MINIREVIEW

Thalamic Mechanism of Pain: Shell Theory of Thalamic Nociception

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Pain is that experience which we associate with actual or potential tissue damage. It is unquestionably a sensation in a part or parts of the body, but it is also unpleasant and therefore also an emotional experience. Hence, pain can be defined as "sensory and emotional experience associated with actual tissue damage, or described in terms of such damage" [11].

Under normal circumstances the conscious experience of pain involves the initial activation of peripheral somatic or visceral nociceptors, followed by activation of certain parts of the central nervous system. Except for the cranial nerve territory, impulses arising from peripheral nociceptors proceed to the spinal cord via the dorsal and ventral roots. In the spinal cord, nociceptive relay neurons are located not only in the dorsal horn (laminae I–VI), but also in the intermediate zone (lamina VII) and ventral horn (lamina VIII). Until about 1960, the most commonly held concept was that nociceptive neurons in the spinal cord conveyed processed information to both the nucleus ventralis posterolateralis (VPL) and the nucleus centralis lateralis (CL) via the lateral and medial components of the spinothalamic pathways, respectively. The lateral and medial components of the spinothalamic pathways were considered to be the routes for the sensory-discriminative and emotional-motivational aspects of pain, respectively.

In the 1960s, it became apparent that spinal cord neurons also projected to the posterior nuclear group (PO) of the thalamus. In addition, two more pathways arising from the spinal cord were proposed. One of these pathways was an indirect route through the brainstem reticular formation to the intralaminar nuclei (spinoreticulothalamic pathway). This indirect route was considered to be an additional component of the pathways related to the emotional-motivational dimension of pain. The second pathway was another indirect route, this one being through the lateral cervical nucleus to the VPL and PO (the spinocervical pathway) [2].

POGGIO and MOUNTCASTLE [22] did not find any neurons in the ventrobasal (VB) complex (including the VPL) of the cat and monkey, which were preferentially
sensitive to noxious stimuli. They found, however, that the majority of neurons recorded in the PO of the cat were sensitive to noxious stimuli [22]. They proposed that the PO, and its cortical projection (to an area which includes the second somatic sensory area) were concerned in a special way with pain sensibility. This proposal was subsequently supported by another group of investigators [9], but other analyses cast doubt on the nociceptive role of PO neurons [8, 18]. Whether or not the PO has a nociceptive function, their large, often bilateral receptive fields and the frequent convergence of auditory and somatosensory input described for them raised doubts that PO neurons could provide the data required to adequately localize a painful stimulus.

On the other hand, nociceptive neurons were found in the VB complex in the cat and monkey in which the dorsal part of the spinal cord was transected [15, 20, 23, 25]. It was suggested that this difference might reflect the withdrawal of tonically active descending inhibitory systems [22]. More recently, however, nociceptive neurons have been found in the VPL of rat [16, 21], cat [1, 10, 24, 27], and monkey [6, 7, 13] with an intact neuraxis. Nociceptive neurons were also found in the nucleus ventralis posteromedialis (VPM) of the cat [28, 30, 31, 33] and monkey [34]. In the cat, nociceptive neurons were located around the periphery of the VB complex, i.e., the VPM proper and VPL. Hence, we proposed the shell theory of thalamic nociception [28]. This paper will deal primarily with this theory.

1. The ventrobasal complex

The diencephalon is subdivided into four regions: dorsal thalamus, hypothalamus, ventral thalamus, and epithalamus. The dorsal thalamus, or as it is more commonly known, the thalamus, is the largest structure in the diencephalon, and is composed of a group of nuclei in the lateral wall of the lateral ventricle. The Y-shaped internal medullary lamina divides the thalamus into anterior, medial, and lateral areas. The anterior group is in the anterior area, the dorsomedial and midline nuclei are in the medial area, and the lateral nuclei are arranged in two tiers, a dorsal tier and a ventral tier, in the lateral area. The nuclei in the dorsal tier, from anterior to posterior, are the dorsolateral nucleus, the lateral posterior nucleus, and the pulvinar. The medial geniculate and lateral geniculate bodies project posteriorly from the ventral surface of the pulvinar. In the ventral tier, from anterior to posterior, are the ventral anterior, the ventral lateral and the ventral posterior nuclei. Between and surrounding these well-defined nuclear groups are layers of neurons forming sheet-like nuclei: the intralaminar nuclei in the Y-shaped border between the major groups, the reticular nuclei around the outside, and the midline nuclei between the two thalami.

Krieg [14] divided the ventral posterior nucleus of the ventral tier into four parts: nucleus arcuatus lateralis, nucleus arcuatus medialis, nucleus posterior lateralis, and nucleus posterior inferior. In Olszewski's [19] nomenclature, they are nucleus ventralis posterior medialis (VPM proper), nucleus ventralis posterior medialis parvocellularis (VPMpc), nucleus ventralis posterior lateralis (VPL), and
nucleus ventralis posterior inferior (VPI), respectively. In higher primates, the VPL is further subdivided into pars oralis (VPLo) and pars caudalis (VPLc). The ventrobasal (VB) complex may be defined as those parts of the ventral posterior nucleus which relay somatosensory information to the somatosensory cortex. In most non-primates, the VB complex is coextensive with the VPM proper and VPL. In the cat, the lateral part of the VPMpc receives ipsilateral trigeminal somatosensory
input [17, 29] but it does not project to the somatosensory cortex. Hence, this part is not included in the VB complex. In primates, the VB complex also excludes the VPLo [12].

2. Trigeminal nociceptive neurons in cat VPM

The VPM proper is the thalamic somatosensory relay nucleus of the craniofacial region. The vast majority of neurons in this nucleus are low-threshold mechanoreceptive (LTM) neurons. They are maximally excited by gentle mechanical stimuli, such as hair movements or light pressure, applied to the contralateral trigeminal integument or pinna, and they are place-specific. This means that they have a circumscribed receptive field, and are somatotopically organized; in other words, the location of the peripheral receptive field is correlated with the location of the neuron within the nucleus. They are also modality-specific; that is, a given neuron can be excited by one particular form of mechanical stimulation.

We have found two additional classes of nociceptive neurons in the VPM proper of the cat thalamus [28, 30, 31]. One class consisted of nociceptive specific (NS) neurons. These did not respond to weak forms of mechanical stimulation, but discharged when intense mechanical stimuli were applied to a circumscribed, contralateral receptive field. The vast majority of these responded with a maintained discharge exclusively to noxious mechanical stimuli, such as noxious pinch with serrated forceps. Some neurons also responded to the application of firm but innocuous pressure with flattened forceps, but discharged more vigorously when

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Fig. 2. An NS neuron. A: the receptive field is indicated by the black area. B: the responses to 3 different types of mechanical stimuli applied to the receptive field. Upper record shows the peristimulus time histogram. The lower record shows spike discharges, as window discriminator output pulses.
The second additional class consisted of wide dynamic range (WDR) neurons. These had a relatively large receptive field on the contralateral trigeminal integument, and exhibited a graded response to brush, pressure, and noxious pinch applied to the center of the receptive field, responding most to noxious pinch. Outside this zone, they did not respond to low-intensity mechanical stimuli, but responded differentially to firm pressure and noxious pinch. This area was further surrounded by an area in which only noxious pinch resulted in spike discharges.

Fig. 3. A WDR neuron. A: receptive field. In the black area, the neuron had a graded response to brush, pressure, and noxious pinch. In the cross-hatched area, the neuron did not respond to brush, but differentially responded to pressure and noxious pinch. In the shaded area, the neuron responded exclusively to noxious pinch. B: responses of the neuron to mechanical stimulation of the 3 different areas of the receptive field. Records a, b, and c show the responses to stimulation of the corresponding areas in A.

Trigeminal NS neurons were located near the dorsal and/or ventral ends of a column of LTM neurons in perpendicular microelectrode penetrations across the caudal third of the VPM proper. They were not encountered in the VPMpc, or in the ventrolateral region of the VPM proper bordering the VPL. Histological examination revealed that they were located at or near the margin of the VPM proper. This marginal area is referred to as the shell region, and the shell region of the caudal third of the VPM proper in which trigeminal NS neurons were found is called the trigeminal NS zone. Trigeminal WDR neurons were also recorded.
from the shell region of the VPM proper, but they were confined to a narrow band approximately 300 µm wide just rostral to the NS zone. This narrow band is called the trigeminal WDR zone [28].

Trigeminal NS and WDR neurons were both somatotopically organized. In general, ophthalmic NS neurons with receptive fields in the contralateral ophthalmic region and ophthalmic WDR neurons with low-threshold receptive field centers in the same region were found in the dorsolateral shell region. Maxillary NS and WDR neurons occurred in the dorsomedial shell region, and mandibular NS and WDR neurons were found in the ventromedial shell region along the border between the VPM proper and VPMpc. In the caudal part of the NS zone only maxillary NS neurons were found in the dorsal shell region, whereas mandibular NS neurons were located in the caudal ventromedial shell region [28, 30, 31]. The distribution of trigeminal nociceptive neurons within the shell region of the VPM proper followed a pattern generally consistent with the somatotopic arrangement established for other somatosensory input to the VPM proper. Both NS and WDR neurons were antidromically excited by electrical stimulation of the somatosensory area I (SI) of the cerebral cortex.

3. Tooth pulp neurons in cat VPM

In the study of pain in the trigeminal system, the receptors associated with trigeminal nerve fibers within the tooth pulp are of particular interest, because the only sensory role assigned for them has been the perception of pain. We used electrical stimulation of the canine tooth pulp of the cat in order to evaluate the role of the shell region of the VPM proper in orofacial nociception. Two classes of neurons responsive to electrical stimulation of the contralateral canine tooth pulp were identified [33]. One class was responsive only to tooth pulp stimulation and these neurons were designated as tooth pulp specific (TPS) neurons. The other class of tooth pulp neurons also responded to mechanical stimulation of the contralateral trigeminal integument. Their receptive field characteristics identified them as WDR neurons responsive to tooth pulp stimulation.

Both classes of tooth pulp neurons were located in the shell region of the caudal VPM proper; TPS neurons were coexistent with trigeminal NS neurons, and were found in both dorsomedial and ventromedial parts of the NS zone. WDR neurons responsive to tooth pulp stimulation were located in the dorsomedial and ventromedial parts of the WDR zone. Tooth pulp neurons in the dorsomedial shell region responded to the maxillary canine tooth pulp, whereas those in the ventromedial shell region responded to the mandibular canine tooth pulp. Some tooth pulp neurons in these two regions were responsive to stimulation of both maxillary and mandibular canine teeth. Both TPS and WDR neurons were antidromically excited by electrical stimulation of the SI area of the somatosensory cortex.
4. Location of neurons relaying trigeminal nociceptive input to VPM

Neurons relaying trigeminal somatosensory input to the thalamus are located in the trigeminal brainstem sensory nuclear complex and its adjacent lateral reticular formation. The trigeminal brainstem sensory nuclear complex comprises the rostrally located main sensory nucleus and the more caudally situated spinal tract nucleus. The trigeminal spinal tract nucleus is divided into subnuclei oralis, interpolaris, and caudalis. A trigeminal tractotomy procedure (Sjöqvist's operation), which interrupts the trigeminal spinal tract near the level of the obex, results in a complete or partial loss of pain and temperature sensibilities with preservation of touch and pressure sensibilities in the trigeminal nerve territory on the side ipsilateral to the lesion. This sensory dissociation suggested that the caudal medulla oblongata is an integral part of the system relaying trigeminal pain to the thalamus.

Previously, we have found three different types of trigeminal nociceptive relay neurons in the caudal medulla oblongata [26]. The first group was made up of trigeminal NS neurons. The second group was made up of trigeminal WDR neurons. Neurons of the third group were called subnucleus reticularis ventralis (SRV) neurons. The SRV neurons were activated by pressure applied either ipsi- or bilaterally to the cornea and frequently also responded to either ipsi- or bilateral noxious mechanical stimulation of the pinna, face and/or tongue. NS relay neurons were located in the marginal layer of the trigeminal subnucleus caudalis. WDR relay neurons were located in the lateral part of the subnucleus reticularis dorsalis, which is ventromedially contiguous with the magnocellular layer of the trigeminal subnucleus caudalis. SRV neurons were located in the dorsolateral part of the subnucleus reticularis ventralis, which is ventral to the trigeminal subnucleus caudalis and subnucleus reticularis dorsalis. Some trigeminal WDR neurons responded to electrical stimulation of ipsilateral tooth pulp afferents, and some SRV neurons responded to electrical stimulation of tooth pulp afferents from both sides of the jaws. There were also TPS relay neurons, these being coexistent with trigeminal NS neurons in the marginal layer of the trigeminal subnucleus caudalis.

Cooling the dorsolateral surface of the caudal medulla oblongata (which interrupts afferent input from the periphery to the trigeminal subnucleus caudalis and its adjacent bulbar lateral reticular formation), reversibly blocked the responses of trigeminal NS and WDR neurons in the shell region of the VPM proper to noxious mechanical stimulation of their cutaneous receptive fields. Cooling this region also reversibly blocked the tooth pulp evoked responses of TPS and WDR neurons. Trigeminal tractotomy just above the level of the obex irreversibly abolished responses of NS, WDR, and TPS neurons, but electrical stimulation of the trigeminal spinal tract at a level caudal to the incision still elicited excitation of these neurons [30, 32]. These findings suggested that NS and TPS neurons in the marginal layer of the trigeminal subnucleus caudalis, and WDR neurons in the lateral part of the subnucleus reticularis dorsalis relay nociceptive afferent impulses from the trigeminal nerve territory to the shell region of the VPM proper.
5. Nociceptive neurons in cat VPL

In the above-mentioned experiments, neither NS nor WDR neurons were found in the ventrolateral region of the VPM proper bordering the VPL. On the other hand, it does seem clear that in the rat, cat, and monkey, the densest termination of fibers in the lateral component of the spinothalamic tract tends to be distributed within and directly surrounding the VPL [3–5]. Furthermore, it has been reported that the marginal area of the VPL contains nociceptive neurons with receptive fields in the spinal nerve territory [10]. Taking these results together, it may be assumed that nociceptive neurons are located in a shell-like fashion around the whole VB complex. We have confirmed that trigeminal as well as spinal nociceptive neurons were in fact located in a shell-like fashion around the ventrobasal complex consisting of the VPM proper and VPL [27, 28]. We have called this marginal area the shell region of the VB complex. Furthermore, we have found that spinal NS and WDR neurons in the VPL were spatially segregated in a manner similar to that of the VPM proper. That is, spinal NS neurons in the VPL were located at the level corresponding to the NS zone of the VPM proper, whilst spinal WDR neurons were located in a narrow band just anterior to the NS zone of the VPL. The border between the NS and WDR zones was slightly curved with its lateral end located more anteriorly. Nevertheless, the WDR zone of the VPL is continuous with the

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Fig. 4. A reconstruction of microelectrode penetrations through the VB complex, showing the sites of NS and LTM neurons in one experiment. Individual pictures show the receptive fields of the corresponding NS neurons which are located in the shell region of the VB complex. Abbreviations are the same as in Fig. 1 legend.

Japanese Journal of Physiology
WDR zone of the VPM proper. Hence, there is a belt around the whole VB complex, in which trigeminal and spinal WDR neurons are located.

Both spinal NS and spinal WDR neurons in the VPL were somatotopically organized, as was the case for trigeminal NS and WDR neurons in the VPM proper. In general, spinal NS neurons in the dorsal shell region of the VPL had receptive fields on the contralateral dorsal surface of the body, whereas spinal NS neurons in the ventral shell region had them on the ventral aspect of the contralateral integument. In the dorsal shell region, neurons responding to noxious stimulation of the uppermost cervical dermatomes were found in the most medial part of the shell region of VPL, whereas those responding to noxious stimulation of successively more caudal dermatomes were located more laterally, and in serial order. NS neurons responding to noxious stimulation of the sacral dermatomes were thus found in the most lateral part. In the ventral NS zone, the pattern was distorted by disproportionately large areas devoted to the fore- and hind-paw pads. The VPL is subdivided by a thin fibrous lamina into a lateral part (VPLl) and a medial part (VPLm). NS neurons having receptive fields in the forepaw pad were found throughout the entire mediolateral extent of the ventral shell region of the VPLm; NS neurons having receptive fields on the hind-paw pad occupied a large portion of the ventral shell region of the VPLl. Scattered among these were NS neurons having receptive fields on the rest of the ventral body surface, these being represented in an orderly sequence, as in the dorsal shell region. Cervical dermatomes were thus represented most medially, and successively more caudal dermatomes were represented progressively more laterally. A similar somatotopic pattern was recognized in the distribution of the low-threshold centers of the receptive fields of WDR neurons.

With regard to the mechanisms by which the position of a painful stimulus may be determined, two possibilities have been suggested [22]. One suggestion was that the localization might depend upon the simultaneous activation of low-threshold mechanoreceptors by the painful stimulus, with the activity being relayed to the topographically precise medial lemniscal system. This implies that the correct localization of the painful stimulus requires a high level of integration of activity, combining qualitative information from the spinothalamic system with data for spatial discrimination derived from the medial lemniscal system. A second suggestion was that the component of the spinothalamic system which projects upon the VB complex contains nociceptive elements which possess discriminative properties similar to those of the medial lemniscal system. POGGIO and MOUNTCASTLE [22] favored the first possibility, it being clear that the nociceptive neurons they found in the PO of the cat were unlikely to provide data concerning the location of a painful event, since they all had very large receptive fields. In contrast, the somatotopic organization of NS and WDR neurons we found in the shell region of the VB complex rather suggests that these neurons may provide data useful for localizing a painful event.
6. **Viscerosomatic convergence onto cutaneous nociceptive neurons in the shell region of the cat VPL**

Sympathetic afferent fibers are essential for the conduction of visceral pain. This concept has been supported both by clinical observations in humans and by animal experiments. It has also been demonstrated that afferent impulses in visceral sympathetic afferent fibers excite cutaneous nociceptive neurons, including spinothalamic neurons, in the dorsal horn of the spinal cord. Neurons in the spinal dorsal horn which are driven exclusively by innocuous stimulation of the skin are, however, rarely excited by visceral afferent input. It seems reasonable to predict that some NS and WDR neurons in the shell region of the VPL, therefore, also receive visceral sympathetic afferent input. We explored the VPL of the cat thalamus for neurons driven by visceral sympathetic afferents from the inferior cardiac, greater splanchnic, and hypogastric nerves. These three sympathetic nerves contain afferent fibers mediating pain arising from the heart, upper abdominal viscera, and pelvic organs, respectively. We found that the vast majority of NS and WDR neurons in the shell region of the VPL received afferent inputs from one or two of these nerves. LTM neurons, which constitute the vast majority of VPL neurons, were not driven by electrical stimulation of visceral sympathetic nerves. Neurons responding only to sympathetic visceral afferents were not found in the VPL [1, 24, 32].

NS neurons which responded to the inferior cardiac nerve had their receptive fields in the dorsal root dermatomes C5-T13. Those responsive to the greater splanchnic nerve had their receptive fields in the dorsal root dermatomes C8-L3. Those which responded to the hypogastric nerve had their receptive fields in the dorsal root dermatomes T13-S2. WDR neurons responsive to these visceral sympathetic nerves had at least a part of their receptive fields in these dermatomes, respectively. There was no overlap in cutaneous receptive fields between NS neurons responsive to stimulation of the greater splanchnic nerve and NS neurons unresponsive to the same nerve. Hence, NS neurons responsive to the inferior cardiac or hypogastric nerve also responded to the greater splanchnic nerve if they had their receptive fields in the dorsal root dermatomes C8-L3. The vast majority of WDR neurons responsive to cardiac or hypogastric afferents were also activated by splanchnic afferents.

NS neurons receiving visceral afferents were located in the dorsal and ventral shell regions except for the medial and lateral sixths. NS neurons responsive to cardiac afferents were found in the dorsal and ventral shell regions of the VPLm, whereas those responsive to hypogastric afferents were found in the dorsal and ventral shell regions of the VPLv. NS neurons responsive to splanchnic afferents occupied the middle half of the dorsal and ventral shell regions. WDR neurons responsive to visceral sympathetic afferents had a similar, but not identical distribution.

These findings suggested that the shell region of the caudal VPL constitutes a thalamic link in a visceral pain pathway, and that the visceral and cutaneous pain
THALAMIC MECHANISM OF PAIN

Pathways share a common projection locus in the shell region of the caudal VPL. It is obvious that the viscerosomatic convergence observed in the shell region of the caudal VPL supports the convergence projection theory of referred visceral pain. In addition, an examination of both the receptive fields, and the locations within the shell region allows comparisons to be made between neurons responding to cardiac, splanchnic, and hypogastric afferents. Receptive fields and thalamic locations of neurons responding to cardiac afferents and those of neurons responding to hypogastric afferents showed virtually no overlap. The vast majority of neurons which responded to splanchnic afferents also responded to cardiac or hypogastric afferents. A significant fraction of the neurons examined, however, responded only to cardiac or hypogastric afferents, and had their own receptive field territories and thalamic locations. These differences may represent a mechanism by which the brain localizes the source of visceral pain.

Fig. 5. A reconstruction of microelectrode penetrations showing the recording sites of NS and LTM neurons, and the receptive fields of NS neurons in a macaque. Filled circles and open circles in the photomicrograph indicate the positions at which NS and LTM neurons were recorded, respectively. Abbreviations: CM, nucleus centrum medianum; LP, nucleus lateralis posterior; VPLc, nucleus ventralis posterolateralis, pars caudalis; other abbreviations are the same as in Fig. 1 legend.

Vol. 39, No. 3, 1989
7. Nociceptive neurons in the VPM of the monkey

The VPM of the Japanese macaque was explored for cutaneous nociceptive neurons [34] in order to confirm the data obtained from the cat.

As was the case for the VPM proper of the cat, trigeminal NS and WDR neurons were found in the shell region of the VPM proper part of the caudal VB complex, the WDR neurons being located in a narrow zone just rostral to the NS zone. There was, however, a difference between cats and macaques in that, except for the most caudal part, the medial edge of the caudal VPM proper of the macaque is concave, surrounding the nucleus centrum medianum (CM) or pars oralis of the pulvinar (PuO). The medial part of the VPM proper, therefore, separated into dorsal and ventral subdivisions. The ventral subdivision protrudes more medially, and beneath the CM or PuO, than does the dorsal subdivision. In the cat, nociceptive neurons were distributed over the whole surface of the caudal VB complex, so that there was no interruption in the location of nociceptive neurons in the transverse plane around the VB complex. In the macaque, nociceptive neurons were not found along the medial edge of the VPM proper just dorsal and lateral to either the CM or PuO, which distorts the VPM proper. They were, however, found in the dorsal and ventral shell regions of the medial protrusion of the ventral subdivision of the VPM proper.

SUMMARY

In both cats and Japanese macaques, there are nociceptive specific (NS) and wide dynamic range (WDR) neurons in the shell region of the caudal ventrobasal (VB) complex of the thalamus. This comprises both the nucleus ventralis posteromedialis proper (VPM proper), and the nucleus ventralis posterolateralis (VPL). These two classes of nociceptive neurons are spatially segregated, WDR neurons being located both more anteriorly and in a narrow belt around the VB complex. Both NS and WDR neurons are somatotopically organized. These two classes of nociceptive neurons may constitute a thalamic link in the pain pathway from both the dorsal horn of the spinal cord and its trigeminal homologue, to the primary somatosensory cortex. Visceral sympathetic afferent inputs also project to the VPL part of the shell region of the caudal VB complex, there being viscerosomatic convergence onto both NS and WDR neurons. Visceral and cutaneous pain pathways thus appear to share a common projection locus in the shell region of the caudal VB complex.

Key words: thalamus, pain, nociception, ventrobasal complex.

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