Innervation of the Cerebral Dura Mater

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SUMMARY – *The trigemino-cardiac reflex during Onyx embolization for dural arteriovenous fistula may be caused by mechanical or chemical stimulus to the terminals of the unencapsulated Ruffini-like receptors stemming from A-axons in the dural connective tissue at sites of dural arteries and sinuses. Slow A (Aδ) and fast A (Aβ) neurons may play a role in the stimulus afferent pathway due to their higher mechanosensitivity and chemosensitivity. These afferent pathway nerves are cholinergic innervations of the dura mater, which also contains vasoactive neuropeptides such as calcitonin gene-related peptide, substance P, and neurokinin A. Stimulation of meningeal sensory fibres can evoke cerebral vasodilation through the peripheral release of neuropeptides, which play a role in headache pathogenesis. These myelinated A-fibers terminate in the deep part (laminae III-V) of the spinal dorsal horn. Its efferent pathway has been defined as the acetylcholinergic vagus nerve. The A11 nucleus, located in the posterior hypothalamus, providing the only known source of descending dopaminergic innervation for the spinal grey matter, can inhibit the neurons in the spinal dorsal horn.*

Background

During endovascular Onyx embolization for intracranial dural arteriovenous fistula, a trigemino-cardiac reflex has been observed^{1,2}. This reflex has been described as the sudden development of cardiac arrhythmia as far as cardiac arrest, arterial hypotension, apnea and gastric hypermobility during stimulation of any of the sensory branches of the trigeminal nerve^{1,2}. Its efferent pathway has been defined as the acetylcholinergic vagus nerve. However, the receptor, afferent nerve, central projections and transmitters of this reflex were not clear. This study reviews the literature with a focus on the cerebral dura mater innervations.

Afferent nerve fibers of the cerebral dura mater

The cerebral dura mater is richly innervated by afferent nerve fibers, most of which originate in the ipsilateral trigeminal ganglion, and by sympathetic fibers predominantly arising from the ipsilateral superior cervical ganglion^{3,4}. For the supratentorial part the main

nerve supply stems from all three branches of the trigeminal nerve. The dorsal rami of the first three cervical nerves, the ventral rami of the first two cervical nerves, the hypoglossal nerve and recurrent branches of the vagus nerve that follow the posterior meningeal artery provide innervation to the posterior cranial fossa dura mater⁵. In addition, a comparatively sparse parasympathetic innervation was described predominantly arising from the ipsilateral sphenopalatine ganglion^{3,4}. Meningeal sensory neurons 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 arborization⁶, and the majority of nerve endings are not in close proximity to arteries⁷. Davidson et al.⁸ investigated changes in the innervation of the human dura with age in 27 individuals aged between 31 weeks of gestation and 60 years of postnatal life. Using immunocytochemistry with antibodies to neurofilament, they found that the density of innervation increased between 31 and 40 weeks of gestation, peaking at term and decreasing in the subse-

quent three months, remaining low until the sixth decade.

Transmitters

Several studies have described neuropeptide immunoreactive nerve fibers in the dura mater⁹. Meningeal nerve fibers immunoreactive for substance P (SP), neurokinin A, and calcitonin gene-related peptide (CGRP) are thought to belong to the afferent (sensory) system, and nerve fibers immunopositive for neuropeptide Y(NPY) are most likely of sympathetic origin while those immunoreactive for vasoactive intestinal peptide (VIP) are of parasympathetic origin. Light and electron microscopic studies of the rat dura mater have shown that peptidergic (sensory) nerve fibers form a dense network both around blood vessels and in non-vascular regions. The cholinergic innervation of the dura mater in the guinea pig, mouse and rat has been investigated. The acetylcholinesterase (AChE)-containing nerve fibers were in close relationship with the main meningeal blood vessels and also appear in the meningeal tissue proper.

A sparse to moderate supply of nerve fibers immunoreactive for NPY, VIP, SP, and CGRP was demonstrated in the walls of human middle meningeal arteries¹⁰⁻¹². Substance P immunoreactive fibers occur in the wall of the superior sagittal sinus and the meningeal artery^{13,14}. An immunocytochemical electron microscopy study found different unmyelinated axons in one Schwann cell may contain nerve fibers with VIP, Substance P and NPY immunoreactivity. This study also observed a colocalization of NPY and norepinephrine in some nerve fibers. Trigeminal sensory nerve fibers from the dura mater have been found to contain vasoactive neuropeptides such as calcitonin gene-related peptide, substance P, and neurokinin A¹⁵. At least a third of these fibers are A β fibers¹⁶. Findings were similar for both CGRP and SP: the supra and infratentorial dura, and convexity and skull base dura had a rich plexus of nerve bundles and a nerve-fiber network^{17,18}.

A rich array of mast cells was noted in the supra and infratentorial calvarial dura and they contain a substantial proportion of total brain histamine. Fewer mast cells occurred in the skull base dura than in the calvaria dura. Mast cells were also identified in the falx cerebri and tentorium cerebelli, but were absent in the dura over the sinus. Activated mast cells

could potentially release mediators that in turn activate meningeal nociceptors. A study on the effect of various doses of acetylcholine (100, 200, and 500 mg/kg) on the mast cells of the albino rat dura mater concluded that acetylcholine has an activating effect on monoamine secretion¹⁹, SP and CGRP-containing neurons that can in turn activate dura mast cells. Vasoactive mediators and cytokines released from mast cells then increase vascular permeability. Mast cell vasodilatory molecules such as histamine nitric oxide NO, tumor necrosis factor TNF and VIP could participate in the vasodilatory phase of migraine, which is associated with the throbbing pain²⁰.

Interactions between autonomic and nociceptive fibers

The autonomic and sensory nerves form a dense network accompanying blood vessels. Interactions between autonomic and nociceptive fibers have been investigated by measuring release of CGRP and prostaglandin E2 (PGE2) from the dura mater *in vitro*. The parasympathomimetic agent carbachol did not change basal release of CGRP or PGE2, whereas it diminished release induced by a mixture of inflammatory mediators. Norepinephrine did not change induced release of CGRP or PGE2, or basal release of CGRP. However, basal release of PGE2 was enhanced by norepinephrine, and this enhancement was reduced by serotonin through 5-HT(1D) receptors. It was found that sympathetic transmitters may control nociceptor sensitivity via increased basal PGE2 levels, a possible mechanism to facilitate headache generation. Parasympathetic transmitters may reduce enhanced nociceptor activity^{19,21}.

CGRP-immunoreactive nerve fibers and trigeminal ganglion cells innervating the meninges are much more abundant than SP-immunoreactive afferents. Co-localization of SP and CGRP was shown in a small portion of trigeminal ganglion cells. Subarachnoid hemorrhage in the rat substantially reduced the SP-immunoreactive nerve fibers of the dura mater, but left the CGRP-immunoreactive innervation unchanged. Taken together, the CGRP-containing trigeminal innervation of the intracranial structures seems to play an important role in meningeal nociception.

Meningeal sensory fibers can be stimulated to release neuropeptides from their peripheral endings in the meninges, where they can

evoke components of neurogenic inflammation, including dural plasma extravasation, as well as dural and pial vasodilation. SP acting at the neurokinin-1 receptor level appears to be responsible for extravasation, whereas CGRP mediates neurogenic vasodilation. Neurogenic inflammation has been hypothesized to play a role in headache pathogenesis. Stimulation of meningeal sensory fibers can evoke cerebral vasodilation through the peripheral release of neuropeptides²².

Types of stimuli of dural primary afferent neurons

To identify the types of stimuli capable of activating meningeal sensory fibers, electrophysiologic recording studies in animals have examined the response properties of primary afferent neurons innervating the cranial dura mater⁷. These studies obtained single-unit recordings from the trigeminal ganglion or the nasociliary nerve. Dural afferents were typically identified by their responses to electrical stimulation of dural sites on or around the dural venous sinuses, namely, superior sagittal or transverse sinuses, or the middle meningeal artery (MMA). Based on their response latencies, the majority of the neurons could be classified as C or A δ , although a substantial number of A β fibers were also present, in agreement with anatomic observations.

Many of the neurons exhibit mechanosensitive receptive fields on the dura from which they can be activated by punctuate probing, stroking or traction. Some neurons also respond to thermal stimuli, in either the warming or cooling direction. In addition, neurons were excited by chemical stimuli, such as hypertonic saline applied either topically to the dura or by intravascular infusion into the superior sagittal sinus (SSS). Neurons could also be activated by dural application of a number of algescic agents, including potassium chloride, capsaicin, buffer solutions of low or high osmolarity, or a mixture of inflammatory mediators (bradykinin, PGE₂, serotonin, histamine). Besides activating the neurons, the inflammatory mediators produced a sensitization, or enhancement, of responses to mechanical stimuli. The polymodal response properties of the dural afferent neurons, and their excitatory and sensitizing responses to algescic and inflammatory agents support the idea that some of these neurons serve a nociceptive function, and that

they might be activated under pathologic conditions such as increased intracranial pressure or meningitis.

Unencapsulated Ruffini-like receptors of A and C axons

These dural nerves contain myelinated (A-axons) and unmyelinated (C-axons) nerve fibers. Myelinated and unmyelinated nerve fibers may traverse midline structures and terminate opposite to their origin⁴. After losing the myelin sheath the unmyelinated branches of the A-fiber mix up with the C-fibers. They can be traced within the densely packed collagenous fiber bundles they innervate. The unmyelinated branches of the A-fibers have a larger diameter than the C-fibers. At several sites, axonal protrusions exhibit a receptor matrix, mitochondria and vesicles. Large areas of the axon branches are not covered by Schwann cell cytoplasm. This arrangement resembles the ultrastructural relationship between nerve terminals and collagenous fibers in unencapsulated Ruffini-like receptors. Within the dura mater this receptor type is mainly distributed at locations where the superior cerebral veins empty into the sinus, and at the confluences of sinuses. The C-axons which follow the unmyelinated branches of the A-axons terminate at a postcapillary venule. The terminal axons are swollen and filled with mitochondria and vesicles. The axonal membrane is in direct contact to the basement lamella of the endothelial cell. A basement lamella may be completely absent around the axonal terminals. This arrangement leads us to suspect that the various afferent units fulfill different receptor functions to monitor various parameters of the chemical composition and/or mechanical condition of the innervated area. From this point of view, it has to be assumed that the different terminals have different transducer properties despite their rather uniform ultrastructural appearance. For instance, these terminals are the best candidates to sense the composition of the blood and the exchange of fluid at the post-capillary venule⁴.

Central projections of sensory nerves innervating the MMA and SSS

Depending on the application site of Cholera toxin subunit b (CTb) or wheat germ agglutinin-horseradish peroxidase conjugate (WGA-HRP)

to the adventitia of the MMA, labeled neurons were predominantly found ipsilaterally in the lateral part of the spinal dorsal horn of segments C1-C3 and in the caudal and interpolar parts of the spinal trigeminal nucleus²³. WGA-HRP-labeled terminations were mainly located in laminae I and II, whereas CTb-labeled terminations were located in laminae III-V. These results indicate that sensory information from the MMA is transmitted through both trigeminal and cervical spinal nerve branches to a region in the central nervous system extending rostrally from the C3 dorsal horn to the interpolar part of the spinal trigeminal nucleus.

Liu et al.²⁴ examined the central projections of the SSS sensory innervation in rat using transganglionic tract tracing techniques. CTb or cholera toxin-conjugated horseradish peroxidase (B-HRP) label both large and small diameter myelinated A-fibers, which mainly originate from low threshold mechanoreceptors and terminate in the deep part (laminae III-V) of the spinal dorsal horn. WGA-HRP preferentially labels unmyelinated C-fibers which terminate in the superficial layers (laminae I and II) and transmit nociceptive stimuli.

Subpopulations

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 subpopulations²⁵. 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 δ range) and fast A (5-25 m/s, which includes neurons in the A β as well as the upper end of the A δ range), as discussed²⁵. 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. 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 mediators²⁶. In contrast, most of the A β neurons had much lower mechanosensitivity than the A δ or C fibers, and a relatively high percentage (33%) had no mechanosensitivity. Further-

more, 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 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 β fibers. One characteristic that many of the fast conducting dural afferents share with cutaneous A β 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 A β fibers may play an important role in TCR and this should be further investigated. 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 innervation²⁷, similar to other visceral tissues. Previously A δ was documented to be the afferent pathway for TCR.

Sensory responses of dural primary afferent neurons

Stimulation of dural afferent C-fibers and greater occipital nerve (GON) increased the background activity, extended the size of cutaneous trigeminal and cervical receptive fields, and decreased the thresholds to mechanical dural stimulation^{24,28}. These findings suggest that dural stimulation may lead to a central sensitization of nociceptive convergent second-order neurons with an increased responsiveness to stimulation of cervical afferents. This mechanism may be important in pain referral from cervical structures to the head and therefore have implications for most forms of primary headache^{24,28}.

The locations of the recording sites of neurons responding to convergent input from the dura mater and the GON were confined to laminae V/VI of the C2 dorsal horn, which is consistent with other studies analyzing responses of convergent neurons to stimulation of dura mater and dural vessels^{22,29-31}. The location of the recorded neurons corresponds to the dorsal horn area that receives projections from the ophthalmic division of the trigeminal nerve⁶, which constitutes the primary source

of afferents from the supratentorial dura mater^{22,30-33}. It has been shown that the trigeminal innervation of the cerebral circulation preferentially employs calcitonin gene-related peptide CGRP in favor of SP^{31,34}. A functional reflection of this can be seen in studies of neuropeptide release. Trigeminal ganglion stimulation in cat and humans increases cranial levels of both CGRP and SP while during migraine and cluster headache substance P release is not seen. In the same way, CGRP is preferentially released in subarachnoid hemorrhage. Similarly, SSS stimulation preferentially releases CGRP in the cat while it has also been shown that increases in facial blood flow following trigeminal ganglion stimulation in guinea pig are primarily due to release of CGRP. Direct stimulation of the nasociliary nerve, the cerebrovascular branch of the ophthalmic division of the trigeminal nerve, leads to a cerebral vasodilator effect that is inhibited by the CGRP antagonist CGRP. It is likely that the neuropeptide measurements represent local overflow from trigeminal nerves innervating the cerebral and extracerebral circulation. Certainly the release is likely to be local since exogenous CGRP only markedly alters cerebral blood flow after blood-brain barrier disruption.

Dural vessels are innervated by an adventitial plexus of sensory nerve fibers which contain vasodilator neuropeptides. These include SP, neurokinin A and CGRP, which are stored within vesicles of the naked nerve endings. Vasoactive neuropeptides can be released from perivascular sensory nerves by axon reflex mechanisms in response to a variety of stimuli (an axon reflex involves antidromic depolarisation within the collateral branches of a single sensory neuron in response to peripheral stimulation of one branch, e.g. the triple response).

Central mechanisms

Expression of c-fos immunoreactivity within the brain or spinal cord can be used to map the distribution of neurons activated by noxious or non-noxious stimuli, and is a useful tool to study the brain's response to painful events³¹. The A11 nucleus, located in the posterior hy-

pothalamus, provides the only known source of descending dopaminergic innervation for the spinal gray matter. Extracellular recordings were made in the trigeminocervical complex (TCC) in response to electrical stimulation of the dura mater. Receptive fields were characterized by mechanical noxious and innocuous stimulation of the ipsilateral ophthalmic dermatome. Stimulation of the A11 significantly inhibited peri-middle meningeal artery dural and a noxious pinch evoked firing of neurons in the TCC. This inhibition was reversed by the D(2) receptor antagonist eticlopride. Lesioning of the A11 significantly facilitated dural and noxious pinch and innocuous brush-evoked firing from the TCC. No dopamine receptors were present in the A11 nucleus itself. However, the A11 does contain dopamine and calcitonin gene-related peptide (CGRP)³⁵.

Conclusions

The trigemino-cardiac reflex during Onyx embolization for dural arteriovenous fistula may be caused by mechanical or chemical stimulus to the terminals of the unencapsulated Ruffini-like receptors stemming from A-axons in the dural connective tissue at sites of dural arteries and sinuses. Slow A (Aδ) and fast A (Aβ) neurons may play a role in the stimulus afferent pathway due to their higher mechanosensitivity and chemosensitivity. These afferent pathway nerves are the cholinergic innervation of the dura mater, which also contains vasoactive neuropeptides such as calcitonin gene-related peptide, substance P, and neurokinin A. Stimulation of meningeal sensory fibers can evoke cerebral vasodilation through the peripheral release of neuropeptides, which play a role in headache pathogenesis. These myelinated A-fibers terminate in the deep part (laminae III-V) of the spinal dorsal horn whose efferent pathway has been defined as the acetylcholinergic vagus nerve. The A11 nucleus, located in the posterior hypothalamus, providing the only known source of descending dopaminergic innervation for the spinal gray matter can inhibit the neurons in the spinal dorsal horn.

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