactive intestinal polypeptide), PACAP (pituitary adenylate cyclase-activating polypeptide). Some keywords were coupled for more relevant search results (e.g., “acetylcholine + migraine”, “carbachol + migraine”, “mast cells + degranulation”). All irrelevant, duplicated and not reliable records, such as records in books of abstracts, were excluded from consideration. Works published from 1953 to September 2016 are presented in the current review.

3. Results

3.1. Parasympathetic Innervation of Meninges

The mechanism and location of migraine pain are the main mysteries of this pathology. One of the most important issues in this field (which determines the therapeutic

strategy) is what the origin site of migraine pain is. According to the prevailing view, meninges, including dura mater and pia matter densely innervated by somatic and autonomous nerves, are supposed to be a main origin site of migraine pain (1-3). However, whereas the trigeminal somatic innervation has attracted most attention from researchers working in this field, much less is known on the function of parasympathetic innervation and cholinergic ACh-mediated control of meninges.

It has been already shown that meninges are essentially innervated by parasympathetic fibers coming from sphenopalatine ganglion (SPG). It was supposed (4) that apart from other local targets, parasympathetic nerves can interact directly with somatic trigeminal fibers, which are located next to meningeal vessels. SPG can even be one of the triggering sites of migraine, as it has been shown (5) that the electrical stimulation of SPG provokes migraine-like effects in the case of rats' dura mater. Moreover, the blockage of SPG in patients with migraine can diminish manifestations of the disorder such as headache (6). In addition, a novel treatment of cluster headache was proposed in a recent study (7): a single injection of onabotulinumtoxin A to the SPG significantly reduced the number of headache attacks. Another argument testifying the SPG role in pathophysiology of migraine is the enrichment of SPG, besides ACh, with the neuropeptide pituitary adenylate cyclase-activating polypeptide (PACAP), as one of the main migraine mediators (8, 9). Finally, in a recent work (10) it has been suggested that parasympathetic mechanisms, in particular the neurotransmitters expressed in SPG, are important for induction of cluster headache.

3.2. Acetylcholine and Carbachol Induce Headache

As mentioned above, the parasympathetic fibers originated from SPG and trigeminal nerves can interact at the level of meninges (4). The main neurotransmitter released from parasympathetic nerves is acetylcholine (ACh). ACh can modulate neuronal activity (11) via ligand-gated widespread nicotinic receptor (nAChR) or metabotropic muscarinic receptor (mAChR). It was shown, for instance, that in-vivo ACh can activate nociceptive fibers innervating rabbit cornea (12). Long time ago, it was noted that ACh is able to induce local pain in human after cutaneous application (13), suggesting a pro-nociceptive potential of this neurotransmitter.

Carbachol, which is a stable synthetic cholinomimetic agent, (14) acts like ACh, through both nicotinic and muscarinic receptors (4). Similar to ACh, carbachol shows a pro-nociceptive action. A previous study demonstrated the ability of carbachol to activate nociceptive fibers in rat skin (15). More recent double-blind crossover study (14) demonstrated that carbachol could induce headache in healthy subjects. It was shown in placebo-controlled study (16) that carbachol can also induce headache in patients with migraine without aura. In a clinical study (7), a blockage of SPG, and hence inhibition of ACh secretion from parasympathetic nerves, decreased the frequency of cluster headache attacks. Likewise, blockade of the stellate ganglion provides analgesia in chronic regional pain syndrome (17). Among other instrumental approaches for pain treatment, the pulsed radiofrequency (18, 19) represents as one of the promising approaches.

The mechanism of carbachol-induced headache seems to involve endothelial production of nitric oxide (NO) which is a pro-nociceptive agent (16). In particular, NO can act as a substrate for HNO (nitroxyl) production, which is an agonist of the pro-nociceptive TRPA1 receptors expressed in sensory neurons (20). Apart from nociceptive firing, the activation of TRPA1 receptors leads to the release of the main migraine mediator, neuropeptide calcitonin-gene-related peptide (CGRP), and subsequent vasodilation through activation of vascular CGRP receptors (20). In addition, carbachol also demonstrated a direct vascular effect due to the ability to dilate human cranial vessels (21).

3.3. ACh-Induced Degranulation of Mast Cells and Migraine Triggers

Another potential target for ACh released from parasympathetic nerves in meninges is dural mast cells, which are abundantly expressed in these tissues (22). Intracranial dural mast cells are immune cells localized in close proximity to dural nociceptive nerve fibers (22, 23). Mast cells which contain, in intracellular granules, a large amount of pro-inflammatory and pro-nociceptive neurotransmitters, hormones and cytokines are likely important players in migraine pathology (24). It is known that both ACh and carbachol are potent inducers of degranulation of mast cells (23). Therefore, it is possible that ACh secreted in meninges from parasympathetic nerves can target directly mast cells to induce degranulation accompanied by a local burst of the 'inflammatory soup'. Thus, degranulation of mast cells can lead to persistent activation of dural nociceptors and this could be a neurochemical mechanism of headache in migraine or other primary headaches (22). This is an interesting issue, which deserves further study, especially in the view of available mast cells stabilizers that potentially can block the pro-nociceptive effect of ACh or other degranulators of mast cells.

3.4. Parasympathetic Regulation in Migrainers

The other potential targets of ACh in meninges are local vessels. Vessels in dura mater are highly innervated

not only by somatic but also by autonomous nerves, and during migraine attack they initially experience dilatation, which is often followed by vasoconstriction (25). This bidirectional effect might be more complex than a simple action of the potent vasodilator CGRP. Apart from vessels in meninges, other head and face tissues are also innervated both by somatic trigeminal nerve branches and autonomous nerves. Therefore, migraine or cluster headache, apart from pain symptoms, are often manifested by local autonomous symptoms in the head and face area. Indeed, it is well known that in the majority of patients with chronic migraine, there are clinical phenomena such as sinusitis, conjunctival injection, lacrimation, nasal congestion, rhinorrhea, eyelid edema, sweating, and facial flushing (26). These phenomena are likely caused by parasympathetic system resulting from activation of the trigemino-autonomic reflex. This increased sensitivity to visual, auditory and olfactory stimulation is probably related to the decreased descending inhibitory pain control (27).

Apart from clear local parasympathetic cranial effects, another important issue is whether general changes in activity of the autonomous system occur in migraine. In a previous study, we showed that patients predisposed to headache had a reduced nose temperature (28). However, this low temperature effect was also observed in human extremities (29), suggesting a more general autonomous disturbance. In the same line, a previous work (30) considered migraine as a systemic vasculopathy, suggesting global changes in the vascular reactivity.

It is commonly accepted that even in the interictal period, many pathophysiological mechanisms of migraine remain active and hence, one would expect that autonomous changes could be detected between attacks. However, clinical testing of the autonomous function during migraine attack or in the interictal period is complicated partially due to various indirect approaches for this evaluation. Several authors found essential but still indirect evidence on parasympathetic regulation in migraine such as enhanced level of the ACh co-transmitter vasoactive intestinal polypeptide (VIP) (31) or increased heart rate variability (32), whereas others reported no significant changes (33, 34). In our recent work (35), we used a combination of several tests, such as tilt-test, deep breathing test, Valsalva maneuver, handgrip test, cold-stress test, and baroreflex assessment, for complex evaluation of the cardiac and vascular reactivity in the interictal period of episodic and chronic migraine. One of the main findings was that in migraine only vasomotor not cardiac autonomous regulation changed. The most significant effect that we found was essentially increased activity of the sympathetic nervous system. In contrast, tests such as Valsalva ratio, heart rate variability at rest and during tilt-test did not indicate abnormal tonus or unusual reactivity of the parasympathetic nervous system. Our obtained results suggested that despite the well-known local changes in the activity of cranial parasympathetic nerves, there is no global disturbance in the state of the parasympathetic regulation in episodic or even in chronic migraine.

3.5. VIP and PACAP as Indicators of Activation of Parasympathetic Nerves

In addition to PACAP, VIP has been found in parasympathetic ganglia along with ACh (36). It is supposed that both VIP and PACAP can contribute to or partially mediate the effect of autonomic nervous system (37). For instance, PACAP has been shown to facilitate ACh effect in the chick embryonic ciliary ganglia (38). In neurons extracted from rat's intracardiac and submandibular ganglia, VIP and PACAP increased the action of nicotinic agonists (37). Moreover, VIP and PACAP can induce mast cell degranulation (39), which as mentioned above, can contain a number of pronociceptive mediators.

Significantly increased level of VIP was shown in the blood of patients during headache attacks (40). In addition, there is a recent report on the release of PACAP in episodic cluster headache patients (41). Importantly, the intravenous infusion of PACAP can induce migraine-like attacks in migrainers (9). Thus, both VIP and PACAP are located in parasympathetic nerves and their release can indicate activation of the autonomic nervous system. Moreover, PACAP can be considered as one of the endogenous agents, which can trigger migraine.

3.6. Tobacco Smoking Triggers Headache

It has been reported that smokers suffer from migraine more often than non-smokers (42, 43) suggesting a potential pro-nociceptive action of nicotine. Tobacco smoking is frequently suggested to be a trigger for acute migraine attacks (44-46). However, this is a highly disputable issue and there are different suggestions about the relationship between tobacco smoking and headache (47). Thus, unlike the idea that tobacco smoking is a trigger of migraine, there are suggestions that migraine and smoking are independent manifestations of the common risk factors. One of the most convincing investigations conducted on 3000 participants in northern Finland reported no correlation between smoking and headache (48). Another opposite view suggests the anti-nociceptive action of nicotine as well as the appearance of headache in the case of abstinence from smoking (49). The anti-nociceptive action of nicotine has been stated repeatedly in in-vivo models (50, 51). One of the reasons for the contradictory results

with nicotine could be the presence of distinct molecular targets different from ACh receptors in the nociceptive system, for instance, interaction with the pro-nociceptive TRPA1 receptors in sensory neurons (52).

Unlike the clear evidence on the degranulating ability of ACh and carbachol, the action of nicotine on mast cells remains unclear. The ability of tobacco smoke to provoke mast cell degranulation has been shown in isolated mast cells (53). The opposite evidence was also obtained demonstrating the stabilizing effect of nicotine (54).

4. Conclusions

In summary, parasympathetic innervation of meninges can be considered as an important part of migraine pathophysiology. Multiple neurotransmitters such as acetylcholine, VIP, and PACAP, which can be released from parasympathetic nerves, play an important role in the mechanism of dural nociception. The AChRs agonist nicotine has demonstrated contradictory results: whereas ones reported pro-nociceptive effect of nicotine, the others considered nicotine as an anti-nociceptive agent. Such contradiction can be explained by involvement of different molecular targets for nicotine, such as TRPA1 receptors, in nociception.

Thus, we can summarize that cholinergic mechanisms of migraine, cluster headache, and other types of headache have a number of conflicting aspects and need further investigation. We believe that future study will clarify the role of parasympathetic nerves and molecular mechanisms and pathways of cholinergic regulation in the peripheral nociceptive system.

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