Response Properties of Dural Nociceptors in Relation to Headache

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INTRODUCTION

The trigeminal nerve, in addition to supplying the major somatosensory innervation to the extracranial tissues of the anterior head and face, also has a much smaller intracranial component that provides a sensory innervation to the cranial meninges (Fang 1961; Penfield and McNaughton 1940). The idea that this intracranial meningeal sensory innervation might be involved in headache dates back at least as far as the observation by Huber (1899) of nerve fibers in the intracranial dura that were myelinated and therefore presumably sensory in function. This idea was strengthened by neurosurgical observations that direct stimulation of the meninges, particularly at vascular sites, could evoke painful, headache-like sensations (Fay 1935; Feindel et al. 1960; Ray and Wolff 1940). The role of the meningeal sensory innervation continues to be a major focus of current thinking on the origin of headache, especially migraine, based on a large and growing body of indirect evidence (Pietrobon and Streissnig 2003; Strassman and Raymond 1997). This review will summarize the results of recent investigations into the properties of the meningeal sensory fibers, particularly neurophysiological investigations into their sensory responses, and discuss the relevance of these findings for the understanding of headache.

Anatomical and physiological properties of meningeal sensory fibers

Anatomical studies in man and animals have shown that major blood vessels of the cranial meninges receive an innervation from sensory fibers that originate primarily in the trigeminal ganglion and, to a lesser extent, the upper cervical dorsal root ganglia (Fang 1961; Keller et al. 1985; Mayberg et al. 1984; O’Connor and van der Kooy 1986; Penfield and McNaughton 1940; Rusnell and Simons 1987). This meningeal sensory innervation supplies both the major cerebral arteries (pial arteries, such as the middle cerebral artery) that carry the blood supply to the brain as well as the dural venous sinuses that carry the venous drainage from the brain. The cerebral arteries are invested with sensory fibers only in their course through the pia (the innermost layer of the meninges) that covers the outer surface of the brain and lose this innervation when they exit the pial layer to penetrate into the brain parenchyma. Both the sensory innervation as well as pain sensitivity are restricted to the meningeal covering around the outside of the brain and do not extend to the brain itself or its intrinsic blood vessels. Because the meninges are the only intracranial sites from which pain can be evoked, headaches that accompany intracranial pathologies (e.g., meningitis, subarachnoid hemorrhage, tumor) are thought to result from meningeal stimulation and consequent activation of meningeal sensory fibers (Wolff 1963). Migraine headache, although not accompanied by any detectable pathology, shares certain clinical features with headaches of intracranial origin (Blau and Dexter 1981) and has also been postulated to result from activation of the meningeal sensory innervation.

Neurophysiological studies in animals have examined the response properties of this meningeal sensory innervation to better understand how it might become activated under physiological or pathophysiological conditions. Such studies have focused on the innervation of the dura rather than the pia because it is more accessible and more readily allows for the delivery of controlled, localized mechanical and chemical stimuli. The lack of information on the response properties of pial fibers potentially represents a significant gap in our understanding of the role of the meningeal innervation in headache.

The first neurophysiological studies of this sensory pathway examined the response properties of second-order neurons in the trigeminal nucleus caudalis (medullary dorsal horn) that
were identified as receiving afferent input from the meninges based on their excitatory responses to electrical or mechanical stimulation of the dura (Davis and Dostrovsky 1986, 1988; Strassman et al. 1986). Such neurons also exhibited facial receptive fields that often included the periorbital region from which they could be activated by noxious mechanical stimulation. The location of these nociceptive facial receptive fields strongly overlapped with the region of pain referral evoked by dural stimulation in humans as well as the typical area of pain in migraine, consistent with a possible role for these neurons in the mediation of pain of meningeal or migrainous origin.

More recently, neurophysiological studies have investigated the primary afferent neurons in the meningeal sensory pathway. One general ongoing question raised by these studies is whether the meningeal sensory neurons are similar to nociceptive neurons in other tissues or, alternatively, whether they have unique properties that might be of significance for headache pathogenesis and drug therapy. Other tissues of the body, including superficial as well as deep somatic and visceral tissues, are innervated by a class of sensory neurons that share a number of common properties and are referred to as nociceptors because they are capable of signaling the presence of noxious stimuli or tissue injury (Raja et al. 1999). One of the characteristic properties common to nociceptors in all tissues is a sensitivity to algesic chemicals, particularly endogenous substances that are produced at sites of tissue injury and inflammation. Such inflammatory mediators cannot only evoke discharge in nociceptors but can also produce sensitization or increased responsiveness to mechanical or thermal stimuli.

In vivo electrophysiological recording studies have indeed found that the intracranial meninges are innervated by neurons that exhibit properties characteristic of nociceptors in other tissues, including chemosensitivity and sensitization. These studies recorded single-unit extracellular discharge activity either from cells in the trigeminal ganglion of the rat (Dostrovsky et al. 1991; Strassman et al. 1996) or from teased fibers in the nasociliary nerve of the guinea pig (Bove and Moskowitz 1997) and identified dural afferents by their response to electrical or mechanical stimuli applied to dural sites on or around the middle meningeal artery or the dural venous sinuses. Conduction velocities in response to single shock electrical stimulation of the dura were most often in the C- or A-delta range, although some faster-conducting neurons were also found (see further discussion of subpopulations in the following text). Neurons could be activated by mechanical, thermal, or chemical stimulation of the dura. In some cases, individual neurons were shown to respond to all three modalities of stimulation (Bove and Moskowitz 1997) as is found for polymodal nociceptors in other tissues. Neurons typically exhibited localized mechanical receptive fields on or adjacent to dural blood vessels from which they could be activated by punctate probing or stroking (Bove and Moskowitz 1997; Strassman et al. 1996) or traction (Dostrovsky 1991). Thermal responses could be evoked by both warming and cooling stimuli (Bove and Moskowitz 1997). Heat thresholds (<42°C) were lower than those of cutaneous nociceptors but were consistent with a nociceptive function for intracranial tissues because such thresholds could result in activation under pathological conditions such as fever or heat stroke, which can be associated with headache. Similar low heat thresholds have also been found for splanchnic afferents (Adelson et al. 1997) and so may be characteristic of deep or visceral nociceptors.

Neurons could be activated by a variety of algesic chemicals, including hypertonic saline applied either topically to the dura or by intravascular infusion into the dural sinuses (Strassman et al. 1996). Neurons also responded to topical application to the dura of KCl, capsaicin, acidic buffer, pH-neutral buffer solutions of low or high osmolarity, and a mixture of inflammatory mediators (histamine, bradykinin, serotonin, and prostaglandin E2, at pH 5) (Bove and Moskowitz 1997; Strassman et al. 1996). The rationale for applying the inflammatory mediators in combination, rather than individually, is that it is a more physiological and effective test stimulus. Multiple mediators are produced during inflammation and injury, and there is some evidence that their actions on nociceptors are synergistic (Vyklicky et al. 1998). The various chemical agents used in these studies are from the class of algesic and inflammatory agents that are effective for activating small-diameter sensory fibers and evoking pain when applied to other tissues of the body. Their effectiveness in activating meningeal afferents does not implicate them specifically in headache mechanisms but rather may be viewed as a further demonstration that tissues throughout the body receive an innervation from a class of predominantly small-diameter sensory fibers that have certain receptive properties in common, including chemosensitivity, that are consistent with a nociceptive function.

Besides activating the neurons, the inflammatory mediators also produced a sensitization to mechanical stimuli such that the neuron’s response threshold was lowered (Levy and Strassman 2002b; Strassman et al. 1996). Such an enhancement of mechanosensitivity in meningeal afferents might be relevant to symptoms that are characteristic of certain headaches that indicate the presence of an exaggerated intracranial mechanism. For example, in migraine, as well as in meningitis, the pain of the headache is increased by normally innocuous activities such as coughing, straining, or sudden head movement (Blau and Dexter 1981), which would all be expected to produce a transient alteration in the distribution of mechanical forces within the intracranial space (e.g., Williams 1976). Similarly, the throbbing quality that is characteristic of migraine has typically been attributed to arterial pulsations, which might activate mechanically sensitized intracranial afferents through the arterial pressure pulse that propagates throughout the closed intracranial space. In addition, the headache that develops after lumbar puncture (post dural puncture headache) has a strict positional dependence that is indicative of a gravity-induced tension or displacement of intracranial tissue (Wolff 1963). These various clinical phenomena point to the presence of mechanosensitive neural elements within the intracranial space that can, under some circumstances, contribute to symptoms of clinically occurring headache.

This raises the question of whether the mechanical response thresholds of the dural afferents are in a range that would result in neural activation from physio- or pathophysiological levels of intracranial pressure. One important caveat in attempting to address this question is that it involves a comparison of two fundamentally different types of stimuli. The experimental stimulus produces a focal indentation of the dura, whereas intracranial pressure is diffusely distributed and also compresses the dura against the intact cranium. Therefore the experimental stimulus would be expected to produce more
tension and shear, but less compression, than would be exerted by increases in intracranial pressure (discussed in Bove and Moskowitz 1997). In addition, intracranial pressure might potentially produce summation of excitation from stimulating multiple receptive spots within a single neuron’s receptive field and so produce greater afferent recruitment than a focal stimulus of equal pressure. An important future advance will be to study neuronal responses during experimentally induced changes in intracranial pressure with the cranium intact. The following discussion is presented with this caveat in mind.

Normal levels of intracranial pressures are extremely low (up to a maximum of ~20 mmHg or 2.6 kPa at the peak of the arterial pulsation) and would be subthreshold even for all but the most sensitive of cutaneous mechanoreceptors. The baseline thresholds of dural afferents are distributed over a wide range (Levy and Strassman 2002a), but the lower end of this range corresponds roughly to the upper limit of normal intracranial pressures (only 3% had thresholds <2.6 kPa), so there would be negligible recruitment of afferent activity expected at these pressures. Pathological elevations in intracranial pressure such as occur during meningitis (~40 mmHg) would be suprathreshold for ~18% of the mechanosensitive dural afferents. Although the majority of dural afferents show adaptation, some neurons are nonadapting or have a nonadapting response component (Levy and Strassman 2002a) and so might be capable of responding to such maintained elevations in pressure.

However, transient increases in intracranial pressure, to even higher levels of ~70 mmHg, can occur in normal subjects during innocuous actions such as coughing (Williams 1976). Approximately one-third of the mechanosensitive dural afferents had baseline thresholds below this level. This raises the question of why such activities are not normally painful. One possibility is that although a substantial number of neurons are activated, the overall level of neural activity is nonetheless subthreshold for evoking conscious sensations. In cutaneous nociceptors, there is evidence that even low levels of discharge (~0.5 Hz) are sufficient to evoke painful sensations (reviewed in Raja et al. 1999), but similar evidence is lacking for nociceptors in other tissues. It is possible that higher levels of discharge are necessary for dural afferents to evoke pain and that some degree of sensitization, such as might occur during headache, is necessary to attain such discharge levels during physiological changes in intracranial pressure. It is further possible that some degree of central sensitization, induced by a sustained period of primary afferent discharge (e.g., Burstein et al. 1998), might also be necessary before such stimuli become painful.

**Subpopulations**

The cutaneous sensory innervation contains clearly defined neuronal subpopulations specialized for mediation of the distinct nociceptive and nonnociceptive sensory modalities represented in the skin (Raja et al. 1999). However, the meningeal sensory innervation is not known to subserve multiple sensory modalities but rather appears to have a selectively nociceptive function. As with many visceral tissues, the only sensation that can be evoked by the meningeal innervation is pain (Ray and Wolff 1940), and it is thought to become activated only under potentially harmful or pathological conditions. The best evidence on this point comes from studies on its role in the regulation of cerebral blood flow. Stimulation of meningeal sensory fibers can evoke cerebral vasodilation through the peripheral release of neuropeptides (Edvinsson et al. 1987; Kurosawa et al. 1995; McCulloch et al. 1986; Williamson et al. 1997a). However, trigeminal deafferentation has no effect on the normal regulation of cerebral blood flow (Branston et al. 1995; Suzuki et al. 1990), indicating that the meningeal sensory innervation is not active under normal conditions. It apparently can become activated by pathological conditions because trigeminal deafferentation does reduce the cerebral vasodilation that accompanies meningitis (Weber et al. 1996), transient cerebral ischemia (Moskowitz et al. 1989), severe hypertension, and seizures (Sakas et al. 1989).

Although the dural afferent population does not appear to mediate distinct sensory modalities, it does show a pattern of variation in mechanosensitivity as a function of conduction velocity that suggests the presence of subpopulations (Levy and Strassman 2002a). The most marked difference was between neurons with conduction velocities more or less than 5 m/s, and consequently this conduction velocity was used to subdivide neurons in the A fiber range into slow A (1.5–5 m/s, corresponding to the low end of the A-delta range) and fast A (5–25 m/s, which includes neurons in the A-beta as well as the upper end of the A-delta range, as discussed in Levy and Strassman 2002a). Slow A neurons had the highest mechanosensitivity, in that they had the highest incidence of mechanosensitivity (97%) as well as the highest stimulus-response slopes and the lowest thresholds. Neurons in the C-fiber range (<1.5 m/s) tended to have somewhat lower mechanosensitivity than the slow A neurons in that they had lower slopes and higher thresholds; the highest thresholds were found in neurons with the lowest C.V.s (<8 m/s). Furthermore, a substantial number of C neurons (18%) had no baseline mechanosensitivity, although in some cases these mechanically insensitive neurons could be sensitized by inflammatory mediators (Levy and Strassman 2002b). In contrast, most of the fast A neurons had far lower mechanosensitivity than the slow A or C fibers, and a relatively high percentage (33%) had no mechanosensitivity. Furthermore, unlike the C-fibers, the fast A neurons that were mechanically insensitive could not be sensitized or activated by chemical stimuli, including 100 mM KCl. The possible sensory function of these mechanically and chemically insensitive neurons is unclear. The finding that the fastest conducting neurons have the lowest mechanosensitivity is the reverse of what is found in the cutaneous innervation, where the most sensitive mechanoreceptors are A-beta fibers. However, this trend might not be unique to dural afferents, as pelvic afferents show a similar trend of an increased percentage of mechanically insensitive fibers among the fastest conducting neurons (Sengupta and Gehburt 1994). One characteristic that many of the fast conducting dural afferents share with cutaneous A-beta fibers is rapid adaptation. However, unlike in cutaneous afferents, rapid adaptation in dural afferents is associated with very high response thresholds and with rapidly fatiguing responses. Such responses might be suited for signaling transient mechanical stimuli such as would result from sudden head movements. The finding of a substantial number of fast-conducting dural afferents was surprising as it has generally been thought that the dura received a predominantly small-fiber sensory innervation (Penfield and McNaughton...
similar to other visceral tissues. Anatomical measurements confirmed that the dural innervation does indeed contain a substantial number of large myelinated fibers, and in fact the proportion of the myelinated fibers that are >5 μm is actually greater in the dural nerves than in the trigeminal nerve as a whole (Strassman et al. 2004).

Patterns of sensitization

A critical question concerning the meningeal afferents is whether their activity, under either baseline or sensitized conditions, can be modulated by anti-migraine agents such as sumatriptan. To optimize the detection of possible drug effects, sensitization was first characterized more quantitatively over different portions of the stimulus-response curve. In particular, neurons were examined for the presence of two possibly distinct components of mechanical sensitization: a decrease in response threshold and an increase in responses to suprathreshold stimuli. These studies found that both of these components of sensitization could be detected, but, surprisingly, they occurred in separate neurons (Levy and Strassman 2002b). That is, individual neurons, if they showed sensitization, showed either a decrease in threshold or an increase in suprathreshold responses but not both. This observation was made using a membrane-permeable analogue of cAMP as the sensitizing agent. cAMP was used because the cAMP/PKA intracellular cascade mediates the sensitizing actions of a number of different inflammatory mediators and also because it is a potential target for the inhibitory actions of the anti-migraine agent sumatriptan (see following text). cAMP also has the methodological advantage that it generally does not produce ongoing discharge, which can interfere with the detection of changes in threshold. However, the selective sensitizing effects produced by cAMP are in a sense artificial in that inflammatory mediators typically depend for their full effects on the combined action of multiple intracellular signaling cascades not the activation of a single cascade in isolation. Although the patterns of sensitization produced by cAMP may be considered unphysiological, they nonetheless may give insight into underlying mechanisms of sensitization.

One potential clue to the mechanism for the dual effects of cAMP is the observation that the two groups of neurons that were distinguished by their pattern of sensitization also differed in other properties. The largest difference was in the slope of the baseline stimulus-response curve, which reflects the neuron’s capacity to discharge at higher rates in response to more intense stimuli. The neurons that sensitized by showing an increase in suprathreshold responses (“STH” neurons) had higher slopes than the neurons that sensitized by showing a decrease in response threshold (“TH” neurons). The STH group also had significantly lower baseline thresholds and higher conduction velocities than the TH group, although both groups included neurons that conducted in the C and A-delta range.

These differences suggest a possible parallel with two subgroups of dorsal root ganglion (DRG) cells that have been defined in a classification system based on the cell’s repertoire of specific voltage-gated currents (Cardenas et al. 1995; Petruska et al. 2000; Scroggs et al. 1994). Two DRG subgroups are of particular interest because they show a striking segregation of two membrane currents that are thought to affect the capacity for repetitive firing. Specifically, one class of neuron (“type 2”) has an exceptionally large $I_H$ (rapidly inactivating outward current), and no $I_A$ (hyperpolarization-activation current), whereas another class (“type 4”) has a very large $I_H$ with no $I_A$. Because repetitive firing capacity is thought to be enhanced by $I_H$ and suppressed by $I_A$ (Ingram and Williams 1996; Rudy 1988), it might be predicted that this capacity would be exceptionally high in type 4 neurons and exceptionally low in type 2 neurons. Furthermore, because cAMP or activators of adenylate cyclase enhance $I_H$ but do not affect $I_A$ (Ingram and Williams 1996; Nicol et al. 1997), one would predict that the already high firing capacity of type 4 neurons would be further increased by cAMP, while that of type 2 neurons would not be affected. This predicted pattern of differences in firing capacity would parallel the findings for the STH and TH groups of dural afferents, if firing capacity were related to stimulus-response slope. A relationship between these two properties might be expected in that slope depends on the ability to fire repetitively at progressively higher rates. One further parallel is that the type 2 and type 4 DRG neurons have a size difference that is in the same direction as the difference in conduction velocities of the TH and STH dural afferents.

These parallels are based on predictions that require making a large leap from in vitro studies of DRG membrane currents to in vivo studies of dural afferent firing properties. However, the parallel is strengthened by the findings of a study that examined the sensitizing effect of serotonin on firing evoked by current injection in type 2 DRG neurons (Cardenas et al. 2001). Serotonin, acting through cAMP, was found to produce a decrease in threshold with no change in suprathreshold responses. This corresponds to the pattern of sensitization found in the TH dural afferents with mechanical stimulation. cAMP is known to lower the threshold of activation for the TTX-resistant sodium current (Englund et al. 1996; Gold et al. 1998), which is present in type 2 but not type 4 DRG cells (Cardenas et al. 1997).

Lack of effect of sumatriptan on sensitization

The serotonin $I_{1D}$ (5-HT$_{1D}$) agonist sumatriptan and other triptans are currently the most effective agents for the abortive relief of migraine headache. Sumatriptan exerts a number of different effects that could contribute to its therapeutic action. It was initially developed as a vasoconstrictor with selectivity for the cranial circulation (Feniuk et al. 1989), but it was subsequently found to have direct neural actions as well, including inhibition of neuropeptide release from both the peripheral and central endings of meningeal sensory neurons (Eltorp et al. 2000; Messlinger et al. 1998). The peripheral blockade of neuropeptide release inhibits neurogenic inflammation in the meninges (Buzzi and Moskowitz 1990; Messlinger et al. 1997; Shepheard et al. 1995; Williamson et al. 1997b), whereas the central blockade would be expected to interfere with sensory transmission to second-order neurons in the brain stem trigeminal complex. Consistent with such a central inhibitory action, triptans inhibit the responses of trigeminal nucleus caudalis neurons to meningeal stimulation (Burstein and Jakubowski 2004; Levy et al. 2004; Storer and Goadsby 1997). This inhibition may be attributed to a prerather than a postsynaptic action because 5-HT$_{1D}$ receptors have been
localized to primary afferent terminals but not cell bodies in the trigeminal nucleus caudalis (Potrebic et al. 2003).

The finding of sensitization in meningeal sensory neurons raised the question of whether the process of sensitization might be another potential target for the action of anti-migraine agents such as sumatriptan. An inhibitory action of sumatriptan on sensitization might be predicted based on the opposing actions of 5-HT$_{1B/D}$ receptors and inflammatory mediators on adenylate cyclase, the synthetic enzyme for cAMP. The 5-HT$_{1B/D}$ receptor is negatively coupled to adenylate cyclase in some types of central neurons (Durham and Russo 2002), whereas a number of inflammatory mediators produce sensitization of primary afferent nociceptors in part through a positive coupling of their membrane receptors to adenylate cyclase, and consequent activation of the cAMP/PKA signaling cascade (Cardenas et al. 2001; Gold et al. 1998; Wang et al. 1996; reviewed in Levy and Strassman 2002b).

However, when sumatriptan was tested by topical application to the dura, no effect could be detected on the mechanically evoked discharge of dural nociceptors, either under baseline conditions or after sensitization with inflammatory mediators (Strassman and Levy 2004). Instead, it was found that sumatriptan itself produced a transient discharge in these neurons. This excitatory effect on discharge might underlie the initial worsening of headache that has been reported after sumatriptan administration, prior to the subsequent onset of headache relief (Burstein et al. 2005; Visser et al. 1996). Systemic administration of sumatriptan also evoked discharge in dural nociceptors, which was more prolonged than that produced by dural application, and in addition was accompanied by mechanical sensitization (Burstein et al. 2005). The additional effects of systemic versus dural administration might result from a difference in the concentration and time course of the drug within the dura as well as a possible additional site of action in the trigeminal ganglion.

The lack of an inhibitory effect of sumatriptan on sensitization raises the question of whether the intracellular signaling mechanisms associated with 5-HT$_{1B/D}$ receptors are different in sensory neurons than what has been found previously for central neurons. A study of trigeminal ganglion cells in culture found that intracellular cAMP levels were not affected by either sumatriptan or inflammatory mediators (Durham and Russo 1999). Instead, sumatriptan induced a moderate sustained calcium influx. Although calcium influx is typically a trigger for neurotransmitter release, the sumatriptan-induced calcium influx had an unusually slow and prolonged time course that instead produced a blockade of neuropeptide release, apparently through activation of protein phosphatases. In view of these findings, studies were done to examine the involvement of calcium in the sumatriptan-induced firing in dural nociceptors. The sumatriptan-induced firing was blocked by removal of calcium from the bathing solution (Strassman and Levy 2004) consistent with the idea that the discharge was dependent on calcium influx. This idea was further supported by the finding that the sumatriptan-induced discharge occurred with a latency of several minutes, similar to the latency of the sumatriptan-induced calcium influx. Calcium removal might also exert effects on discharge as a result of the influence of extracellular calcium levels on excitability, independent of any effects on calcium influx. However, the suppressive effect of calcium removal on the sumatriptan-induced discharge was not the result of a general decrease in excitability because it was accompanied by a large increase in mechanically evoked discharge. A similar effect of calcium removal on mechanosensitivity was found for visceral afferents that innervate the airways and was attributed to a suppressive effect of extracellular calcium on a nonspecific cation current (Undem et al. 2003).

These observations on dural afferent neurons, taken together with the studies on trigeminal ganglion neurons, indicate that sumatriptan induces a calcium influx that, on the one hand, induces discharge, but on the other, also blocks neuropeptide release and thus prevents sensory transmission to central neurons. The central effect would be expected to occur with a longer delay than the peripheral effect because of the slow rate at which sumatriptan crosses the blood-brain barrier. This could account for the initial worsening of headache after sumatriptan administration, prior to the onset of its therapeutic effect. (This is in addition to sumatriptan’s actions of vasoconstriction and suppression of peripheral neuropeptide release, which potentially could also contribute to its therapeutic action.)

Vasodilation and activation of meningeal sensory neurons

Throughout the history of migraine research, investigators have debated the idea that the headache results from dilation of cranial blood vessels, presumably through the activation of perivascular sensory nerve fibers. This idea was based in part on reports of abnormal vasodilation occurring during migraine attacks (Wolff 1963) and was further supported by the observations that headache can be induced by nitric oxide-generating vasodilator agents such as nitroglycerin (Olesen et al. 1995) and relieved by vasoconstrictor agents such as sumatriptan (Humphrey and Feniuk 1991). However, each of these lines of evidence is questionable or open to alternative interpretations. Following Wolff’s original report of extracranial vasodilation during migraine (Graham and Wolff 1938), subsequent studies have failed to find consistent evidence of vasodilation occurring during migraine attacks that is any greater than the normal variation in vessel diameter that occurs in the absence of headache in either intracranial or extracranial vessels (Iversen et al. 1990; Thomsen et al. 1995). Furthermore, both the headache-generating agents such as nitroglycerin, as well as headache-relieving agents such as sumatriptan, are now known to have direct neural actions in addition to their effects on blood vessel diameter.

In view of these questions, studies were carried out to investigate whether vasodilator agents can in fact produce activation of perivascular sensory fibers in the meninges, as proposed by the vasodilation theory. It was found that dural application of sodium nitroprusside, a nitric oxide donor and vasodilator, did not itself evoke discharge in dural nociceptors but did affect mechanically evoked discharge (Levy and Strassman 2004). However, these effects were complex, in that both inhibition and facilitation was observed, in different neurons. Such mixed effects may be related to the multiple actions on ion channels that have been described for nitric oxide that could account for both inhibitory and facilitatory effects on excitability (Ahern et al. 2000; Klyachko et al. 2001; Li et al. 1998; Renganathan et al. 2002).
To clarify the role of vasodilation in the dural afferent responses, further studies were done to examine the effect on dural afferents of another powerful vasodilator, the neuropeptide calcitonin gene-related peptide (CGRP). Unlike nitric oxide, CGRP is not known to have effects on nociception when administered peripherally. These studies found that neither dural nor systemic administration of CGRP, at a dose that evoked dural vasodilation, had a detectable effect on either ongoing or mechanically evoked discharge in dural nociceptors (Levy et al. 2005). This finding not only fails to support the vasodilation theory but also would potentially seem to be at odds with the large body of evidence on the role of CGRP in headache. This evidence initially included the finding that venous levels of CGRP are increased during migraine attacks (Goadsby et al. 1990), although this has not been corroborated in subsequent studies (Tvedskov et al. 2005). Of particular importance are the recent findings that migraine attacks can be induced by CGRP (Lassen et al. 2002) and relieved by CGRP antagonists (Olesen et al. 2004). However, it is possible that the involvement of CGRP in headache is through its role as a central neurotransmitter rather than through vasodilation and activation of meningeal nociceptors (discussed in Levy et al. 2005). In fact, CGRP apparently has not been shown to have an effect on discharge in any population of primary afferent nociceptors, nor does it evoke pain or hyperalgesia on peripheral administration (Chu et al. 2000; Nakamura-Craig and Gill 1991; Pedersen-Bjergaard et al. 1991; Weidner et al. 2000) (although it produces normalization of behavioral responses in a mouse strain with abnormally low heat sensitivity) (Mogil et al. 2005).

Moreover, there appears to be no evidence demonstrating an instance in which either sensory neuron activation or pain could be evoked by vasodilation when the vasodilation was a result of relaxation of vascular smooth muscle. Pain can be evoked from blood vessels by intraluminal distention, as in angioplasty (Arndt and Klement 1991; Martins et al. 1993), as well as by extraluminal probing or indentation (Ray and Wolff 1940), but it is likely that such focal stimuli are fundamentally different from smooth muscle relaxation in the distribution and amplitude of forces exerted. It is possible that the degree of stretching or distention of vascular or perivascular tissue that results from even maximal vascular relaxation is insufficient to activate perivascular mechanonociceptors. On the other hand, it is also possible that the intracranial tissue might be an exception in this regard, as a result of being contained within an essentially closed space. Vasodilation of meningeal vessels in particular might conceivably result in compression of the vascular wall against the rigid cranium, a phenomenon that would not occur in other tissues. One potentially important caveat to the finding that CGRP-induced vasodilation had no effect on dural afferents is that the experimental preparation included a cranial opening to allow access to the neurons’ dural receptive fields. This opening might itself alter the neural response to dural vasodilation, and so it would be of interest to also test effects of vasodilation in a “closed cranium” preparation in which the dural receptive fields are not exposed.

One further caveat is that, as noted earlier, all neurophysiological studies of meningeal sensory neurons have been done on the innervation of the dura, and the innervation of the pial (cerebral) arteries may have different properties, particularly with respect to the effects of vasodilation. Although the dural sensory innervation is often referred to as a vascular innervation, it is not specifically or even preferentially vascular, in that it supplies both vascular and nonvascular dural territories. As in skin, nerve bundles in the dura initially course alongside the arteries en route to their territory of innervation, but the individual nerve fibers typically exit the main bundle and travel some distance away from the artery before reaching their main territory of arborization (Strassman et al. 2004), and the majority of nerve endings are not in close proximity to arteries (Messlinger et al. 1993). (This does not apply to the autonomic fibers, which do have a specifically arterial distribution.) Although the dural venous sinuses are densely encircled by sensory nerve endings, they have a relatively thin smooth muscle layer (Andres et al. 1987) and appear to exhibit minimal capacity for dilation (Upton et al. 1994). Further evidence against a role for dilation of venous structures came from a study that failed to find a consistent effect of cephalic venous dilatation on migraine pain (Daugaard et al. 1998). Unlike the dural arteries, the pial arteries are covered by a dense network of sensory fibers, and so it may be particularly important to investigate the possibility of vasodilatory responses in these nerve fibers.

Do meningeal sensory neurons have unique properties?

In general, studies of meningeal sensory neurons have not found evidence of unique properties or qualitative differences that distinguish them from nociceptive neurons in other tissues. In addition to the properties of chemosensitivity and sensitization, dural afferents also exhibit resistance to tetrodotoxin (Strassman and Raymond 1999), indicating that they possess a class of voltage-gated sodium channels that are characteristic of nociceptors in other tissues and that are not found in any other type of neurons in the peripheral or CNS. The meningeal sensory neurons also express the same constellation of neuropeptides that are found in other sensory innervations (Jansen-Olesen and Edvinsson 2000). Although in clinical practice triptans are used specifically for the treatment of headache, no evidence has been found for a preferential action on meningeal afferents. Potrebic et al. (2003) found no difference between trigeminal and dorsal root ganglia in the percentage of neurons that express 5-HT1D receptors, and there is substantial evidence of 5-HT1D effects on sensory neurons outside the trigeminal system (Bingham et al. 2001; Jenkins et al. 2000; Kajekar et al. 1995; Pierce et al. 1996; Zochodne and Ho 1994). However, it is possible that there might exist quantitative, rather than qualitative differences, that have not been detected by current techniques but that might nonetheless be important for mechanisms of headache pathogenesis and treatment. In fact, one study reported finding an enrichment of CGRP content in meningeal sensory neurons compared with trigeminal ganglion cells that innervate extracranial skin (O’Connor and van der Kooy 1988). This observation has not been pursued, but it is particularly intriguing in view of the recent evidence implicating CGRP in migraine. Although 5-HT1D receptors are not unique to the meningeal sensory innervation, studies have not yet investigated the possibility of quantitative differences in the level (density) of expression. This possibility is noteworthy considering that sumatriptan exhibits a relative rather than an absolute selectivity for cranial versus peripheral vessels in its
action as a vasoconstrictor (Feniuk et al. 1989; Razzaque et al. 2002).

Ultimately the distinctive clinical characteristics of headache may prove to be related not so much to any differences in the intrinsic molecular or cellular properties of the meningeal sensory neurons but rather to the distinctive properties of the tissue that they innervate. The intracranial space has unusual properties, both in terms of being an indistensible, closed space that is uniquely sensitive to changes in pressure and also in being a chemically privileged site. An important direction for future research will be to investigate how the activity of meningeal sensory neurons is affected by the distinctive physiological processes that occur within the intracranial tissues. One such phenomenon is cortical spreading depression, a slowly propagating ionic disturbance within the cerebral cortex that has been implicated in the migraine aura (the nonpainful neurological symptoms that precede the headache in some migraine attacks) (Hadjikhani et al. 2001; Lauritzen 1994; Milner 1958). Recent evidence has supported the idea that the excitatory chemicals released in the cortex during spreading depression can activate meningeal sensory fibers (Bolay et al. 2002) and thus generate the headache, although direct evidence of such activation in neurophysiological studies is still lacking (Ebersberger et al. 2001). Another distinctive feature of the intracranial tissues is the ability to support a delayed inflammatory reaction involving dural macrophages and mast cells, which can be evoked by administration of chemicals such as the headache-causing agent nitroglycerin (Reuter et al. 2001). Mast cells, which are a prominent feature of the intracranial dura (Dimlich et al. 1991; Strassman et al. 2004), can become activated in response to a range of physiological and immunological stimuli, including potential migraine triggers such as stress and female sex hormones (Rozniecki et al. 1999; Theorides et al. 2005). Activated mast cells could potentially release mediators that in turn act on meningeal nociceptors. A major challenge for future research on the role of meningeal sensory neurons in headache will be to move beyond the study of responses to direct, local meningeal stimulation and examine their activity under more complex physiological conditions that may have greater relevance to the understanding of headache pathogenesis.

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References


