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Review

Neurobiology in primary headaches

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Abstract

Primary headaches such as migraine and cluster headache are neurovascular disorders. Migraine is a painful, incapacitating disease that affects a large portion of the adult population with a substantial economic burden on society. The disorder is characterised by recurrent unilateral headaches, usually accompanied by nausea, vomiting, photophobia and/or phonophobia. A number of hypothesis have emerged to explain the specific causes of migraine. Current theories suggest that the initiation of a migraine attack involves a primary central nervous system (CNS) event. It has been suggested that a mutation in a calcium gene channel renders the individual more sensitive to environmental factors, resulting in a wave of cortical spreading depression when the attack is initiated. Genetically, migraine is a complex familial disorder in which the severity and the susceptibility of individuals are most likely governed by several genes that vary between families. Genom wide scans have been performed in migraine with susceptibility regions on several chromosomes some are associated with altered calcium channel function. With positron emission tomography (PET), a migraine active region has been pointed out in the brainstem. In cluster headache, PET studies have implicated a specific active locus in the posterior hypothalamus. Both migraine and cluster headache involve activation of the trigeminovascular system. In support, there is a clear association between the head pain and the release of the neuropeptide calcitonin gene-related peptide (CGRP) from the trigeminovascular system. In cluster headache there is, in addition, release of the parasympathetic neuropeptide vasoactive intestinal peptide (VIP) that is coupled to facial vasomotor symptoms. Triptan administration, activating the 5-$HT_{1B/1D}$ receptors, causes the headache to subside and the levels of neuropeptides to normalise, in part through presynaptic inhibition of the cranial sensory nerves. These data suggest a central role for sensory and parasympathetic mechanisms in the pathophysiology of primary headaches. The positive clinical trial with a CGRP receptor antagonist offers a new promising way of treatment.

Theme: Sensory system
Topic: Pain modulation: anatomy and physiology

Keywords: Migraine; Cluster headache; CGRP; VIP; Trigeminovascular reflex; Autonomic nerves

Contents

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1. Introduction

The primary headaches include migraine, tension-type headache (TTH), cluster headache, other trigeminal autonomic cephalalgias and other headaches [147]. Tension-type headache is the most common of these in the general population, however, since little data exist for a neurovascular component, we have only described those briefly below [5]. Migraine headaches are ascribed as neurovascular disorders which world-wide afflict up to 15–20% of the general population. The socio-economic implications are extensive with considerable impact on productivity and quality of life. In Europe alone, it is calculated that 600,000 days of work are lost daily. Migraine, which is the most common type, is characterised by attacks of moderate to severe headache that last for 4–72 h, often unilateral, pulsating and associated with photophobia/phonophobia and/or nausea/vomiting [146]. In migraine with aura, the headache is preceded by transient focal neurological symptoms, most often contralaterally [84].

Cluster headache is another of the primary headaches; it has a distinct clinic with devastating pain. Some of the features of cluster headache overlap with those of other primary vascular headaches. The pain usually occurs around the eye and is described as retro-orbital or temporal. This implies involvement of the ophthalmic (first) division of the trigeminal nerve. In addition to the pain, there are signs of parasympathetic overactivity, e.g., lacrimation, nasal congestion and injection of the eye. Short-lasting headaches associated with autonomic symptoms may sometimes be confused with cluster headache. Although the exact causes of the primary headaches remain unknown, some pieces of the pathophysiological puzzle are starting to fall into place, particularly after a series of elegant positron emission tomography (PET) studies [132–134]. During the last 20 years, there has been a heated debate whether the primary headaches are neurogenic or vascular in origin. However, current molecular and functional studies suggest a way to incorporate the different aspects into an integrated hypothesis as neurovascular headaches [39,84,156].

In susceptible individuals, changes in environmental or physiological states are known to trigger the migraine headache. Migraine susceptibility has been linked to mechanisms regulating central sensitization. The systems that govern neuronal excitability involve homeostatic mechanisms and intracellular signalling pathways. The demonstration that mutations in the calcium channel gene CACNA1A, in approximately 50% of families suffering from the rare and severe familial hemiplegic migraine (FHM), has offered some hope that there is a molecular genetic cause also of the more common types of migraine [150,188]. However, it is well recognised that the central nervous system (CNS) is devoid of sensory pain receptors, and intracranially, it is only blood vessels in the dura and the circle of Willis that are supplied with sensory nerves and receptors that can respond to thermal, mechanical or distensional stimuli [147,159].

2. Where does the attack start?

Some researchers have suggested that migraine is a disease comprised of two main subtypes, migraine with aura and migraine without aura. In the former, the aura is characterized most often by visual field disturbances, but sometimes also by additional somatosensory disturbances. In these patients, changes in cortical blood flow correlate with areas of hypoperfusion, but no subsequent spreading from the area of hypoperfusion can be demonstrated, possibly because these patients have been studied late during the attacks. Olesen et al. [144] were the first to observe in patients examined early at the onset of induced migraine attacks, a pattern of localized blood flow decrease that spread contiguously over the cerebral cortex. This pattern of “spreading oligemia” or “spreading hypoperfusion” was apparent only in patients who had migraine with aura. The hypoperfusion was ipsilateral to the headache and contralateral to the symptoms of the aura. In one subject who suffered a migraine attack during a series of cerebral blood flow measurements with PET [201], the headache

was associated with bilateral hypoperfusion which started in the occipital lobes and spread anteriorly into the temporal and parietal lobes. This provided high-resolution evidence of the spreading nature of the hypoperfusion associated with a spontaneous migraine attack. This view was further supported by a study of blood oxygenation level dependent (BOLD) signal changes reflecting the balance between oxygen delivery and oxygen consumption. In one patient, two attacks of induced migraine aura showed an increase in the mean magnetic resonance (MR) signal (5%) restricted to the occipital cortex contralateral to the visual aura [94]. These initial changes were followed by a decrease in the mean MR signal (by 5%), corresponding to the localised scotoma. The average velocity of the spread of the hypoperfusion over the cortex was 3.5 mm/min, being in concert with previous experimental studies [121]. In three spontaneous attacks of migraine with aura that were captured within 20 min of the onset of visual symptoms; the BOLD data revealed increases in the amplitude of the MR signal [94].Thus, this study supports previous reports of spreading depression as an initial cortical grey matter hyperaemia with a characteristic velocity that is followed by hypoperfusion. It lends support to studies in animals that the hypoperfusion spreads along the cortical surface at a relatively constant rate, sparing the cerebellum, the basal ganglia and the thalamus, and ultimately spanning the vascular distributions of the four major cerebral arteries [121]. A plausible explanation for the blood flow changes seen in association with the aura in a migraine attack is that they are the result of spreading depression—a transient marked reduction in electrical activity in the grey matter which advances across the cortical surface. The rate of advance is consistent with the spread of symptoms observed and is associated with decreases in blood flow [121]. Spreading depression can move transcallosally to homologous regions of the opposite hemisphere in animals, and transcallosal spread may account for the bilaterality observed at the onset of the headache [201]. One conclusion that has been raised from the studies is that the migraine aura is not evoked by ischemia, but evoked by aberrant firing of neurones and related cellular elements. An important question that can be raised is how the event is linked to activation of the trigeminovascular reflex [136]. One tempting way would be to link the cortical spreading depression to neurogenic inflammation in the dura mater and from there activation of sensory and autonomic reflexes [18]. However, the dura mater is an extracerebral structure, separated from the brain by, e.g., CSF and is nourished by the external carotid artery [147]. Alternatively, specific cell bodies projecting from the brainstem to cerebral vessels such as the extensive adrenergic and serotonergic efferents from nuclei of the locus coeruleus and of the raphe nuclei, respectively, could be involved. In fact, there are some data to support this suggestion [19,46,161] showing close association between intracerebral nerve fibers and cerebral blood vessels. This has been examined at depth subse-

quently revealing a direct neurogenic control by intrinsic serotonergic (5-HT) neurons on the cerebral microvascular bed [29].There exist close association between the 5-HT neurons and microarterioles, capillaries and perivascular astrocytes; this is more apparent in regions where manipulation of the intrinsic 5-HT neurons elicits uncoupling between flow and metabolism [28,29].

In patients with migraine without aura, the situation is somewhat more intricate [199]. During attacks, small increases in blood flow were observed in the cingulate, auditory and visual association cortices, and in brainstem regions. These changes normalized after injection of sumatriptan and induced complete relief from headache as well as from phono- and photophobia. However, the changes were small and could only be significant if the PET data from all nine subjects were normalized, thus being by and large in agreement with previous negative studies with the xenon method which lacks the precision of PET [144]. Further support for the importance of a brainstem region was obtained in a patient that developed an attack of migraine without aura after glyceryl trinitrate administration. Bahra et al. [13]observed activation in the dorsal rostral brainstem region and hence reproduced those data seen previously by Weiller et al. In addition, the authors observed a neuronally driven vasodilatation and activation of regions associated with pain processing [13,199].

A PET study in patients with attacks of cluster headache and of capsaicin-induced head pain has reported blood flow changes that suggest, in part, a response that is primarily generated by the pain [132,133]. In this study, the anterior cingulate cortex was activated as would be expected, as part of the affective response. Activation was also seen in the frontal cortex, the insulae and the ventroposterior thalamus contralateral to the side of the pain. The only activated area that was particular to cluster headache was the ipsilateral hypothalamus. This region is important in the control of circadian rhythm and can be linked to the neurohormonal imbalance seen in cluster headache. This raised the possibility that the pathophysiology of cluster headache is driven partially or entirely from the CNS. The episodic nature of the disorder suggests involvement of at least the suprachiasmatic region, possibly associated with the human biological clocks. Spontaneous as well as nitroglycerin-induced cluster headache attacks were both associated with cerebral vasodilatation, interpreted as occurring via a neuronal mechanism [134]. Vasodilatation of the cranial vessels was not considered to be specific to any particular headache syndrome, but generic to cranial neurovascular activation involving both sensory and parasympathetic reflex mechanisms as evidenced previously by the release of the sensory neurotransmitter CGRP and the parasympathetic messenger VIP in man [74] and experimentally in animal [75,204].

PET scans of patients with acute attacks of cluster headache demonstrated an unilateral activation in the ipsilateral hypothalamic grey matter [132]. It is likely that the fundamental driving process arises in dienceph-

pacemakers. While migraine and cluster headache share much in the expression of the pain, their underlying initiator mechanisms distinguish them. Indeed, it is the CNS triggering or driving process that ultimately characterizes many of the primary headache syndromes. In contrast, PET scans of capsaicin-induced pain or in migraine [133,199] showed no hypothalamic activation. In patients with capsaicin-induced pain blood flow changes were seen in an area consistent with the cavernous sinus/carotid artery just as there are blood flow changes in these vessels in cluster headache. This implies that the activation of the carotid artery does not relate specifically to cluster headache, but rather a trigeminovascular autonomic reflex. The flow changes may therefore be epiphenomena of the trigeminal activation, and not part of the disease generation process.

A possible way to link recently documented alterations in the intracranial circulation to the genetic theory is via the observation that genetically defect ion channels may more easily be activated (due to altered membrane potential and/or function) and result in excitation of neurons in situations where they are exposed to excessive stress. Proof for involvement of brainstem nuclei in migraine came from a PET study by Weiller et al. [199] and has now been supported by others [13]. During acute attacks, increased local blood flow was observed in brainstem regions (specifically midbrain and pons regions). The brainstem activation persisted after injection of sumatriptan. These findings support the idea that the pathogenesis of migraine (and the associated emesis) is related to an imbalance in the activity of brainstem nuclei regulating nociception and vascular control. On the other hand, it could equally well be an activation of the periaqueductal grey (PAG) acting as a filter to inhibit the pain [66]. The study revealed activation of the dorsal raphe nucleus (DRN) and the locus coeruleus (LC). It is well known that these centers have a dense supply of serotonergic and adrenergic fibers, respectively. The fibers may evoke vasoconstriction (via catecholamines or 5-HT) and hence explain the connection with the trigeminovascular reflex. Alternatively, the DRN and LC send descending fibers to the trigeminal nucleus caudalis (TNC) and dorsal root ganglia (DRG) where they act in a gate-control function and the PAG acts to inhibit this. Thus, sensory transmission associated with the TNC appears to be regulated by a complex system. It is still unclear whether the brainstem finding reveal the origin of the disease or if it is an accompanying activation designed to limit the symptoms of the migraine headache.

3. The ion channel connection

Clinical studies have revealed that migraine patients usually have a family history [84]. In the two main types of migraine, with aura and without aura, the familial aggregation cannot be explained by simple mendelian inheritance patterns. FHM is the only variety of migraine in which a mendelian type of inheritance has been clearly established. A few years ago, a candidate region on chromosome 19 was identified as a gene that encodes an α_1 A subunit of a voltage-gated P/Q-type calcium channel [110,111,150]. FHM with cerebellar signs was subsequently linked to mutations in CACNA1A [15,35,69,150,188,195]. Thus, this type is now called FHM 1 and has been associated with mutations in CACNA1A [150], but in others, a second locus has been mapped on chromosome 1 [34,71] and is called FHM 2. In still other cases, the disorder is linked to neither site, suggesting the existence of a third locus, FHM 3 [34]. Eight mutations in CACNA1A have been identified in 18 families affected by hemiplegic migraine and in two patients with sporadic hemiplegic migraine [1,150]. CACNA1A is specifically transcribed in cerebellum, cerebral cortex, thalamus, hypothalamus and upper brainstem. The opening and closing of voltage-gated calcium channels are controlled by changes in voltage across the cell membrane and mediate the entry of calcium into the cell. These channels are of critical importance because the gradient between intracellular and extracellular calcium controls neurotransmitter release, neuronal excitation and other neuronal functions. The calcium channel is present in axons and dendrites, suggesting that it has both presynaptic and postsynaptic roles in modulating cell-to-cell communication.

Several different missense mutations in the CACNA1A gene have been detected in unrelated FHM families [150]. Generally, patients with FHM have missense mutations and these alter the gating properties of the channel [36,150]. The first FHM mutation (R192Q) occurs in a region that is believed to be part of the voltage sensor domain of the calcium channel. The second, most prevalent of the FHM mutations (T666M) is found within the pore-forming hairpin loop of the second domain of the channel. Two other FHM mutations (V714A and I1811L) are located in the transmembrane segments that may influence calcium channel inactivation, thereby blocking calcium transfer. The functional consequences of FHM 1 mutations are now receiving much attention subsequent to producing a knock-in mouse that carry the human FHM 1 R192Q mutation [196]. The researchers found gain-of-function effects that include increased $CA_R2.1$ current density in cerebellar neurons, enhanced neurotransmission at the neuromuscular junction, and a reduced treshold and increased velocity of cortical spreading depression [196]. The data suggest that this mutation may result in increased susceptibility to cortical hyperexcitability and link spreading depression and aura in migraine.

The gene for FHM 2 was recently identified when an Italian research group found two different missense mutations in the ATP A2 gene, coding for the alpha 2 subunit of the Na^+,K^+-ATPase in two families with pure FHM 2 [33], and this has been confirmed in two Dutch families [197]. This subunit binds sodium, potassium and ATP, and utilizes ATP hydrolysis to extrude Na^+ ions. The Na^+ pumping provides the steep Na^+ gradient essential for the transport of

amino acids and calcium. Hypothetically, a mutation like this may result in loss of function which could make the brain more susceptible to spreading depression, however, more experimentation is needed.

4. Nerves in the walls of intracranial vessels

Since intracranial vessels are the only source for eliciting intracranial pain and in particular referred pain [159], the understanding of the vascular innervation by autonomic and sensory nerves is a prerequisite for the understanding of intracranial pain as it occurs in primary headaches. The intracranial blood vessels are supplied with nerve fibers that emanate from cell bodies in ganglia belonging to the sympathetic, parasympathetic and sensory nervous systems (Fig. 1) [92]. In addition, cerebral resistance vessels may be innervated by fibers that originate within the brain itself thereby representing an intrinsic nerve supply [40].

4.1. Sympathetic nervous system

The sympathetic nerves that supply the cerebral vessels arise mainly from the ipsilateral superior cervical ganglion [142], while some nerve fibers that supply the vertebral and basilar arteries originate from the inferior cervical ganglion and the stellate ganglion [3]. The activation of these fibers results in vasoconstriction, modulation of cerebrovascular autoregulation, reduction of intracranial pressure and a decrease of cerebral blood volume and cerebrospinal fluid production [40]. The responses are mainly mediated by noradrenaline (NA) and neuropeptide Y (NPY) [47,48], at least 40–50% of the NA-positive cells contain NPY [12,186].

The neurotransmitter content in the nerve cell bodies is influenced by various factors: Activation may increase catecholamine synthesis and NPY mRNA [96], while denervation results in depletion of NA and NPY [48]. However, some time after sympathectomy, there is an upregulation of NPY-containing fibers of parasympathetic origin [17]. Furthermore, there are age-dependent changes in sympathetic neurons; in old rats, there is a selective loss of NPY with a concomitant increase of nerve fibers containing vasoactive intestinal peptide (VIP) and calcitonin gene-related peptide (CGRP) around cerebral blood vessels [21]. In man there is a significant reduction with age of NPY, VIP, substance P (SP) and CGRP [52].

Electronmicroscopic and functional studies have revealed that NA, NPY and adenosine triphosphate (ATP) are co-stored in large dense-cored vesicles [21]. Stimulation of the sympathetic nerves results in the release of these transmitters, the stimulus intensity determines the relative contribution of NA and NPY. At resting conditions, little NPY is released, and hence sympathetic vasoconstriction is largely due to adrenoceptor and purinergic receptors whereas in situations of high sympathetic activity, the contribution of NPY becomes prominent [129].

It has been suggested that the small pial vessels on the cortical surface are supplied by NA-containing fibers emanating from an intracerebral source such as the LC

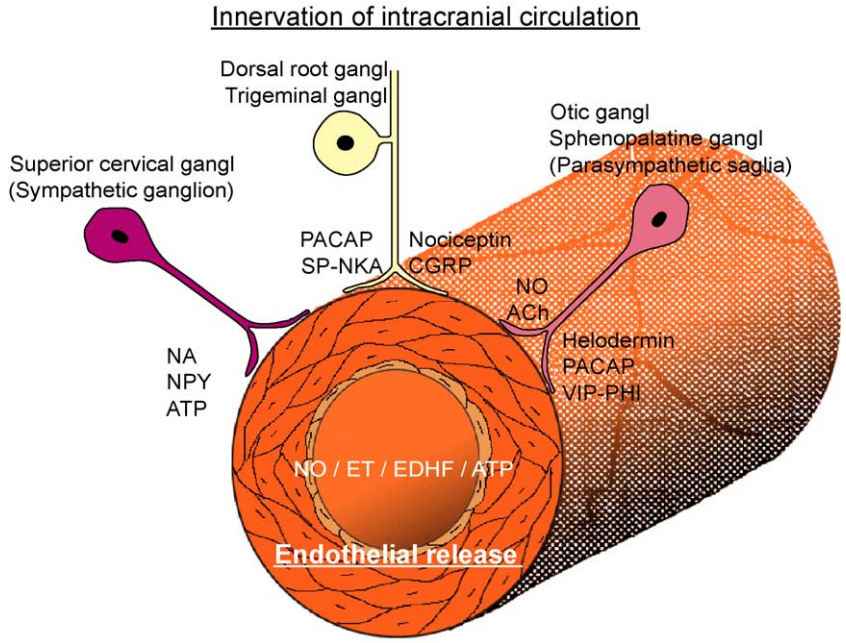

Fig. 1. Schematic illustration of the perivascular nerves in intracranial arteries. Sympathetic nerves originate in the superior cervical ganglion and store noradrenaline, ATP and neuropeptide Y. The presynaptic fibres originate in the sympathetic chain. Parasympathetic nerves have their major origin in otic and sphenopalatine ganglia and store VIP, PACAP, nitric oxide and acetylcholine. Sensory fibers originate mainly in the trigeminal ganglion and store CGRP, substance P, neurokinin A, PACAP and nitric oxide [92].

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