# Experimental models of migraine both *in vitro* and *in vivo*

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## Abstract

Animal models have been critical to our understanding of the neurobiology of migraine. Model systems have the advantage of being able to control experimental variables to a much greater degree than in human studies. Over the past decade, a number of animal models of migraine have been developed. However, each animal model of migraine has its own merits and demerits. It is imperative that animal model selection shall be based on the neurobiological mechanisms of migraine one chooses to study. The review summarizes numerous animal models of migraine. In our review, we classified migraine models into five categories: i) models based on anastomoses and isolated blood vessels; ii) models based on neurovascular involvement; iii) Superior Sagittal Sinus stimulation; iv) nitroglycerin induced model; v) genetically modified mouse models. This review discussed above mentioned models covering implications of each model.

## Introduction

Migraine is a common neurological disorder which causes significant personal and societal burdens due to high prevalence, loss of productivity and the cost of treatments which are not always effective for patients.[1] Furthermore, there is relatively little basic research conducted on migraine[2] and as a result available treatment options and understandings of this condition are limited. Migraine is diagnosed in women three times more frequently than men[3] and while the mechanisms behind these sex difference is not well understood. Migraine is the most common primary headache syndrome during childhood and adolescence. However the pathophysiology of migraine is not fully understood. The proposed theory for classical migraine pathophysiology is trigeminovascular theory. The propagation of the cortical spreading depression to the pain sensitive trigeminal sensory fibres is believed to induce the headache. Migraine is a multi-factorial primary headache disorder, is characterized by unilateral intense and pulsatile headaches.[4]

## Models based on anastomoses and isolated blood vessels

### Based on anastomoses

In the late 1930's, Harold Wolff became the first researcher to place migraine on a scientific basis, Wolf measured the diameter of the extracranial (temporal) arteries in patients suffering migraine attacks and found them to be dilated. These patients were treated with vasoconstrictors (ergotamine) which relieved the pain and decreased the arterial dilation.[5] Thus dilation of cranial blood vessels including carotid arteriovenous anastomoses is involved in headache phase of migraine. Arteriovenous anastomoses are precapillary communications between the arteries and veins; they are predominantly located in the head skin, ears, nasal mucosa, eyes and dura mater in several species, including humans and pigs.[6] Indeed, migraine patients also experience facial paleness, a decline in facial temperature, and rise in temporal artery pulsations and swelling of the frontal vein on the side of the headache besides their headaches.[7,8] Therefore, Heyck determined the oxygen saturation difference between arterial and external jugular venous blood samples (A-V $SO_2$ difference) during and after the headache phase of migraine and compared it with those of healthy controls. The A-V $SO_2$ difference was decreased during the headache phase of migraine, possibly due to dilatation of carotid arteriovenous anastomoses, which was normalized after spontaneous or drug induced mitigation of the headache.[9]

On account of this hypothesis, *in vivo* animal models of pharmacologically evoked carotid vasodilation have been developed.[10,11] For instance, in conscious pigs, shunting of blood by carotid anastomoses accounts for less than 3% in the jugular venous circulation whereas this fraction is augmented up to 80% under pentobarbital anesthesia as detected by radioactive microspheres.[12] As a result, opening of the carotid arteriovenous anastomoses during migraine shunts a large quantity of oxygenated blood directly into the veins thus resulting in facial pallor, reduction of skin temperature and raise in vascular pulsations. The above mentioned shunt model has been functional effectively to evaluate the blood flow effects of abortive anti-migraine drugs. Those drugs that demonstrate desired effects on carotid A-V anastomotic blood flow in pig or on the external carotid bed in dogs (*e.g.* triptans) show abortive activity in acute migraine.[10,11]

The major advantage of this model is that different vascular beds can be studied simultaneously in order to evaluate the cranioselectivity of anti-migraine drugs.[10] The major limitation is that this model will only pick up potential anti-migraine drugs acting via vascular mechanisms.[13] Another limitation is that this model cannot reflect the complexity that constitutes migraine disorder. However, it remains to be determined in which ways, if any, A-V shunting relates to migraine pathogenesis or in which ways shunt opening and closing evokes pain. It appears that 5-hydroxytryptamine (5-HT) 1B/D receptors, relevant to the triptan effect, cause constriction within a relevant population of blood vessels opening and closing A-V shunts. Therein lies the value of this model and its impact on migraine till date.[14]

### Based on isolated blood vessels

*In vitro* studies on isolated blood vessels,

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Key words: Animal models; Migraine; Review; *In vitro*; *In vivo*; Preclinical.

Acknowledgments: the authors are grateful to Prof. G. Devala Rao Garikapati and management of KVSR Siddhartha College of Pharmaceutical Sciences for providing resources for the preparation of manuscript.

Contributions:UBN was involved in the preparation of manuscript; SRC edited and revised it.

Conflict of interest: the authors declare no potential conflict of interest.

Funding: none.

Received for publication: 5 June 2018.
Revision received: 4 September 2018.
Accepted for publication: 4 September 2018.



*Licensee PAGEPress, Italy*
*Pre-Clinical Research 2023; 1:7772*
*doi:10.4081/pcr.2023.7772*

using vascular segments mounted in organ baths[15] have proved to be of high value, particularly in characterizing the pharmacologic profile of prospective anti-migraine drugs such as triptans or ergot derivatives. Any blood vessel with a minimal internal diameter of about 75 microns can be studied.[16] However, the following specific blood vessels have been frequently used in migraine related studies are bovine cerebral arteries and dog or rabbit saphenous vein as these preparations possess certain similarities with human cranial or coronary arteries. Studies on isolated blood vessels offer several advantages: i) drug receptor interactions at equilibrium, ii) the possibility to carry out a detailed pharmacological analysis, mounting multiple segments of blood vessel in parallel, iii) no influence by pharmacokinetic factors, iv) exclusion of central and autonomic mechanisms as well as the effects produced by circulating hormones, distending pressure, *etc*., v) the possibility to remove the endothelium from the blood vessel, which provides information whether the receptors are present on the endothelium or in the vascular smooth muscle of arteries, vi) the possibility to gain insight into downstream signaling, such as measurements of second messengers[17] and most notably vii) the possibility to study human preparations.[18] *In vitro* models using isolated blood vessels have been applied successfully to test the efficacy of anti-migraine drugs on constriction of cranial arteries.[19] The therapeutic efficacy of acutely acting anti-migraine drugs is most likely, at least for a major proportion, mediated by constriction of dilated cranial arteries.[17,20,21] Cumulative concentration response curves are used to determine the vasoconstrictor potency and efficacy of the prospective anti-migraine agent although *in vitro* vascular models do not reflect the complexity of migraine nor inform us about pharmacokinetics, they became the workhorse for the development of triptan drugs and continue to provide detailed information about vascular smooth muscle pharmacology. However, it still remains unclear whether the receptor most relevant to the abortive migraine effect resides on vascular smooth muscle. Human isolated coronary arteries are useful in analyzing the coronary side effect potential of anti-migraine drugs. Although the chest symptoms (chest pressure, tightness and pain) commonly experienced after the use of anti-migraine drugs[22] are in most cases not likely to be due to coronary vasoconstriction, cardiac ischemia after anti-migraine drugs has indeed been reported.[23]

### Models based on neurovascular involvement

Neurovascular models focus on the interplay between neurovascular changes observed during migraine attacks and the consequences of trigeminovascular activation. A basic assumption is that migraine pain is caused by activation of trigeminal axons near blood vessels and surrounding meningeal tissues. Several techniques have been developed to study the effects of activation of the trigeminovascular system. By doing so, neuroinflammatory peptides are released antidromically from perivascular nerve fibers (calcitonin gene related peptide – CGRP – SP and NK-A) to promote vasodilatation,[24] activation of the endothelium with increased transendothelial transport, mast cell activation, enhanced local platelet aggregation and adhesion.[25,26] All these mechanisms promote extravasation of plasma protein into dura mater, although, not all techniques reproduce this phenomenon. At the same time, the orthodromic activation of the C-fibers releases glutamate, substance P, CGRP, NKA in the Sp5c with activation of second order neuron.[27]

### Trigeminal ganglion stimulation

CGRP from perivascular axons[28] and can be blocked by Triptans,[29] ergot alkaloids, indomethacin, and also acetylsalicylic acid.[30] Plasma protein leakage is detected quantifying the ratio of radio isotopes [I-BSA] or dyes (Evans Blue) in the perfused meninges of the stimulated versus non-stimulated side.[31,32] Blood flow measurements using laser Doppler recordings are another endpoint used to indirectly assess neurovascular responses following electrical stimulation of the dura mater.[33] Building upon this model and the concept of neurovascular dilation, intravital microscopy was developed to analyze diameter changes in dural vessels *in vivo* and for studying the consequences of activating the peripheral branches of the trigeminovascular system in this model, electrical field stimulation causes a reproducible dilation of dural and pial blood vessels via release of CGRP from pre-synaptic trigeminal nerve endings.[34] Inhibition of neurogenic dural vasodilation can assess anti-migraine drug efficacy, as has been shown for the Triptans[34] and a CGRP receptor antagonist.[35,36]

### Meningeal stimulation

Meningeal stimulation by autologous blood or capsaicin activates primary sensory fibers and induces *c-fos* expression in a dose-dependent manner.[37,38] Stimulation of sensory nerve fibres results in the release of neuropeptides in both the central and peripheral nervous system.[39] Studies show that sensory nerves innervating the cerebral vasculature contain substance P and CGRP.[40] Strassman and colleagues demonstrated that topical meningeal application of an *inflammatory soup* (histamine, 5-HT, prostaglandin E2 at pH 5.0 and bradykinin) sensitizes meningeal afferents, activating Sp5C neurons to mechanical stimuli.[41] Early administration of sumatriptan effectively blocks the enhanced sensitivity to mechanical stimuli.[42] In this model, a small catheter is placed into the cisterna magna through the atlanto-occipital membrane of anesthetized rats, mice or guinea pigs. A test compound or vehicle is administered intravenously or intraperitoneally and approximately 1h after catheter placement an irritant substance, either autologous blood; carrageenin or capsaicin is injected intracisternally. End points used in this model is Plasma protein extravasation and expression of c-Fos mRNA and Fos immunoreactivity within the superficial laminae of trigeminal nucleus caudalis.[43,44]

## Dural neurogenic plasma extravasation

It provided the basis for meningeal inflammation hypothesis for migraine.[45] It is based on the stimulation of trigeminal nerve by electrical or chemical stimuli which results in the release of neuropeptides from perivascular nerve fibres, vasodilation is enhanced, endothelial cells and mast cells are activated and platelets tend to aggregate and increase their adhesion. These mechanisms if set altogether, promote the extravasation of plasma protein into the dura mater. In dural neurogenic plasma extravasation (DNPE) electrical or chemical stimulation of the trigeminal ganglion was preceded or immediately followed by the intravenous injection of 125 I albumin. The measurement of DNPE as an index of meningeal inflammation was based on the amount of radio labeled albumin accumulated in the dura after leaking out of meningeal blood vessels. Radolabelled albumin was significantly present in the area of dura innervated by stimulated trigeminal ganglion. The amount of DNPE was significantly reduced by a variety of agents also known to be clinically effective in the treatment of migraine head ache in humans such as ergot alkaloids, triptans and NSAIDS. Recently, human models of migraine is developed the model is based on using single photon emission computerized tomography with intravenous injection of tc-99m human serum albumin and have explored the possibility that DNPE can be detected in human during a migraine attack.[46] SPECT technology may give a useful contribution to the field of migraine

research. SPECT may be used not only to study underlying mechanisms of migraine but also the efficacy of pharmacological treatment on migraine related DNPE.

## Superior sagittal sinus stimulation

Another major model is superior sagittal sinus stimulation in cats,[47] monkeys[48] and rats.[49] The superior sagittal sinus stimulation (SSS), the tributary veins and adjacent dura are intracranial structures densely innervated by a separate branch of the ophthalmic division of the trigeminal nerve, the tentorial nerve. Stimulation of the SSS electrically[50] or mechanically,[51] induces the release of neuro peptides in a pattern similar to that observed during migraine attacks[52] this model gives valuable information of the site of action of anti-migraine drugs in a non-inflammatory paradigm, for example sumatriptan does not inhibit *c-fos* induced by SSS stimulation, while zolmitriptan does. This argues in support of a central mechanism of action of zolmitriptan, which is lipophilic, without disposal of peripheral mechanisms. The fact that sumatriptan was only effective in this model after BBB disruption strongly supports a peripheral mode of action.[53] This model is preferred by those who do not believe that neurogenic inflammation underlies migraine. *C-fos* gene is expressed in this type of models has greatly improved the understanding of pathophysiology and pharmacology of trigemino vascular system establishing itself as one of the most effective experimental model.[54]

## Nitroglycerin induced model

By far, the best validated and most studied human migraine model uses intravenous infusion of nitroglycerin, also called glyceryl trinitrate (GTN). It is now generally accepted that infusion of GTN induces migraine attacks in migraineurs that are indistinguishable from spontaneous attacks in normal volunteers without migraine,[55] GTN induces milder head ache which has some but not all characteristics of migraine.[56] A fairly large number of attempts have been made to transfer the GTN model to animals. Most of these studies have used rats and most of them have been done in anaesthetized animals[57] or have used intraperitoneal injection of GTN.[58] Unfortunately, the latter route of administration seems to require enormous doses of GTN in order to elicit changes in the brain that may be compatible with migraine. There are other problems with these studies. GTN does not dissolve in saline and usually must be dissolved in a mixture of alcohol and propylene glycol. Many studies using intraperitoneal GTN have, however, used saline for control and not vehicle.[58,59] Because very large amounts of GTN are necessary, the amount of injected alcohol and propylene glycol are considerable. Furthermore, it is unknown what the effect of alcohol and propylene glycol into the peritoneum might be. Hence, specificity of the responses obtained in most of these animal experiments is questionable. The infusion of nitroglycerin (NTG) induces an inflammatory state in perivascular meningeal tissues of rat via the activation, inter alia, of nuclear factor kappa B (NF-kB). The huge doses of GTN induce a marked and prolonged blood pressure decrease in rats.[60] Although it has been reported that intraperitoneal injection of 10 mg/kg GTN has no effect on blood pressure in mice many attempts have been made to develop animal models predictive of efficacy of anti-migraine drugs. We are not there yet but development of such a model seems to be one of the most important avenues of headache research today.[61]

## Genetically modified mouse models

Previously, it has been shown that genetic factors play an important role in migraine pathophysiology[62] the first two migraine genes, CACNA1A and ATP1A2 were discovered in families with hemiplegic migraine a severe subtype of migraine with aura. CACNA1A encodes alpha 1 subunit of voltage gated calcium channel; the second migraine gene ATP1A2 encodes alpha 2 subunit of sodium potassium pump.[63]

## Transgenic knock in mouse models

Two knock-in mouse models of FHM1 have been generated to study the functional outcomes of FHM mutations and to identify pathophysiological mechanisms potentially involved in FHM and hence possibly also in non-hemiplegic migraine.[63,64] By use of a gene-targeting approach, the human pathogenic Arg192Gln or Ser218Leumissense mutation were inserted into the mouse orthologous *Cacna1a* by homologous recombination. Arg192Gln was chosen because it is associated with a mild pure FHM phenotype without additional clinical features, modeling migraine as closely as possible. Ser218Leu was selected because it is associated with probably the most severe FHM1 phenotype. Comparison of functional changes in both mouse models enabled a disease severity dependent analysis and the differentiation of possible pathways for migraine and its associated features.[65] Identification of responsible mutations in patients suffering from FHM through a gene targeting approach supports the concept that FHM, and possibly a few other more common types of migraine, are ionopathies that lead to cortical network hyperexcitability in patients with migraine.

## Conclusions

Current animal models of migraine test only part of the whole rather than entire picture. Each model focuses on a particular pathophysiological system. Hence, one needs to test the drug candidate in various animal model systems. If a molecule was found to be ineffective in a single model, it does not mean that drug is ineffective. It may be possible that drug is not working in a mechanism of animal models that one has chosen. Each model has its unique features. Comparisons, interpretations of results of various animal models would help researcher to draw meaningful conclusions.

## References

1. Akerman S, Holland PR, Hoffmann J. Pearls and pitfalls in experimental in vivo models of migraine: dural trigeminovascular nociception. Cephalalgia 2013;33:577.
2. Schwedt TJ, Shapiro RE. Funding of research on headache disorders by the National Institutes of Health. Headache 2009;49:162.
3. Buse DC, Loder EW, Gorman JA, et al. Sex differences in the prevalence, symptoms, and associated features of migraine, probable migraine and other severe headache: results of the American Migraine Prevalence and Prevention (AMPP) Study. Headache 2013;53:1278.
4. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd ed. (beta version). Cephalalgia 2013;33:629.
5. Graham JR, Wolf HG. Mechanism of migraine headache and action of ergotamine tartrate. Arch Neurol Psych 1938;39:737.
6. Saxena PR. Cranial arteriovenous shunting, an in vivo animal model for

migraine. In: Olesen J, Moskowitz MA, eds. Experimental headache models. Philadelphia, USA: Lippincott-Raven Publishers; 1995. pp 189-198.
7. Drummond PD, Lance JW. Extracranial vascular changes and the source of pain in migraine headache. Ann Neurol 1983;13:32.
8. Drummond PD, Lance JW. Facial temperature in migraine, tension-vascular and tension headache. Cephalalgia 1984;4:149.
9. Heyck H. Pathogenesis of migraine. Research clinical study. Headache 1969;2:1.
10. De Vries P, Villalon CM, Saxena PR. Pharmacological aspects of experimental headache models in relation to acute antimigraine therapy. Eur J Pharmacol 1999;375:61.
11. Totaro R, De Matteis G, Marini C, et al. Sumatriptan and cerebral blood flow velocity changes during migraine attacks. Headache 1997;37:635.
12. Den Boer MO, Van Woerkens LJ, Somers JA, et al. On the preservation and regulation of vascular tone in arteriovenous anastomoses during anesthesia. J Appl Physiol 1993;75:782.
13. Willems E, De Vries P, Heiligers JP, Saxena PR. Porcine carotid vascular effects of eletriptan (UK-116,044): a new 5-HT1B/1D receptor agonist with anti-migraine activity. Naunyn Schmiedebergs Arch Pharmacol 1998;358:212.
14. Eikermann-Haerter K, Moskowitz MA. Animal models of migraine headache and aura. Curr Opin Neurol 2008;21:294
15. Petersen KA, Nilsson E, Olesen J, Edvinsson L. Presence and function of the calcitonin gene-related peptide receptor on rat pial arteries investigated in vitro and in vivo. Cephalalgia 2005;25:424.
16. Bergerot A, Holland PR, Akerman S, et al. Animal models of migraine: looking at the component parts of a complex disorder. Eur J Neurosci 2006;24:1517.
17. Gupta S, Lozano-Cuenca J, Villalon CM, et al. Pharmacological characterisation of capsaicin-induced relaxations in human and porcine isolated arteries. Naunyn Schmiedebergs Arch Pharmacol 2007;375:29.
18. Maassenvandenbrink A, Chan KY. Neurovascular pharmacology of migraine. Eur J Pharmacol 2008;585:313.
19. Maassenvandenbrink A, van den Broek RW, de Vries R, et al. Craniovascular selectivity of eletriptan and sumatriptan in human isolated blood vessels. Neurology 2000;55:1524.
20. Van den Broek RW, MaassenVanDenBrink A, de Vries R, et al. Pharmacological analysis of contractile effects of eletriptan and sumatriptan on human isolated blood vessels. Eur J Pharmacol 2000;407:165.
21. Razzaque Z, Heald MA, Pickard JD, et al. Vasoconstriction in human isolated middle meningeal arteries: determining the contribution of 5-HT1B- and 5-HT1F-receptor activation. Br J Clin Pharmacol 1999;47:75.
22. Brown EG, Endersby CA, Smith RN, Talbot JC. The safety and tolerability of sumatriptan: an overview. Eur Neurol 1991;31:339.
23. Dodick D, Lipton RB, Martin V, Triptan Cardiovascular Safety Expert Panel. Consensus statement: cardiovascular safety profile of triptans (5-HT agonists) in the acute treatment of migraine. Headache 2004;44:414.
24. Jansen-Olesen I, Mortensen A, Edvinsson L. Calcitonin gene related peptide is released from capsaicin-sensitive nerve fibres and induces vasodilation of human cerebral arteries concomitant with activation of adenylyl cyclase. Cephalalgia 1996;16:310.
25. Dimitriadou V, Buzzi MG, Moskowitz MA, Theoharides TC. Trigeminal sensory fiber stimulation induces morphological changes reflecting secretion in rat dura mater mast cells. Neuroscience 1991;44:97.
26. Dimitriadou V, Buzzi MG, Theoharides TC, Moskowitz MA. Ultrastructural evidence for neurogenically mediated changes in blood vessels of the rat dura mater and tongue following antidromic trigeminal stimulation. Neuroscience 1992;48:187.
27. Samsam M, Covenas R, Ahangari R, et al. Simultaneous depletion of neurokinin A, substance P and calcitonin gene-related peptide from the caudal trigeminal nucleus of the rat during electrical stimulation of the trigeminal ganglion. Pain 2000;84:389.
28. Moskowitz MA. The neurobiology of vascular head pain. Ann Neurol 1984;16:157.
29. Buzzi MG, Moskowitz MA. The antimigraine drug, sumatriptan (GR43175), selectively blocks neurogenic plasma extravasation from blood vessels in dura mater. Br J Pharmacol 1990;99:202.
30. Cutrer FM, Moskowitz MA. Wolff Award 1996. The actions of valproate and neurosteroids in a model of trigeminal pain. Headache 1996;36:579.
31. Markowitz S, Saito K, Moskowitz MA. Neurogenically mediated leakage of plasma protein occurs from blood vessels in dura mater but not brain. J Neurosci 1987;7:4129.
32. Shepheard SL, Williamson DJ, Williams J, et al. Comparison of the effects of sumatriptan and the NK1 antagonist CP-99,994 on plasma extravasation in Dura mater and c-fos mRNA expression in trigeminal nucleus caudalis of rats. Neuropharmacology 1995;34:255.
33. Williamson DJ, Hargreaves RJ, Hill RG, Shepheard SL. Intravital microscope studies on the effects of neurokinin agonists and calcitonin gene-related peptide on dural vessel diameter in the anaesthetized rat. Cephalalgia 1997;17:518.
34. Williamson DJ, Hill RG, Shepheard SL, Hargreaves RJ. The antimigraine 5-HT(1B/1D) agonist rizatriptan inhibits neurogenic dural vasodilation in anaesthetized guinea-pigs. Br J Pharmacol 2001;133:1029.
35. Petersen KA, Birk S, Doods H, et al. Inhibitory effect of BIBN4096BS on cephalic vasodilatation induced by CGRP or transcranial electrical stimulation in the rat. Br J Pharmacol 2004; 143:697.
36. Olesen J, Diener HC, Husstedt IW; BIBN 4096 BS Clinical Proof of Concept Study Group. Calcitonin gene-related peptide receptor antagonist BIBN 4096 BS for the acute treatment of migraine. N Engl J Med 2004;350: 1104.
37. Mitsikostas DD, Sanchez del Rio M, Waeber C, et al. The NMDA receptor antagonist MK-801 reduces capsaicin-induced c-fos expression within rat trigeminal nucleus caudalis. Pain 1998;76:239.
38. Mitsikostas DD, Sanchez del Rio M, Waeber C. 5-Hydroxytryptamine (1B/1D) and 5-hydroxytryptamine1F receptors inhibit capsaicin-induced c-fos immunoreactivity within mouse trigeminal nucleus caudalis. Cephalalgia 2002;22:384.
39. Edvinsson L. Blockade of CGRP receptors in the intracranial vasculature: a new target in the treatment of headache. Cephalalgia 2004;24:611.
40. Fusco M, D'Andrea G, Micciche F, et al. Neurogenic inflammation in primary headaches. Neurol Sci 2003;24:S61.
41. Strassman AM, Raymond SA, Burstein R. Sensitization of meningeal sensory neurons and the origin of headaches. Nature 1996;384:560.
42. Burstein R, Jakubowski M. Analgesic triptan action in an animal model of

intracranial pain: a race against the development of central sensitization. Ann Neurol 2004;55:27.
43. Williamson DJ, Hargreaves RJ. Neurogenic inflammation in the context of migraine. Microsc Res Tech 2001;53:167.
44. Clayton JS, Gaskin PJ, Beattie DT. Attenuation of Fos-like immunoreactivity in the trigeminal nucleus caudalis following trigeminovascular activation in the anaesthetised guinea-pig. Brain Res 1997;775:74.
45. Moskowitz MA, Buzzi MG. Neuroeffector functions of sensory fibres: implications for headache mechanisms and drug actions. J Neurol 1991;238:S18.
46. Knotkova H, Pappagallo M. Imaging intracranial plasma extravasation in a migraine patient: a case report. Pain Med 2007;8:383.
47. Kaube H, Keay KA, Hoskin KL, et al. Expression of c-Fos-like immunoreactivity in the caudal medulla and upper cervical spinal cord following stimulation of the superior sagittal sinus in the cat. Brain Res 1993;629:95.
48. Goadsby PJ, Hoskin KL. The distribution of trigeminovascular afferents in the nonhuman primate brain Macaca nemestrina: a c-fos immunocytochemical study. J Anat 1997;190:367.
49. Strassman AM, Potrebic S, Maciewicz RJ. Anatomical properties of brainstem trigeminal neurons that respond to electrical stimulation of dural blood vessels. J Comp Neurol 1994;346:349.
50. Zagami AS, Goadsby PJ, Edvinsson L. Stimulation of the superior sagittal sinus in the cat causes release of vasoactive peptides. Neuropeptides 1990;16:69.
51. Kaube H, Hoskin KL, Goadsby PJ. Activation of the trigeminovascular system by mechanical distension of the superior sagittal sinus in the cat. Cephalalgia 1992;12:133.
52. Edvinsson L, Goadsby PJ. Neuropeptides in migraine and cluster headache. Cephalalgia 1994;14:320.
53. Hoskin KL, Goadsby PJ. Comparison of more and less lipophilic serotonin (5HT1B/1D) agonists in a model of trigeminovascular nociception in cat. Exp Neurol 1998;150:45.
54. May A, Goadsbay PJ. Substance p receptor antagonists in the therapy of migraine. Expert Opinion Invest Drugs 2001;10:673-8.
55. Thomsen LL, Kruuse C, Iversen HK, Olesen J. A nitric oxide donor (nitroglycerin) induces genuine migraine attacks. Eur J Neurol 1994;1:73.
56. Christiansen I, Thomsen LL, Daugaard D, et al. Glyceryl trinitrate induces attacks of migraine without aura in sufferers of migraine with aura. Cephalalgia 1999;19:660.
57. Read SJ, Smith MI, Hunter AJ, Parsons AA. Enhanced nitric oxide release during cortical spreading depression following infusion of glyceryl trinitrate in the anaesthetized cat. Cephalalgia 1997;17:159.
58. Bates E, Nikai T, Brennan K, et al. Sumatriptan alleviates nitroglycerin-induced mechanical and thermal allodynia in mice. Cephalalgia 2010;30:170.
59. Greco R, Tassorelli C, Armentero MT, et al. Role of central dopaminergic circuitry in pain processing and nitroglycerin-induced hyperalgesia. Brain Res 2008;1238:215.
60. Yao D, Sessle BJ. Nitroglycerin facilitates calcitonin gene-related peptide-induced behavior. Neuroreport 2008;19:1307.
61. Tassorelli C, Joseph SA. NADPH-diaphorase activity and Fos expression in brain nuclei following nitroglycerin administration. Brain Res 1995;695:37.
62. De Fusco M, Marconi R, Silvestri L, et al. Haploinsufficiency of ATP1A2 encoding the Na+/K+ pump alpha2 subunit associated with familial hemiplegic migraine type 2. Nat Genet 2003;33:192.
63. van den Maagdenberg AM, Pietrobon D, Pizzorusso T, et al. A Cacna1a knockin migraine mouse model with increased susceptibility to cortical spreading depression. Neuron 2004;41:701.
64. van den Maagdenberg AM, Pizzorusso T, Kaja S, et al. High cortical spreading depression susceptibility and migraine-associated symptoms in Ca(v)2.1 S218L mice. Ann Neurol 2010;67:85.
65. Ferrari MD, Klever RR, Terwindt GM, et al. Migraine pathophysiology: lessons from mouse models and human genetics. Lancet Neurol 2015;14:65.