## The dura and migraine

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This article concerns the possible role of dural changes in migraine pain. The hypothesis that changes in the dura are important in migraine pain has become widely accepted among migraine scientists. A critical examination of the evidence for and against dural involvement in migraine pain shows that in spite of the extensive research that has been carried out on dural physiology and pathophysiology, there is no hard evidence that dural changes actually occur in humans during a migraine. On the contrary, the available evidence appears to indicate that it is unlikely that dural changes are part of the migraine pain process.

The current focus on the dura as an important element in the pathogenesis of migraine originated approximately 60 years ago with the observation that mechanical stimulation of the dura causes headache [1,2]. A relationship between neurogenic inflammation (NI) and migraine was first proposed by Dalessio [3], and the possibility of dural involvement in migraine received a major stimulus from the work of Moskowitz et al., who proposed that migraine pain is related to NI and vasodilatation in the dura [4-6]. The description of the trigeminovascular system, which by definition included the meningeal arteries as the 'vascular' component, lent further impetus to the concept [7], and research into the peripheral component of the migraine cascade has since then focused almost exclusively on sensitization of the extracerebral intracranial structures, and in particular, on the dura mater and its arterial supply. However, the evidence that supports the current thinking that the dural meningeal sensory innervation plays a major role in migraine headache is inferential [8,9]. In this critical analysis of the literature, the shortcomings of the evidence in favor of dural involvement in migraine are elucidated. It is concluded that there is no reliable evidence available at present to support the theory that changes in the dura are involved in the generation of migraine pain.

## Animal studies

Studies on laboratory animals have provided medical science with a great deal of valuable information, but care should be taken not to extrapolate the results of animal studies too freely to humans because there are marked interspecies differences in both the anatomy and the physiology. Therefore, it cannot be assumed that data obtained from animal models unambiguously reflect CNS changes that occur in humans [10]. When the results of animal studies are incorrectly extrapolated to human conditions such as migraine, misleading information may be propagated, as illustrated below:

- The cerebral arteries of some laboratory animals receive a dense supply of CGRP fibers, but human cerebral vessels only contain a sparse network [11], and the walls of human cerebral vessels only contain a sparse supply of CGRP [12]. This difference may, however, be related to inaccurate measurements during histochemical studies, depending on the antibodies used and other methodological differences;
- In most species, VIP-containing nerves are most abundant in the circle of Willis and the major cerebral arteries. The density of the nerve plexus is highest in the carotid system and diminishes in a caudal direction. In man, the VIP-immunoreactive nerve supply is sparse in both cerebral arteries and veins [12]. Although VIP-immunoreactive fibers have little to do with migraine, this example is included to demonstrate the existence of species differences;
- Stimulation of the trigeminal ganglion increases cerebral blood flow in cats [13]. In monkeys, however, it has no effect on cerebral blood flow, although on the contrary, it increases external carotid blood flow [14].

Great care must therefore be exercised when extrapolating data obtained from animal models to humans, as it does not automatically follow that animal data accurately reflect what occurs in humans [10]. A further confounding factor is that animal specimens are usually taken from the young under controlled laboratory conditions, while human material is usually from autopsy material long after death.

#### Keywords

= dura = meninges

migraine pain



# Evidence for dural involvement in migraine pain

Stimulation of dural arteries

Direct stimulation of the dural arteries in humans can give rise to painful, headache-like sensations that are referred to similar cephalic locations as the pain of migraine [1,15]. The notion that migraine headache results from the dura and its related blood vessels was based primarily on these findings [16]. While dural stimulation can indeed give rise to headache, similar headache-like pain can also be caused by direct stimulation of other cranial structures innervated by the trigeminal nerve, such as the lateral ventricle and the superficial temporal, supraorbital and occipital arteries, findings that must logically also implicate these structures as possible sources of migraine pain [1]. It has also been shown that in migraine sufferers, painful stimulation of the temple induces migraine-like attacks, with nausea, headache and extracranial vasodilation [17.18].

## Activation of meningeal trigeminal nociceptors in humans

Mechanical and chemical stimulation of the dura activates the meningeal trigeminal sensory fibers and can cause headache pain in humans [1,2]. Neurons in the trigeminal ganglion respond to punctuate probing, stroking, traction and to heating or cooling of the dura, or to the application of hypertonic saline to the dura in laboratory animals [19-21]. These response properties of dural afferent neurons confirm that they are in fact nociceptors, and consequently are also capable of being activated under pathologic conditions such as increased intracranial pressure or meningitis [19,22]. However, no such mechanical, chemical, temperature change or pathologic stimulus has been shown to occur in the dura during migraine.

## Neuroanatomy of dura

The pathway of sensory innervation from the dura to the trigeminal subnucleus caudalis (Vc) is via the trigeminal nerve and the trigeminal ganglion [23]. Anatomical studies in laboratory animals demonstrate that the dura and the meningeal arteries are innervated by trigeminal nociceptive neurons [24,25], most of which contain neuropeptides similar to those found in nociceptive neurons innervating other tissues [26,27]. However, it is important to note that although the dura and dural blood vessels receive their nociceptive innervation from trigeminal neurons [24,25], only a small component of the trigeminal nerve provides

sensory innervation to the meninges. The main trunks of the trigeminal nerve supplies somatosensory innervation to the extracranial tissues [28-30]. Trigeminal nociceptive afferents from the meninges project mainly onto neurons within the medullary dorsal horn of the spinal trigeminal nucleus [31]. However, an important feature of neurons within the medullary dorsal horn is that there is extensive convergence of different afferent inputs, including from the cranial muscles [32]. Considerable proportions of wide dynamic range and nociceptive-specific neurons in the Vc have afferent inputs from the jaw muscles, the temporomandibular joints and the neck muscles. These neurons generally also have localized mechanoreceptive fields involving cutaneous afferents [32]. That the dura is innervated by the trigeminal nerve simply indicates that the trigeminal nerve is able to transmit nociceptive impulses from the dura to the Vc, but this does not constitute proof that it actually does so in migraine.

## Raised cytokine levels

There is evidence of raised cytokine levels in migraine, and it has been claimed that this favors the possible occurrence of a meningeal inflammatory process during a migraine [16]. However, the evidence cited to support this claim is less than convincing. One of the three cited studies measured cytokine levels in peripheral blood, so the actual origin of the increased cytokines in this study is unknown [33]. In the second and third studies, cytokine levels in internal jugular blood were measured, which would of course have excluded blood from the middle meningeal and other dural vessels, as the dural vessels are part of the external carotid system and drain into the external jugular vein [34,35].

## Secondary headache

The development of migraine-like headaches in meningitis together with other migraine-related symptoms such as photophobia, phonophobia and nausea has been cited as providing confirmation of the possible involvement of meningeal inflammation in migraine [16]. These symptoms are not, however, exclusively caused by meningeal inflammation. According to the International Headache Society classification, photophobia, phonophobia and nausea also occur in tension-type headache where meningeal inflammation has not been implicated [36]. If migraine-like headaches and associated symptoms occur in the absence of meningitis, then the possibility of meningeal inflammation being the cause of migraine remains hypothetical.

Animal studies: NI & dural vasodilatation

The theory that migraine pain is a consequence of dural NI and dilatation of the dural blood vessels was first proposed by Moskowitz et al. [4-6]. The theory proposed that neuropeptides involved in NI were released from sensory afferents innervating the dural blood vessels. The proposed mechanism is that depolarization of the trigeminal sensory C-fibres that innervate the meningeal blood vessels results in the release of neuropeptides, which interact with the blood vessel walls, causing dilatation, plasma protein exudation and the activation and degranulation of mast cells [37]. Studies have indeed shown that meningeal sensory fibers can be stimulated to release neuropeptides from their peripheral endings in the meninges, resulting in dural plasma protein extravasation (PPE) and dural vasodilatation [4,11,38,39]. However, these studies were all carried out on laboratory animals, and, as has been demonstrated, there are significant interspecies anatomical and physiological differences. In addition, human dural arteries are prevented from dilating because of anatomical constraints [29,40].

#### Animal studies: CGRP

CGRP has been shown to evoke vasodilatation of dural blood vessels in laboratory animals [41-43] and it has been claimed that "the dense innervation of the cerebral circulation by trigeminal CGRP-containing nerve fibers is central to its involvement in primary headaches" [44]. It is true that in cats there is dense innervation of the cerebral circulation by CGRP-containing fibers [39,45], but this is not the case in humans. Marked species variations are observed in the density of CGRPimmunoreactive cerebrovascular nerve fibers. While the cerebral arteries of laboratory animals may well receive a dense supply of CGRP fibers, human cerebral vessels contain only a sparse network [11], and the walls of human cerebral vessels contain only a sparse supply of CGRP [12]. Animal studies are often of great value, but caution must be exercised when extrapolating results from animal studies to humans.

### Evidence against dural involvement in migraine pain NI & PPE

The hypothesis that dural PPE is important in migraine was based on animal experimental evidence only, and relates to the dural PPE aspect of NI in laboratory animals [46,47]. Dural PPE has not, however, been demonstrated in humans. In the rat model of NI, dural PPE can be generated by high-intensity electrical stimulation of the trigeminal ganglion, which causes increased endothelial permeability and leakage of albumin (PPE) in both the dura mater and the retina. In humans though, it is not possible to examine the dural vessels for the possible presence of PPE; however, the retinal vessels, which originate from the intracerebral branches of the ophthalmic artery, and reflect the state of the intracranial dural vessels, are easy to access. There is in fact no increased endothelial permeability in human retinal vessels during migraine, so the rat model has no demonstrated correlate in humans [46].

Furthermore, Peroutka *et al.* reported that eight selective PPE inhibitors failed to be effective in the acute treatment of migraine [48–52]. Peroutka concluded that data that support the existence of dural PPE in humans is simply lacking and that the dural NI theory of migraine "is no longer tenable" [49].

## Dural anatomy

The principal blood supply of the dura is via the middle meningeal artery, one of the terminal branches of the maxillary division of the external carotid artery [29]. Although in recent years there have been some elegant studies on cerebral blood flow, in none of these studies has it been possible to measure possible changes in blood flow or diameter of the intracranial dural arteries [53,54]. As it is not possible with available techniques to measure changes in human dural blood flow [44], there has been no experimental confirmation of the dural vasodilatation hypothesis. On the contrary, as the meningeal arteries lie mainly in the outer, or endosteal layer of the dura, which in humans is a tough membrane that is rigid, resistant to stretching and is tightly attached to the cranial bones, [29,40] the dural meningeal arteries are effectively prevented from dilating especially when we consider that vasodilatation in migraine is not due to increased hemostatic pressure actively dilating the vessels, but is passive, due to relaxation of the muscular arterial walls [40]. The gross anatomy of the dural meningeal arteries therefore mitigates against the likelihood of dural arterial dilatation migraine.

## CGRP

The involvement of CGRP in migraine pathophysiological mechanisms is suggested by the facts that plasma levels of CGRP are higher during spontaneous headache compared with controls [55], there is an increase in plasma CGRP levels during experimentally induced migraine attacks [56], there is a lowering of plasma CGRP levels with the administration of antimigraine drugs [57], CGRP can induce migraine [58], that two CGRP antagonists, olcegepant [59] and telcagepant [60,61], are effective in the treatment of migraine attacks [62] and the intensity and duration of migraine headache correlates with plasma CGRP levels [63]. CGRP is postulated to be involved in several pathophysiological processes in migraine, including dilation of cerebral and dural blood vessels [64,65]. CGRP is the most potent of the known peptidergic dilators of peripheral and cerebral blood vessels [39,66]. In the trigeminovascular system, cell bodies in the trigeminal ganglia constitute the main source of CGRP. Activation of the trigeminal ganglion causes CGRP to be released from perivascular nerve endings [65]. CGRP is present in human superficial temporal arteries [67], and although one study reported no increase in CGRP in external jugular blood, CGRP has been found in the extracerebral circulation in migraineurs in several studies, even interictally, supporting a role for CGRP in migraine [68-72]. Furthermore, relief of migraine pain by triptan administration coincides with reduction in or normalization of CGRP concentrations in the extracranial blood [70,73-75]. Conversely, CGRPinduced headache did not correlate with dilatation of intracranial arteries [58], making an intracranial vascular mechanism unlikely in migraine. Furthermore, the bulk of the blood in the external jugular vein comes from the extracranial tissues, with only one-fifth originating in the cerebral circulation, which indicates that changes in CGRP found in the external jugular vein most likely reflect what is going on in the extracranial tissues [62]. It is also interesting to note that in rats, CGRP-invoked vasodilatation of the dural blood vessels did not evoke neuronal firing in the cells of the Vc [76]. Therefore, it is unlikely that the raised CGRP levels in the external jugular blood in migraine originate from the dura. Furthermore, in rats, although both systemic and topical administration of CGRP caused significant increase in dural blood flow, neither method of administration resulted in the activation of meningeal nociceptors [77].

#### Discussion

Changes in the dura have been implicated as a possible cause for migraine pain, but the anatomical location of the dura within the cranium has made this hypothesis difficult to verify. That direct stimulation of the meningeal arteries and dural sinuses in humans leads to painful headache-like sensations similar in location to some migraine pain [1,2], and that mechanical and chemical stimulation of the dura can activate meningeal trigeminal sensory fibers and cause headache pain, [19-21] suggest that migraine pain could possibly originate in the dura. However, there are other structures that receive their sensory innervation from the trigeminal nerve, and direct stimulation of these structures, such as the lateral ventricle and the superficial temporal, supra-orbital and occipital terminal branches of the external carotid artery also gives rise to headache-like pain [1]. Indeed, there is compelling evidence that the terminal branches of the external carotid artery are a source of migraine pain. In addition, painful stimulation of the temple not only induces migraine-like attacks in migraine sufferers, but also results in nausea and extracranial vasodilatation in migraineurs, which indicates that extracranial nociceptive input may play a part in the genesis of migraine pain [17,18].

The importance of central sensitization driven by peripheral sensitization in the generation of migraine pain has been well documented [78,79], but there is little or no evidence to show with certainty which peripheral pain fibers are sensitized and what actually causes their initial sensitization [80]. Meningeal nociceptors are inflammatory sensors [19,22,81] and because release of inflammatory mediators in the vicinity of their peripheral receptive field can lead to their ongoing activation [21,82], it has been suggested that there is a link between intracranial inflammation and migraine pain. However, the presence in the dura of nociceptive neurons that contain neuropeptides similar to those found in trigeminal nociceptive neurons innervating other tissues [26,27] indicates only that physiologically, dural nociceptors, in common with trigeminal nociceptors elsewhere, are capable of responding to noxious stimuli. This is not evidence that dural nociceptors are actually involved in the pathogenesis of migraine pain.

The presence of increased cytokine levels in peripheral blood has been claimed to provide support for the possible occurrence of a meningeal inflammatory process during migraine [16]. Increased cytokine levels in peripheral blood in migraine [33] are most certainly not proof of meningeal inflammation, as the cytokine could originate from other structures. Similarly, raised cytokine levels in internal jugular blood do not reflect the state of the dural arteries, which drain into the external carotid system [34,35].

The notion that migraine pain is a consequence of dural NI and dural vasodilatation is based solely on the rather shaky foundation of inferential evidence. The theory is based on the fact that the dura, its blood supply and its innervation possess clinical, anatomical, physiological and pathophysiological qualities that would make it possible for the dura to be involved in migraine pain [4,11,38,39]. However, these qualities are not unique to the dura, but are found in many other tissues that receive their sensory innervation from the trigeminal nerve. Consequently, the fact that the dura possesses these qualities cannot be construed as proof of its involvement in migraine pain to the exclusion of other trigeminally innervated tissues.

Animal studies have also been extensively cited as evidence of dural involvement, but because of significant species differences, the results of these studies cannot be applied to humans. The reader's attention is directed to the following: first, there is development of dural NI and dural vasodilatation in laboratory animals following stimulation of dural sensory fibers [4,11,38,39]. There has been no analogous finding of dural NI in human migraineurs. In animals, dural plasma extravasation is accompanied by extravasation from the retinal artery [46], and if dural plasma extravasation occurred in humans, then it would also reasonably be expected to be accompanied by retinal plasma extravasation. Retinal plasma exravasation does not, however, occur in human migraineurs, indicating that it is also unlikely that its analog, dural plasma extravasation, occurs in migraine [46]. Second, CGRP released from perivascular nerves in the dura of laboratory animals undisputably evokes vasodilatation of dural vessels [41-43]. This finding has been used to justify the assertion that dural release of CGRP plays a role in migraine, but this does not take into account the anatomical differences [83]. In cats, there is dense innervation of the cerebral circulation by CGRP-containing fibers [39,45]. In humans, however, the cerebral vessels contain only a sparse network of CGRP-containing fibers [11]. In cats, the dural arteries can dilate, but in humans they cannot [29,40]. Third, electrophysiological studies on the meningeal sensory innervation have demonstrated the ability of meningeal sensory neurons to encode and transmit noxious mechanical, thermal and chemical stimuli to nociceptive afferents innervating other tissues, further suggesting the possible importance of meningeal sensory innervations in migraine [19,21,84-86]. What the cited studies demonstrated however, was simply that the meningeal sensory innervation functions in the same way as the sensory innervation elsewhere. These studies did not actually demonstrate any meningeal involvement in migraine pain. The confusion that results

from the inappropriate use of animal studies is aptly illustrated in the following statement that apppears in a chapter of '*The Headaches*' titled 'CGRP Involvement in Migraines' – "CGRP released from perivascular nerves in the meninges, has been conclusively demonstrated experimentally to evoke clear vasodilatation in pain producing intracranial structures" [83].

What the authors did not clarify was that these experiments were on laboratory cats and rats [41-43], in which the dural arteries are not anatomically constrained from dilating. The information cannot with impunity be cited in a discussion on migraine, as there is clear evidence that human dural arteries are unable to dilate because of anatomical constraints [29,40]. In any event, it has been shown that CGRP-induced increased dural vasodilatation does not cause sensitization of meningeal nociceptors [77].

Anatomical studies in laboratory animals have also shown that the dura and its arteries are densely innervated by trigeminal nociceptive neurons [24,25], most of which contain neuropeptides similar to those found in trigeminal nociceptive neurons innervating other tissues [26,27]. While it has clearly been shown that in cats there is dense innervation of the cerebral circulation by CGRP-containing fibers [39,45], this is not the case in humans. Furthermore, although the dura and dural blood vessels receive their nociceptive innervation from trigeminal neurons [24,25], only a small component of the trigeminal nerve provides sensory innervation to the meninges. The larger branches of the trigeminal nerve supply somatosensory innervation to the extracranial tissues [28-30], and nociceptors supplying the extracranial tissues have the same properties as dural nociceptors [26,27]. In the light of this, it is difficult to exclude the possibility of the extra cranial tissues being a source of migraine pain.

Bearing in mind that in humans the dural vessels are unable to dilate due to anatomical constraints [29,40], and that retinal plasma extravasation has been demonstrated in animals but not in humans, the conclusion must be that neither dural vasodilatation nor dural PPE are likely to occur in humans [46]. Support for this conclusion is provided by Peroutka, who listed no fewer than eight substances that reduced PPE in animals, but which had no beneficial effect on migraine [49].

#### Conclusion

The supposition that dural nociceptors, dural NI and dural vasodilatation are part of the migraine chain of pathophysiological events has been based on inference and on the results of animal experimentation, which in the case of migraine has to be treated with circumspection because of important interspecies differences. Indeed, the anatomy and physiology of the dura and the dural vasculature makes it most unlikely that the dura is involved in migraine. "A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die, and a new generation grows up that is familiar with it". – Max Planck, Nobel Laureate for Physics,

1918

Future perspective

Although there is no conclusive evidence of dural involvement in migraine, it is one of those ideas that seemed logical at the time, but has never been adequately substantiated by scientific investigation. It has, however, been repeated so often, and has been championed by so many prestigious people, that its basic error has eventually, in spite of the lack of direct evidence, come to be perceived as truth. To reverse this perception will no doubt take many years. Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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#### Executive summary

#### Animal studies

Animal studies do not necessarily reflect what happens in humans and should be used with circumspection.

Evidence for dural involvement in migraine pain: stimulation of dural arteries

Headache-like pain can also be caused by direct stimulation of many cranial structures other than the dura.

- Evidence for dural involvement in migraine pain: activation of meningeal trigeminal nociceptors in humans
- No mechanical, chemical, temperature change or pathologic stimulus has been shown to occur in the dura during migraine.

Evidence for dural involvement in migraine pain: neuroanatomy of dura

There is extensive convergence of different afferent inputs, not only from the dura onto neurons within the medullary dorsal horn of the spinal trigeminal nucleus.

Evidence against dural involvement in migraine pain: neurogenic inflammation & plasma protein extravasation

There are no data to support the existence of dural plasma protein extravasation and neurogenic inflammation in humans.

#### Evidence against dural involvement in migraine pain: dural anatomy

The anatomy of the dura precludes the dural meningeal arteries from dilating.

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