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REVIEW ARTICLE

THE ROLE OF THE THALAMUS IN MODULATING PAIN

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The thalamus is one of the structures that receives projections from multiple ascending pain pathways. The structure is not merely a relay centre but is involved in processing nociceptive information before transmitting the information to various parts of the cortex. The thalamic nuclei are involved in the sensory discriminative and affective motivational components of pain. Generally each group of nucleus has prominent functions in one component for example ventrobasal complex in sensory discriminative component and intralaminar nuclei in affective-motivational component. The thalamus is also part of a network that projects to the spinal cord dorsal horn and modulates ascending nociceptive information. In the animal models of neuropathic pain, changes in the biochemistry, gene expression, thalamic blood flow and response properties of thalamic neurons have been shown. These studies suggest the important contribution of the thalamus in modulating pain in normal and neuropathic pain condition.

Key words *: thalamus, pain, electrophysiology, imaging*

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Is there a role for the thalamus in modulating pain?

The classic pain pathway as was previously understood consists of a three-neuron chain that transmits pain information from the periphery to the cerebral cortex (1). The first order neuron has its cell body in the dorsal root ganglion and two axons, one extending distally to the tissue it innervates while the other extending proximally to the dorsal horn of the spinal cord (2). In the dorsal horn, this axon synapses with the second order neuron which in turn will cross the spinal cord through the anterior white commissure and ascends through the lateral spinothalamic tract to the thalamus. In the thalamus, the second order neuron synapses with the third order neuron, which ascends through the internal capsule and corona radiata to the postcentral gyrus of the cerebral cortex (1). This pathway is organized such that within tracts and nuclei up to the cortex, topological relations are maintained and different parts of the body are represented in an ordered arrangement in the postcentral gyrus. This arrangement is called somatotopy (3).

The pain pathway is now understood to be a dual system at each level and the sensation of pain that arrives in the central nervous system is composed of the sensory discriminative component of pain (first pain), and the affective-motivational component of pain (second pain), which is carried separately (1). In addition, there are also afferents from the spinal cord to pain-mediating areas of the brain stem, local modulating circuits in the spinal cord, and descending pain pathways from the cortex, hypothalamus, and brain stem to the spinal cord that make up the descending facilitation and descending inhibition of pain (4). The spinothalamic pathway that is thought to be concerned with the sensory discriminatory qualities of the stimulus originates primarily from neurons in the neck of the dorsal horn and terminates within the ventroposterior and ventrobasal thalamus, which then project upon the cortex (1). The second pathway (affective-motivational), which is more extensive, is derived mainly from lamina 1 neurons of the dorsal horn that express the neurokinin 1 (NK1) receptor and terminates within the parabrachial area and periaqueductal grey. These areas in turn project on brain areas such as the hypothalamus and amygdala

that modulate the affective dimensions of pain and control autonomic activity.

Integration of sensory discriminative, affective motivational and cognitive-evaluative components contributes to the pain response in an individual (5). The sensory discriminative aspects of pain include quality, location and intensity processing (6) while affective-emotional component of pain comprises the unpleasant character of pain perception (7). The cognitive component is involved in the attention, anticipation and memory of past experiences and this component can interact with the other components giving rise to modulation of pain (8). Studies have been conducted to investigate the involvement of supra-spinal structures in pain modulation (9, 10, 11, 12, 13).

The thalamus is one of the supra-spinal structures that has been extensively investigated as it receives projections from multiple ascending pathways. Spinal lamina I neurons project extensively to the ventrobasal complex (ventral posterolateral + ventral posteromedial) and to the posterior group thalamic nuclei (14, 15, 16). The nociceptive neurons from the ventrobasal complex mainly project to the primary somatosensory cortex and this pathway constitutes the lateral pain system that plays an important role in the discrimination of stimuli (6, 17). The affective-motivational aspect of pain is mediated by the medial pain pathway, which includes the intralaminar thalamic nuclei (18) and posterior aspect of ventromedial thalamic nuclei (19) that project to somatosensory cortex and limbic structures (20). The deeper spinal lamina (V/VI) conveys nociceptive messages to the parabrachial internal lateral nucleus that project mainly to the paracentral nucleus (PC) or other intralaminar nuclei (21, 22). The fibers from PC targeted cortical structures e.g. the lateral orbital, lateral agranular and the dorsomedial prefrontal areas (23) that have an important role in cognitive functions, aggressive behaviour and emotional states (24, 25, 26). Neurons originated from lamina VII/VIII project to the medullary reticular formation (27, 28), ventrolateral periaqueductal (29) and intralaminar thalamic nuclei (30). There is extensive projection from the intralaminar nuclei to the cortex, including to the anterior cingulate cortex, subserving the motivational aspects of pain (31). These brain structures including the thalamus are parts of a neural network that are involved in pain modulation that require further investigations to understand the complexity of pain perception.

Electrophysiological studies

The ventral posterolateral (VPL) thalamic nucleus is one of the termination sites for the spinothalamic tract. VPL neurons respond to innocuous and noxious mechanical stimuli and some of the neurons respond to visceral nociception e.g. intraperitoneal injection of bradykinin (32) and uterine distension (33). Electrophysiological studies have reported the excitatory responses of neurons to nociceptive stimulation in (34) other thalamic nuclei including the intralaminar complex (35), nucleus submedius (36), posterior complex (37) and ventromedial thalamus (38). In contrast, nociceptive inputs inhibit a significant proportion of neuronal evoked responses in reticular thalamic nucleus (39) and reticular thalamic (RT) projections to VPL or ventrobasal complex may serve to modulate the ascending information and thus, RT has an important role in processing the sensory information (40).

Studies have shown that VPL nociceptive neurons have restricted receptive fields and precisely encode the intensity of noxious stimuli (32, 41) and these characteristics are consistent with the functions of lateral pain pathway. The nociceptive neurons in other nucleus might have a larger receptive field including the ventromedial nucleus that respond to noxious mechanical and thermal stimulation from any part of the body (42). The ventromedial nociceptive neurons do not respond to innocuous stimuli and these neurons project to widespread areas of the neocortex (42). These fibres might be part of a neural network that is involved in the attentional reactions and/or the coordination of motor responses to pain (19, 42). Another thalamic structure, posterior complex (Po), has a close relationship with the retroinsular cortex and probably has an important role in the motivational affective responses of pain (43). The Po thalamic neurons respond to noxious mechanical stimuli (37) and electrical tooth pulp stimulation (44). It is reported that in cats, some of the neurons have large bilateral receptive field (45) while another report described that of a smaller restrictive field in monkeys (37). The different characteristics of Po neurons might be due to different species used (46) or due to high sensitivity of Po neurons to anaesthetics (47, 48).

There is a large amount of evidence that describe the important contribution of the thalamus to hyperalgesic (increase painful response to noxious stimuli) responses associated with peripheral injury. Studies in rats have shown that following hindpaw inflammation or peripheral nerve injury, ventrobasal (Ventral posterolateral plus ventral posteromedial)

thalamic neurons exhibited lowered thresholds and enhanced peripherally-evoked responses (49, 50, 51, 9). At the spinal level, some reports have demonstrated that there were no changes in neural responses following hind paw inflammation (52) and peripheral nerve injury (53, 54) and this suggested that the heightened responses of VPL neurons are not merely due to peripheral sensitization or changes at the spinal level.

Another thalamic nucleus that receives considerable attention is the nucleus submedius (Sm). The Sm has a close relationship with ventrolateral orbital cortex (VLO) and periaqueductal region (55, 56, 57) that forms a part of descending inhibiting system (58, 59). Extracellular recordings demonstrated that the Sm neurons responded to noxious electrical, chemical stimuli (60), mechanical and thermal stimuli (61). A few studies have also reported that the Sm neurons respond to visceral stimulation including colorectal balloon distension (62; 63) and intraperitoneal injection of formalin or hypertonic saline (60). The response to noxious stimuli can be excitatory or inhibitory (60, 61). The excitatory and inhibitory evoked responses could be eliminated or depressed by intravenous administration of morphine and the effects could be reversed with opioid antagonist, naloxone (61). The presence of two types of cells, that is on cells and off cells have been reported in other region e.g. rostral ventromedulla (64, 65) and periaqueductal region (66). Reports have shown that opioid antinociception is mediated by inhibition of on-cells and excitation of off-cells that activate the Sm-VLO-PAG pathway that modulates nociceptive inputs at spinal cord level (61, 67). The modulating role of Sm is supported by studies that show electrical stimulation of Sm leads to inhibition of noxious evoked responses of dorsal horn neurons (68) and depression of tail-flick reflex in rats (69).

Imaging studies

Noxious stimulation activates the neural pain pathway and increases the neural activity in certain areas of the brain and the activity can be indicated by increases in the regional cerebral blood flow (CBF) in positron emission tomography (PET) or blood oxygen level dependent (BOLD) signal in functional magnetic resonance imaging (fMRI). The changes in the cerebral blood flow are mediated by interaction of sympathetic b-receptors, ATP sensitive potassium channels and the release of nitric oxide (70). Imaging studies have been widely used to investigate the haemodynamic of brain responses to pain in human and animals (10, 11, 12, 71, 72, 73, 74, 75). Investigations on how the brain structures contribute to the overall pain experience are being conducted to improve understanding of nociceptive processing in the central nervous system. The functional imaging investigation is a reliable method to determine the pain response in different brain regions as signal intensity and activated areas are different during noxious and innocuous stimulation (76). Furthermore the signal intensity correlates parametrically with the pain response (77). The thalamus is one of the areas activated as a response to noxious stimulation in normal subjects (78, 79, 80). Application of painful laser stimulation on human subjects produced greater activation in the contralateral primary somatosensory cortex and thalamus (81). Another report has shown the functional association between medial thalamus and the anterior cingulated cortex (ACC). Electrical stimulation of the medial thalamic nuclei produced an increase in the signal in the anterior cingulated cortex (ACC) (20) suggesting involvement of the medial thalamus in affective-motivational component of pain.

Attention is an aspect of cognitive component of pain and it is well known that distraction during painful stimulation reduces the subjective pain sensation in a subject (82, 83, 84). Attention to a noxious stimulus e.g. thermal, activate a large neural network including the prefrontal, posterior parietal, anterior cingulated cortices and thalamus (85). Distraction from the thermal stimuli significantly increased the activation in posterior part of the insular cortex (86), periaqueductal gray (PAG) and posterior thalamus (8). Valet et al (2004) (8) has suggested that the functional interactions between PAG and the posterior thalamus are likely to be involved in the network of pain modulation.

Involvement of the thalamus in processing and modulating nociceptive information in neuropathic pain has been shown in various imaging studies. In unstimulated rats (basal) cerebral blood flow in multiple thalamic nuclei including the VPL, ventral medial and posterior nuclear group, was increased in neuropathic rats compared to sham-operated rats (73) and this finding is consistent with the spontaneous pain related behaviour exhibited by the neuropathic rats. It is also interesting to note the correlation of pain behaviour e.g. mechanical allodynia, that was maximal for two weeks after the nerve injury, matched the changes of blood flow in ventral lateral and VPL, in neuropathic rats (74). Imaging studies conducted in human supported the

role of the thalamus in the development of neuropathic pain (71, 72, 75). Reports demonstrate an enhanced activity in the medial pain pathway, including the medial thalamus and anterior insula, with application of an innocuous thermal stimulus in human subjects presenting with heat allodynia (87, 88). The enhanced activity of the medial thalamus was not seen in subjects who have normal heat pain (87, 88). A different study reported a reduction in thalamic signals in patients with chronic neuropathic pain and this might be related to alteration in the thalamic blood flow and neural activity (89). All these observations are different presentations of the thalamus in neuropathic pain condition and are suggestive of supraspinal plasticity involving the thalamus following peripheral injury.

Other studies

It has been observed from electrophysiological and functional imaging studies that functional changes occur in the thalamus in neuropathic pain condition. The important contribution of the thalamus in neuropathic pain is also supported by other studies including immuno-histochemistry studies. The expression of an early gene, c-fos, is considered as an early marker of long-term functional changes in the neuronal activity. Following noxious stimulation, induction of c-fos expression has been shown in a number of thalamic nuclei e.g. midline nuclei, intralaminar nuclei, paraventricular nucleus and VPL (70, 90, 91). The level of c-fos increased in a few supraspinal regions including the thalamus, frontal cortex and periaqueductal gray four days after sciatic nerve ligation (92). Reorganization of thalamic neurons can be observed within six hours after ligation of sciatic nerve with changes in receptive fields evoked responses to noxious stimuli and the strength of cross-correlation of firing of the thalamic neurons (93). Following peripheral nerve injury, biochemical abnormalities are also reported in the thalamus e.g. reduced serotonin (5-HT) release in the contralateral ventrobasal complex (94) that can reduce the inhibitory input to the spinal cord projections and thalamic relay neurons (95). This will ultimately lead to diminish antinociception or even facilitation of neurons that increases the pain perception.

Studies have shown that NMDA receptors are involved in the somatosensory and nociceptive transmission in the thalamus (95, 96). The NMDA receptors in VPL are important in the development and maintenance of hyperalgesia in the rats (97, 98). Blockade of NMDA receptors in the thalamus reduced nociceptive transmission in neuropathic (98, 99) and normal rats (100). Although NMDA receptor subunits have been found in the medial thalamus (101), its role in mediating nociception in the structure e.g. Sm, has not been proven (102) and requires further investigation.

Conclusion

Studies have suggested that the thalamus is an important structure that mediates different components of pain: sensory discriminative (lateral pain pathway) and affective-motivational (medial pain pathway) components. The thalamus is also involved in the descending inhibition to modulate nociceptive inputs at the dorsal horn of the spinal cord. Changes in the biochemistry, immediate early gene expression, thalamic blood flow and the response properties of thalamic neurons have been demonstrated in neuropathic pain models. These data indicate that the thalamus has an important role to play in the modulation of nociception in normal and neuropathic pain syndrome.

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