

## Parasympathetic cholinergic and neuropeptide mechanisms of migraine

Mikhailov N., Mamontov O., Kamshilin A., Giniatullin R.  
Kazan Federal University, 420008, Kremlevskaya 18, Kazan, Russia

---

### Abstract

© 2016, Iranian Society of Regional Anesthesia and Pain Medicine (ISRAPM). 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.

<http://dx.doi.org/10.5812/aapm.42210>

---

### Keywords

Cholinergic, Headache, Mast cells, Migraine, Nicotine, Trigeminal pain

### References

- [1] Messlinger K. Migraine: where and how does the pain originate?. *Exp Brain Res.* 2009; 196 (1): 179-93. doi: 10.1007/s00221-009-1756-y. [PubMed: 19288089].
- [2] Zhang Y, Zhao S, Rodriguez E, Takatoh J, Han BX, Zhou X, et al. Identifying local and descending inputs for primary sensory neurons. *J Clin Invest.* 2015; 125 (10): 3782-94. doi: 10.1172/JCI81156. [PubMed: 26426077].

- [3] Zakharov A, Vitale C, Kilinc E, Koroleva K, Fayuk D, Shelukhina I, et al. Hunting for origins of migraine pain: cluster analysis of spontaneous and capsaicin-induced firing in meningeal trigeminal nerve fibers. *Front Cell Neurosci.* 2015; 9: 287. doi: 10.3389/fncel.2015.00287. [PubMed: 26283923].
- [4] Ebersberger A, Takac H, Richter F, Schaible HG. Effect of sympathetic and parasympathetic mediators on the release of calcitonin gene-related peptide and prostaglandin E from rat dura mater, in vitro. *Cephalalgia.* 2006; 26 (3): 282-9. doi: 10.1111/j.1468-2982.2005.01035.x. [PubMed: 16472334].
- [5] Delepine L, Aubineau P. Plasma protein extravasation induced in the rat dura mater by stimulation of the parasympathetic sphenopalatine ganglion. *Exp Neurol.* 1997; 147 (2): 389-400. doi: 10.1006/exnr.1997.6614. [PubMed: 9344563].
- [6] Cady R, Saper J, Dexter K, Manley HR. A double-blind, placebocontrolled study of repetitive transnasal sphenopalatine ganglion blockade with tx360 ((R)) as acute treatment for chronic migraine. *Headache.* 2015; 55 (1): 101-16. doi: 10.1111/head.12458. [PubMed: 25338927].
- [7] Bratbak DF, Nordgard S, Stovner LJ, Linde M, Folvik M, Bugten V, et al. Pilot study of sphenopalatine injection of onabotulinumtoxinA for the treatment of intractable chronic cluster headache. *Cephalalgia.* 2016; 36 (6): 503-9. doi: 10.1177/0333102415597891. [PubMed: 26232105].
- [8] Edvinsson L, Uddman R. Neurobiology in primary headaches. *Brain Res Brain Res Rev.* 2005; 48 (3): 438-56. doi: 10.1016/j.brainresrev.2004.09.007. [PubMed: 15914251].
- [9] Guo S, Vollesen ALH, Hansen RD, Esserlind AL, Amin FM, Christensen AF. Part I: Pituitary adenylate cyclase-activating polypeptide-38 induced migraine-like attacks in patients with and without familial aggregation of migraine. *Cephalalgia.* 2016.
- [10] Steinberg A, Frederiksen SD, Blixt FW, Warfvinge K, Edvinsson L. Expression of messenger molecules and receptors in rat and human sphenopalatine ganglion indicating therapeutic targets. *J Headache Pain.* 2016; 17 (1): 78. doi: 10.1186/s10194-016-0664-3. [PubMed: 27587062].
- [11] Giniatullin R, Nistri A, Yakel JL. Desensitization of nicotinic ACh receptors: shaping cholinergic signaling. *Trends Neurosci.* 2005; 28 (7): 371-8. doi: 10.1016/j.tins.2005.04.009. [PubMed: 15979501].
- [12] Tanelian DL. Cholinergic activation of a population of corneal afferent nerves. *Exp Brain Res.* 1991; 86 (2): 414-20. doi: 10.1007/BF00228966. [PubMed: 1756814].
- [13] Armstrong D, Dry RM, Keele CA, Markham JW. Observations on chemical excitants of cutaneous pain in man. *J Physiol.* 1953; 120 (3): 326-51. doi: 10.1113/jphysiol.1953.sp004898. [PubMed: 13070204].
- [14] Schytz HW, Wienecke T, Oturai PS, Olesen J, Ashina M. The cholinomimetic agent carbachol induces headache in healthy subjects. *Cephalalgia.* 2009; 29 (2): 258-68. doi: 10.1111/j.1468-2982.2008.01715.x. [PubMed: 19143771].
- [15] Steen KH, Reeh PW. Actions of cholinergic agonists and antagonists on sensory nerve endings in rat skin, in vitro. *J Neurophysiol.* 1993; 70 (1): 397-405. [PubMed: 8103089].
- [16] Schytz HW, Wienecke T, Olesen J, Ashina M. Carbachol induces headache, but not migraine-like attacks, in patients with migraine without aura. *Cephalalgia.* 2010; 30 (3): 337-45. doi: 10.1111/j.1468-2982.2009.01929.x. [PubMed: 19614687].
- [17] Imani F, Hemati K, Rahimzadeh P, Kazemi MR, Hejazian K. Effectiveness of Stellate Ganglion Block Under Fluoroscopy or Ultrasound Guidance in Upper Extremity CRPS. *J Clin Diagn Res.* 2016; 10 (1): 09-12. doi: 10.7860/JCDR/2016/14476.7035. [PubMed: 26894152].
- [18] Imani F, Rahimzadeh P. Gabapentinoids: gabapentin and pregabalin for postoperative pain management. *Anesth Pain Med.* 2012; 2 (2): 52-3. doi: 10.5812/aapm.7743. [PubMed: 24223337].
- [19] Imani F. Using pulsed radiofrequency for chronic pain. *Anesth Pain Med.* 2012; 1 (3): 155-6. doi: 10.5812/kowsar.22287523.4047. [PubMed: 24904784].
- [20] Will C, Messlinger K, Fischer MJ. Vessel diameter measurements at the medullary brainstem in vivo as an index of trigeminal activity. *Brain Res.* 2016; 1632: 51-7. doi: 10.1016/j.brainres.2015.12.013. [PubMed: 26707407].
- [21] Grande G, Nilsson E, Edvinsson L. Comparison of responses to vasoactive drugs in human and rat cerebral arteries using myography and pressurized cerebral artery method. *Cephalalgia.* 2013; 33 (3): 152-9. doi: 10.1177/0333102412468340. [PubMed: 23197351].
- [22] Levy D, Kainz V, Burstein R, Strassman AM. Mast cell degranulation distinctly activates trigemino-cervical and lumbosacral pain pathways and elicits widespread tactile pain hypersensitivity. *Brain Behav Immun.* 2012; 26 (2): 311-7. doi: 10.1016/j.bbi.2011.09.016. [PubMed: 22019552].
- [23] Rozniecki JJ, Dimitriadou V, Lambracht-Hall M, Pang X, Theoharides TC. Morphological and functional demonstration of rat dura mater mast cell-neuron interactions in vitro and in vivo. *Brain Res.* 1999; 849 (1-2): 1-15. doi: 10.1016/S0006-8993(99)01855-7. [PubMed: 10592282].
- [24] Levy D, Burstein R, Kainz V, Jakubowski M, Strassman AM. Mast cell degranulation activates a pain pathway underlying migraine headache. *Pain.* 2007; 130 (1-2): 166-76. doi: 10.1016/j.pain.2007.03.012. [PubMed: 17459586].

- [25] Brennan KC, Beltran-Parrazal L, Lopez-Valdes HE, Theriot J, Toga AW, Charles AC. Distinct vascular conduction with cortical spreading depression. *J Neurophysiol.* 2007; 97 (6): 4143-51. doi: 10.1152/jn.00028.2007. [PubMed: 17329631].
- [26] Gelfand AA, Reider AC, Goadsby PJ. Cranial autonomic symptoms in pediatric migraine are the rule, not the exception. *Neurology.* 2013; 81 (5): 431-6. doi: 10.1212/WNL.0b013e31829d872a. [PubMed: 23897870].
- [27] Noseda R, Burstein R. Migraine pathophysiology: anatomy of the trigeminovascular pathway and associated neurological symptoms, cortical spreading depression, sensitization, and modulation of pain. *Pain.* 2013; 154 (1): 44-53. doi: 10.1016/j.pain.2013.07.021.
- [28] Zaproudina N, Narhi M, Lipponen JA, Tarvainen MP, Karjalainen PA, Karhu J, et al. Nitroglycerin-induced changes in facial skin temperature: 'cold nose' as a predictor of headache?. *Clin Physiol Funct Imaging.* 2013; 33 (6): 409-17. doi: 10.1111/cpf.12042. [PubMed: 23701267].
- [29] Zaproudina N, Teplov V, Nippolainen E, Lipponen JA, Kamshilin AA, Narhi M, et al. Asynchronicity of facial blood perfusion in migraine. *PLoS One.* 2013; 8 (12): 80189. doi: 10.1371/journal.pone.0080189. [PubMed: 24324592].
- [30] Tietjen GE. Migraine as a systemic vasculopathy. *Cephalalgia.* 2009; 29 (9): 987-96. doi: 10.1111/j.1468-2982.2009.01937.x. [PubMed: 19689607].
- [31] Cernuda-Morollon E, Martinez-Cambor P, Alvarez R, Larrosa D, Ramon C, Pascual J. Increased VIP levels in peripheral blood outside migraine attacks as a potential biomarker of cranial parasympathetic activation in chronic migraine. *Cephalalgia.* 2015; 35 (4): 310-6. doi: 10.1177/0333102414535111. [PubMed: 24847167].
- [32] Koenig J, Williams DP, Kemp AH, Thayer JF. Vagally mediated heart rate variability in headache patients—a systematic review and meta-analysis. *Cephalalgia.* 2016; 36 (3): 265-78. doi: 10.1177/0333102415583989. [PubMed: 25962595].
- [33] Mosek A, Novak V, Opfer-Gehrking TL, Swanson JW, Low PA. Autonomic dysfunction in migraineurs. *Headache.* 1999; 39 (2): 108-17. doi: 10.1046/j.1526-4610.1999.3902108.x. [PubMed: 15613203].
- [34] Yerdelen D, Acil T, Goksel B, Karatas M. Heart rate recovery in migraine and tension-type headache. *Headache.* 2008; 48 (2): 221-5. doi: 10.1111/j.1526-4610.2007.00994.x. [PubMed: 18070058].
- [35] Mamontov OV, Babayan L, Amelin AV, Giniatullin R, Kamshilin AA. Autonomous control of cardiovascular reactivity in patients with episodic and chronic forms of migraine. *J Headache Pain.* 2016; 17: 52. doi: 10.1186/s10194-016-0645-6. [PubMed: 27167136].
- [36] Braas KM, May V, Harakall SA, Hardwick JC, Parsons RL. Pituitary adenylate cyclase-activating polypeptide expression and modulation of neuronal excitability in guinea pig cardiac ganglia. *J Neurosci.* 1998; 18 (23): 9766-79. [PubMed: 9822736].
- [37] Liu DM, Cuevas J, Adams DJ. VIP and PACAP potentiation of nicotinic ACh-evoked currents in rat parasympathetic neurons is mediated by G-protein activation. *Eur J Neurosci.* 2000; 12 (7): 2243-51. doi: 10.1046/j.1460-9568.2000.00116.x. [PubMed: 10947803].
- [38] Margiotta JF, Pardi D. Pituitary adenylate cyclase-activating polypeptide type I receptors mediate cyclic AMP-dependent enhancement of neuronal acetylcholine sensitivity. *Mol Pharmacol.* 1995; 48 (1): 63-71. [PubMed: 7623776].
- [39] Bhatt DK, Gupta S, Olesen J, Jansen-Olesen I. PACAP-38 infusion causes sustained vasodilation of the middle meningeal artery in the rat: possible involvement of mast cells. *Cephalalgia.* 2014; 34 (11): 877-86. doi: 10.1177/0333102414523846. [PubMed: 24563332].
- [40] Goadsby PJ, Edvinsson L. Human in vivo evidence for trigeminovascular activation in cluster headache. Neuropeptide changes and effects of acute attacks therapies. *Brain.* 1994; 117 (Pt 3): 427-34. doi: 10.1093/brain/117.3.427. [PubMed: 7518321].
- [41] Tuka B, Szabo N, Toth E, Kincses ZT, Pardutz A, Szok D, et al. Release of PACAP-38 in episodic cluster headache patients—an exploratory study. *J Headache Pain.* 2016; 17 (1): 69. doi: 10.1186/s10194-016-0660-7. [PubMed: 27475101].
- [42] Le H, Tfelt-Hansen P, Skytthe A, Kyvik KO, Olesen J. Association between migraine, lifestyle and socioeconomic factors: a populationbased cross-sectional study. *J Headache Pain.* 2011; 12 (2): 157-72. doi: 10.1007/s10194-011-0321-9. [PubMed: 21390550].
- [43] Blau JN, Thavapalan M. Preventing migraine: a study of precipitating factors. *Headache.* 1988; 28 (7): 481-3. doi: 10.1111/j.1526-4610.1988.hed2807481.x. [PubMed: 3243710].
- [44] Aamodt AH, Stovner LJ, Hagen K, Brathen G, Zwart J. Headache prevalence related to smoking and alcohol use. The Head-HUNT Study. *Eur J Neurol.* 2006; 13 (11): 1233-8. doi: 10.1111/j.1468-1331.2006.01492.x. [PubMed: 17038038].
- [45] Kelman L. The triggers or precipitants of the acute migraine attack. *Cephalalgia.* 2007; 27 (5): 394-402. doi: 10.1111/j.1468-2982.2007.01303.x. [PubMed: 17403039].
- [46] Robberstad L, Dyb G, Hagen K, Stovner LJ, Holmen TL, Zwart JA. An unfavorable lifestyle and recurrent headaches among adolescents: the HUNT study. *Neurology.* 2010; 75 (8): 712-7. doi: 10.1212/WNL.0b013e3181eee244. [PubMed: 20720191].

- [47] Taylor FR. Tobacco, Nicotine, and Headache. *Headache*. 2015; 55 (7): 1028-44. doi: 10.1111/head.12620. [PubMed: 26140522].
- [48] Nikiforow R, Hokkanen E. An epidemiological study of headache in an urban and a rural population in northern Finland. *Headache*. 1978; 18 (3): 137-45. doi: 10.1111/j.1526-4610.1978.hed1803137.x. [PubMed: 669944].
- [49] Ward MM, Swan GE, Jack LM. Self-reported abstinence effects in the first month after smoking cessation. *Addict Behav*. 2001; 26 (3): 311-27. doi: 10.1016/S0306-4603 (00) 00107-6. [PubMed: 11436924].
- [50] Marubio LM, del Mar Arroyo-Jimenez M, Cordero-Erausquin M, Lena C, Le Novere N, de Kerchove d'Exaerde A, et al. Reduced antinociception in mice lacking neuronal nicotinic receptor subunits. *Nature*. 1999; 398 (6730): 805-10. doi: 10.1038/19756. [PubMed: 10235262].
- [51] Yamamoto A, Kiguchi N, Kobayashi Y, Maeda T, Ueno K, Yamamoto C, et al. Pharmacological relationship between nicotinic and opioid systems in analgesia and corticosterone elevation. *Life Sci*. 2011; 89 (25-26): 956-61. doi: 10.1016/j.lfs.2011.10.004. [PubMed: 22036617].
- [52] Schreiner BS, Lehmann R, Thiel U, Ziemba PM, Beltran LR, Sherkheli MA, et al. Direct action and modulating effect of (+)-and (-)-nicotine on ion channels expressed in trigeminal sensory neurons. *Eur J Pharmacol*. 2014; 728: 48-58. doi: 10.1016/j.ejphar.2014.01.060. [PubMed: 24512725].
- [53] Thomas PS, Schreck RE, Lazarus SC. Tobacco smoke releases performed mediators from canine mast cells and modulates prostaglandin production. *Am J Physiol*. 1992; 263 (1 Pt 1): 67-72. [PubMed: 1636731].
- [54] Kageyama-Yahara N, Suehiro Y, Yamamoto T, Kadowaki M. IgE-induced degranulation of mucosal mast cells is negatively regulated via nicotinic acetylcholine receptors. *Biochem Biophys Res Commun*. 2008; 377 (1): 321-5. doi: 10.1016/j.bbrc.2008.10.004. [PubMed: 18848921].