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Thalamus: the 'promoter' of endogenous modulation of pain and potential therapeutic target in pathological pain.

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Abstract

More recently, the thalamic mediodorsal (MD) and ventromedial (VM) nuclei have been revealed to be functioned as ‘nociceptive discriminator’ in discriminating noxious and innocuous peripheral afferents, and exhibits distinct different descending controls of nociception. Of particularly importance, the function of thalamic nuclei in engaging descending modulation of nociception is ‘silent’ or inactive during the physiological state as well as in condition exposed to insufficient noxious stimulation. Once initiation by sufficient noxious or innocuous C afferents associated with temporal and spatial summation, the thalamic MD and VM nuclei exhibit salient, different effects: facilitation and inhibition, on noxious mechanically and heat evoked nociception, respectively. Based on series of experimental evidence, we here summarize a novel hypothesis involving thalamic MD and VM nuclei functioned as ‘promoter’ in initiating descending facilitation and inhibition of pain with specific spatiotemporal characteristics. We further hypothesize that clinical remedy in targeting thalamic VM nucleus by enhancing its activities in recruiting inhibition alone or decreasing thalamic MD nucleus induced facilitation may provide promising way in effectively control of pathological pain.

Keywords:

Thalamus; Thalamic ‘nociceptive discriminator’; Endogenous modulation of pain; Innocuous warm-needle therapy

1. Historic background and some unsolved scientific issues

Pain is an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage (Raja et al., 2020). Internal and external noxious stimuli can evoke pain, which is accompanied by escapable behavior, i.e. nociceptive flexion reflex (also known as the nociceptive withdrawal reflex), followed by various physiological responses potentially associated with emotions (Besson & Chaouch, 1987; Millan, 1999). Pain has been proposed to be 'the fifth vital sign' in addition to the other four life signs that are breathing, pulse, body temperature, and blood pressure (Campbell, 2016), emphasizing the importance of pain research within the field of life and health science research.

In the 21st century, due to the application of novel molecular biology techniques pain research has achieved considerable progress at cellular and molecular levels. However, there are still apparent gaps between findings in the basic research laboratories and the clinic. Despite better understanding of various molecular mechanisms and intracellular signaling cascades, the mechanisms underlying physiological and particularly pathological pain are still only partly known. In the present review, we address questions related to the induction, occurrence, and development of pathological pain and mechanism-based treatment strategies that deserve more attention, with emphasis on distinct thalamic mechanisms related to discrimination and descending control of nociception.

1.1 Major theories of pain and related controversies

As early as in the 17th century, Descartes described that pain is produced by a direct, straight-through transmission system from injured tissues to a certain pain center, i.e. pineal gland in the brain, activation of which in turn evokes escapable activities (Descartes, 1972). Thereby, Descartes provided the first physiological and anatomical explanation for arousing pain sensation in animals and humans exposed to noxious stimuli. In line with this, the first systematic pain theory: Specificity theory, was hypothesized by von Frey (von Frey, 1895). According to the specificity theory, pain sensation is evoked following activation of specialized peripheral receptors (nociceptors) from which the signal is carried by nociceptive A-⍰ and C fibers to the spinal cord relay and further to the specific thalamic nuclei, and the brain to induce a pain sensation. The specificity theory has a long history, it was supported by various types of experimental and clinical findings, and the existence of specific somatic projection pathways demonstrated also by current methods is in line with it. Interestingly, von Frey filament is still widely used in animal and human pain experiments to evaluate pain sensitivity. The specificity theory has, however, certain shortcomings, which cannot be omitted (Goldscheider, 1894). For instance, free nerve endings that are the simplest organ to detect noxious inputs, are not exclusively activated by painful stimuli, but they are sensory organs with a wide range of functions that include detection of certain innocuous stimuli. In addition, clinical phenomena such as phantom limb pain and central pain after stroke have been associated with pain without any external stimulation or with innocuous stimulation-evoked pain, which observations do not support the concept that pain results only from activation of a fixed, pain-specific point-to-point pathway (Borghi, 2014). Taken together, the shortcomings of the specificity theory are the inadequate consideration of the diffuse nonspecific conduction pathways and that of the endogenous descending facilitation and inhibition of the ascending pain pathways (Basbaum & Fields, 1978; Cervero et al., 1985; Heinricher et al., 2009).

The pattern theory was proposed by Nafe, who described that there is no specific somatosensory receptor for the perception of pain (Nafe, 1929). Instead, various stimuli excite different numbers of nonspecific nerve endings, causing each nerve ending to emit impulses at different frequencies. Due to the differences in transmission time of nerve impulses and the associated spatial configuration differences in the afferent volley, different sensations are formed. Excessive stimulation generates a large amount of impulses, due to which pain is elicited in the brain. Pattern theory appears to be in agreement with some clinical phenomena, but it is too broad leaving out the physiological fact of a high-degree of receptor specialization, and there are few experimental data supporting it. But still, the pattern theory has its merits. For example, it emphasizes the decisive influence of temporal and spatial summation of the incoming impulse discharge on sensation, which provides a meaningful explanation for some specific pain-related phenomena, such as wind-up in the spinally-organized sensory and motor response to low frequency, i.e. 0.5-5 Hz, of repeated stimulation at C-fiber intensity (Mendell, 1966; You et al., 2003).

The third well known pain theory is the gate control theory introduced by Melzack and Wall that sparked a vivid debate and provided a vigorous stimulus for pain researchers. It took into account plausible aspects of the specificity theory and the pattern theory, and provided a new theoretical model to explain mechanisms that evoke and control pain perception (Melzack & Wall, 1965). The gate control theory had its background in the discovery of descending inhibition (Hagbarth & Kerr, 1954) and the development of the in-depth studies of pre-synaptic inhibition and neuronal transmission in the spinal cord (Wall, 1964). According to the gate control theory, the substantia gelatinosa (SG) cells located in the dorsal horn (DH) layers II and III of the spinal cord are the gate of the spinal information transmission. These spinal SG cells modulate nerve impulses arriving the spinal transmission (T) cells receiving afferent information from fine fibers innervating the skin, internal organs, and muscles. Additionally, T cells receive descending inhibitory influence from the supraspinal system. Spinal SG cells pre-synaptically inhibit the discharge level of spinal T cells. The impulses in large-diameter primary afferent fibers excite SG cells, whereas impulses in small-diameter primary afferent fibers inhibit SG cells. According to the gate theory, the occurrence of pain sensation mainly depends on the number and frequency of ascending impulses relayed by spinal T cells that are under a peripheral control through the SG gate. In addition to local segmental control, supraspinal centers can control the ascending pain signal by opening and closing the SG gate through the descending control system.

The gate control theory receives at least partial support from experimental studies, and it explains some pain phenomena that are difficult to explain by either the specificity theory or the pattern theory. However, the gate control theory has been severely criticized for several reasons (Nathan, 1976). Among aspects receiving criticism are the following ones. First, the theory is based on the assumption that pain can be attenuated by activation of coarse, myelinated A-fibers, but not C-fibers that are supposed to carry only signals inducing pain. However, there are also non-nociceptive primary afferent C-fibers contributing to itch, warmth, and touch (Besson & Chaouch, 1987; Schmelz et al., 1997; Olausson et al., 2010). Moreover, unlike predicted by the gate control theory, C-fiber activation can induce analgesia e.g. during acupuncture (Zhu et al., 1990; Radhakrishnan & Sluka, 2005). Actually, the analgesic effect has increased with the intensity of C-fiber stimulation both when C-fibers were activated by electroacupuncture (Zhao, 2008), and by natural noxious stimulation as in the DNIC (diffuse noxious inhibitory controls) procedure (Villanueva & Le Bars, 1995). Second, electrophysiological studies on pre-synaptic inhibition of pain-related signals by large myelinated fibers in the spinal DH provided results that were not invariably in line with the gate control theory, or were even opposite to the theory (Franz & Iggo, 1968; Mendell 1970; Zimmermann, 1968). While the exact wiring proposed by the gate control theory has not been invariably supported by earlier experimental studies assessing pre-synaptic inhibition from local field potentials, recent whole-cell patch-clamp recordings indicate that an afferent volley in thick myelinated primary afferent nerve fibers can contribute to the pre-synaptic inhibition of C-fiber inputs to the presumed pain-relay neurons in the spinal DH (Fernandes et al., 2020). Although some aspects of the gate control theory may not have been right, it has been influential in emphasizing that pain is not an invariable result of the excitation of nociceptive primary afferent nerve fibers. Moreover, the gate control theory has had an impact on the stimulation of further experimental and theoretical studies on pain (Nathan, 1976).

1.2 Research on central sensitization of pain

Central sensitization refers to a phenomenon involved in the maintenance of pain and occurring, at least in part, independent of peripheral inputs (Woolf, 1983). The specificity, pattern or the gate control theories explain poorly phenomena related to central sensitization of pain. In the following text and chapters, we propose a hypothesis, according to which endogenous pain modulatory circuits, with emphasis on distinct circuits looping through the thalamus, provide an extension to specificity, pattern and gate control theories by providing a framework that covers some of the key phenomena related to central sensitization of pain.

Study of mechanisms underlying central pain sensitization requires appropriate models. While there are a number of experimental animal models that have been used in studying central sensitization (Coderre & Laferrière, 2020), a limitation in many of them is that it is difficult to dissociate between peripheral and central factors contributing to pain sensitivity changes. An interesting model for assessing centrally mediated changes in pain sensitivity following a peripheral injury is a model of secondary hyperalgesia developed more than eight decades ago (Lewis, 1936). Both human and animal experiments using this model have demonstrated that following skin injury, hyperalgesia to heat and mechanical stimulation develops at the injured area (primary mechanical and heat hyperalgesia), whereas the adjacent healthy zone exhibits only mechanical hyperalgesia (secondary mechanical hyperalgesia), with only little if any thermal hyperalgesia (Lewis, 1936; Hardy et al., 1952) (for review see Treede et al., 1992). Secondary hyperalgesia, which can also be manifested as 'mirror pain' in the healthy skin of the contralateral limb has been considered to reflect central sensitization (Treede, 2006). When studying central sensitization using the traditional secondary hyperalgesia model (i.e.; studying skin area adjacent to the injury area), it is often challenging to exclude the possibility that noxious stimulation of the secondary hyperalgesia area coactivates at least partly primary afferent fibers innervating the adjacent primary hyperalgesia area. Determining injury-induced pain sensitivity changes in the healthy skin area of the contralateral limb (i.e.; mirror area) is expected to give a more selective index for the central component in potential pain sensitivity change. The assessment of the mirror area combined with manipulations of the pain processing and control pathways at various levels of the neuraxis allows determining the roles of various neural structures and neurotransmitter mechanisms in centrally-mediated pain sensitivity changes, without a confounding influence of peripheral changes. In line with this approach, one successfully used experimental procedure for assessing centrally mediated changes in pain sensitivity (secondary or mirror hyperalgesia), independent of peripheral hyperalgesia, is to induce acute muscle nociception by intramuscular (i.m.) injection of hypertonic (5.8%) saline into the gastrocnemius muscle of one hind limb in the rat. This procedure induces bilaterally long-lasting pain sensitivity changes that can be conveniently assessed in the hind paws that represent a dermatome different from that of the unilaterally injured muscle (You et al., 2010). The direction of the long-lasting (> 7 days) bilateral secondary pain sensitivity change induced by unilateral muscle nociception is submodality-dependent, as shown by hyperalgesia to mechanical stimulation and hypoalgesia to heat stimulation (You et al., 2010, 2013; Lei et al., 2011, 2014, 2015). Interestingly, secondary mechanical hyperalgesia in this model has an early onset (<30 min after induction of muscle nociception), whereas secondary heat hypoalgesia has a late onset (1 day after the i.m. injection). These differences in secondary pain sensitivity changes induced by the unilateral muscle nociception model allow investigating separately central (secondary) pain facilitatory versus inhibitory mechanisms by appropriately choosing the submodality of test stimulation and the time window for testing.

2. Endogenous modulation of pain and its pathways

Currently, there is a wide consensus that nociceptive information ascending from the periphery to the cerebral cortex is controlled at various levels of the neuraxis by endogenous descending modulatory systems originating in multiple areas of the central nervous system (Millan, 2002; Pertovaara & Almeida, 2006). Among neural structures contributing to descending inhibition and/or facilitation of pain have been shown to be e.g. the cerebral cortex, thalamus, and various brain stem nuclei. The first study of the descending modulation of pain reported that sustained analgesia can be elicited by electrical stimulation of the midbrain periaqueductal grey matter (PAG) (Reynolds, 1969). This finding promoted further studies on endogenous descending inhibition of pain (Basbaum & Fields, 1978). Following discovery of descending inhibition, also descending facilitatory effect on spinal nociception was demonstrated when assessing the descending effect induced by electrical stimulation of the nucleus raphe magnus (NRM), a brainstem structure which was initially supposed to exhibit only suppressive effects on nociception (Cervero & Wolstencroft, 1984; Cervero et al., 1985).

Since the end of 1980s, many research groups have addressed the question whether the endogenous descending pathways exert facilitatory and/or inhibitory controls of pain in a tonic fashion (Duggan & Morton, 1988; Laird & Cervero, 1990; Tjølsen, et al., 1991). It may be argued that if the endogenous descending modulation of pain exerts a tonic action, its physiological significance can be compared with other neural systems that in a tonic fashion maintain the homeostasis, such as the tonic control exerted by the sympathetic nervous system or that exerted on the proprioceptive afferents. On the other hand, a non-tonic component of the endogenous modulation of pain raises questions about factors (such as the nature of peripheral stimuli) needed to initiate and maintain it under physiological and various pathophysiological conditions, and about its functional role (such as suppression of distracting nociceptive inputs from injury area to promote fight-or-flight behavior, or enhancement of nociceptive discharge to promote rest and avoidance, and thereby healing of the injury). The mechanisms involved in the initiation, maintenance, and plastic changes of the endogenous regulation of pain in physiological and pathophysiological conditions are expected to play a significant role in central sensitization, one index of which is secondary hyperalgesia. Thereby, better understanding of the underlying neural mechanisms may help in developing treatment strategies that effectively attenuate pathological pain caused by central sensitization.

2.1 Thalamus: anatomy and fiber connections

It is well known that the spinothalamic pain transmission pathway that is traditionally considered the main ascending pathway for mediating signals inducing conscious pain sensations contains a minimum of three neurons on its way from the dorsal root ganglion neuron, through the spinal cord DH neuron to the thalamus. The thalamus is the final important sensory and cognition relay station for transmission of ascending information in animals with a well-developed cerebral cortex (Guyton & Hall, 2006; Halassa & Kastner, 2017). The incoming information from various sensations throughout the body (except the olfaction) is transmitted to neurons in the thalamus and it eventually relays the information to different areas of the cerebral cortex. In addition to serving as a sensory relay, thalamus mediates motor information from the basal ganglia and the cerebellum to the cerebral cortex. Furthermore, certain thalamic nuclei, such as the pulvinar, receive information from the cortex and relay it back to the cortex thereby distributing cortical information from one area to another.

Clinical neurologists proposed as early as over a century ago that the thalamus plays an important role in the processing of pain (Head & Holmes, 1911). This proposal is in line with the anatomy of the pain-related pathways. Nociceptive signals originating in the periphery can ascend from the spinal cord to the thalamus directly through the spinothalamic tract, or indirectly through various pathways that include the spinoreticular tract, spinomesencephalic tract, and the postsynaptic dorsal column pathway (Todd, 2010). Morphological studies focusing on the spinal cord showed that the fibers originating in the superficial layer (laminae I-II) neurons mainly project to the mediodorsal (MD) nucleus, ventral posterior (VP) nucleus, and the posterior (PO) nucleus in the thalamus (Dostrovsky & Craig, 2009). The fibers originating in spinal layer I neurons of primates project also to the ventromedial (VM) nucleus of the thalamus, a nucleus in which neurons are selectively activated by noxious or thermal (cold) stimulation (Craig et al., 1994). The ascending fibers of the neurons in the deep layers of the DH of the spinal cord (laminae V-VII) mainly project to the intralaminar region, such as the central lateral (CL) and paracentral nucleus (PC) in the thalamus (Carstens & Trevino, 1978; Gauriau & Bernard, 2004).

Among prominent features of the thalamus is that it has complex connections with the cerebral cortex. Anatomical studies have shown that there are dense reciprocal fiber connections between the VP nucleus of the thalamus and the cortical region considered important for the sensory-discriminative aspects of pain, the S1/S2 cortex (Liao &Yen, 2008; Liao et al., 2010). While ascending connections from the VP nucleus mediate somatic signals to the S1/S2 cortex, the descending cortical connections predominantly facilitate neuronal discharge in the thalamus (Yuan et al., 1986). The fibers of the thalamic MD nuclei mainly project to the anterior cingulate cortex (ACC), a region associated with pain affect, whereas information from the thalamic VM nucleus projects to the insular cortex, another region associated with pain affect (Treede et al., 1999). Additionally, thalamic intralaminar nuclei have connections with the cingulate cortex, the limbic cortex, the orbital cortex, and the insular cortex, which are brain areas that all have been related to the perception of affective aspects of pain (Coghill et al., 1994; Rainville et al., 1997).

2.2 Thalamus: function as ‘discriminator’ in control of nociception

In the ventral posterolateral nucleus (VPL) of the thalamus, there are neurons that have firm receptive fields and that are capable of encoding information evoked by noxious stimuli at different intensities applied not only to a somatic area, but also to a visceral area (such as intraperitoneal injection of bradykinin or the dilatation of the uterus) (Guilbaud et al., 1980; Berkley et al., 1993). Peripheral nociceptive stimuli can also cause excitement of other thalamic nuclei, such as the intralaminar nuclei, submedius (SM) nucleus, the PO nucleus, and the VM nucleus (Peschanski et al., 1981; Miletic & Coffield, 1989; Apkarian & Shi, 1994; Bester et al., 1999; Monconduit et al., 2003). In contrast to the excitation of nociceptive thalamic neurons in the VPL that is considered to play an important role in relaying pain-related sensory-discriminative information to the cortex, noxious stimulation inhibits neurons in the thalamic reticular nucleus (Yen & Shaw, 2003). This finding is in line with evidence that the thalamic reticular nucleus has projections to the thalamic VPL and the ventral basal nucleus group, and with the proposal that the thalamic reticular nucleus plays a role in gating of transthalamic information flow (Takata, 2020).

Electrophysiological recordings in patients with stroke- or spinal cord injury-induced chronic pain indicate that the functional properties of thalamic neurons exhibit plastic changes in pathophysiological conditions (Anderson et al., 2006). In patients with limb amputation, the thalamic representation of the missing limb remains functional and its stimulation can produce phantom limb pain in the affected limb (Davis et al., 1998). Animal studies in rats exposed to peripheral nerve injury or hind limb inflammatory nociception showed that the ventral basal nucleus of the thalamus, including the VPL and VPM nuclei, exhibits significantly decreased neuronal excitation thresholds (Guilbaud et al., 1986, 1990). In line with this, increased spontaneous firing and increased responses to noxious stimulation were reported in the mediodorsal (MD) thalamic neurons in animals with chronic pain induced by spinal cord injury (Whitt et al., 2013).

As mentioned above, the model of bilateral secondary hyper-/hypoalgesia model induced by unilateral muscle nociception was used in a series of studies assessing the role of specific thalamic nuclei in discrimination and descending control of nociception (You et al., 2010). Pain sensitivity in the secondary hyper-/hypoalgesia areas was assessed following electrolytic lesions or activations and inhibitions of the studied thalamic nuclei by microinjections of drugs. After screening each nucleus in the thalamus, the MD nucleus and VM nucleus of the thalamus were found to be mechanical and thermal 'nociceptive discriminators' in precisely distinguishing the incoming noxious information *per se*, and in turn generating the descending facilitatory and inhibitory activities, respectively (You et al., 2013, 2014, 2016; Lei & You et al., 2013; Lei et al., 2015, 2017, 2020a,b) (Table 1). This finding is consistent with earlier evidence indicating that descending pathways have facilitatory as well as inhibitory effects on nociception (Urban & Gebhart, 1999). Moreover, the finding further extends and supports the hypothesis that specific thalamic nuclei are involved in activating descending facilitatory and inhibitory circuits that have a major contribution to secondary (or mirror) mechanical hyperalgesia and secondary heat hypoalgesia. As summarized in table 1, neither the thalamic MD nucleus-driven descending facilitation nor the thalamic VM nucleus-driven descending inhibition is continuously active during a physiological state. This is indicated by the finding that lesions of the thalamic MD or VM nuclei had no influence on baseline nociception in uninjured animals (You et al., 2013). Instead, activation of these descending controls needs to be triggered and initiated by a C-afferent volley that requires spatial and temporal summation to reach the triggering threshold. Importantly, the triggering thresholds for the activation of the facilitatory MD versus inhibitory VM nucleus are distinctly different: the activation threshold of facilitation is low and that of inhibition is high.

There is accumulating clinical and experimental evidence indicating that pain may vary with sex; in general, females are more sensitive to noxious stimuli than males (Berkley, 1997; Mogil, 2020). Interestingly, the intensity of peripheral conditioning stimulation needed to recruit descending pain modulatory pathways varies with sex. Female rats have a lower triggering threshold for recruiting descending facilitation than male rats, whereas the triggering threshold for recruiting descending inhibition is, in contrast, significantly higher in female than male rats (Lei et al., 2011) (Table 1). This finding suggests that among mechanisms contributing to higher pain sensitivity in females are sex-related differences in the descending pain control circuitries triggered by peripheral stimulation and presumably looping through the thalamus.

When assessing centrally-mediated changes in pain sensitivity in various pathophysiological conditions, it should be noted that the assessment of descending inhibition using mechanical test stimuli or descending facilitation using thermal test stimuli may be associated with a potential bias and thus give rise to incorrect interpretations. This because there is experimental evidence indicating that an injury discharge recruiting descending pain controls leads to descending facilitation of mechanical nociception through a relay in the thalamic MD nucleus accompanied by descending inhibition of heat nociception through a relay in the thalamic VM nucleus (You et al., 2013). Thereby, studies assessing changes in descending pain controls may miss changes in descending inhibition if only mechanical test stimuli are used, whereas changes in descending facilitation may be missed if only heat stimuli are used for assessing pain sensitivity.

Based on earlier neuroanatomical findings on projections of thalamic nuclei (Dostrovsky & Craig, 2009) and a series of studies using FOS expression to assess neuronal activation in various areas of the cortex, brainstem and spinal cord following exposure to noxious mechanical or heat stimulation with and without recruitment of descending controls by conditioning stimulation (Chen et al., 2013; Lei & You, 2013; Lei et al., 2014, 2015; Xiao et al., 2015), it was hypothesized that two neural circuits are specifically involved in discrimination and modulation of spinally-organized nociception evoked by noxious mechanical and heat stimuli. 'Thalamic MD nucleus – cingulate cortex – dorsolateral (dl) PAG/dorsal column – superficial layer (Laminae I-II) of DH of the spinal cord'-circuit monitors mechanical nociception and exerts a descending facilitatory effect on mechanical nociception. In contrast, ‘thalamic VM nucleus – insular cortex – ventrolateral (vl) PAG – dorsal lateral funiculus (DLF) – deep layer (Laminae IV-VI) of DH of spinal cord’-circuit, is activated by innocuous and noxious heat, and it exerts a descending inhibitory effect on thermal nociception (Figure 1). Of particular interest is the finding that the descending inhibitory effect mediated by the thalamic VM nucleus can be initiated by both noxious and innocuous heat stimuli, i.e. by heat stimuli applied at the temperature of 46°C and 43°C, respectively (You et al., 2014). Due to the existence of polymodal mechanoheat-sensitive nociceptors (Besson & Chaouch, 1987), 46°C noxious heat stimuli can also trigger and initiate the mechanical nociception-detecting circuit that involves the thalamic MD nucleus and that drives a descending facilitatory effect on mechanical nociception (You et al., 2014). The thalamic MD and VM nuclei act as thalamic ‘nociceptive discriminators’ and they are involved in two distinct neural circuits constituting an endogenous dual regulatory pathway of pain and nociception that either facilitates responses to nociceptive mechanical stimulation-induced or inhibits those to thermal stimulation.

With respect to the role of other thalamic nuclei in descending control of pain, it has been reported that the nucleus submedius (SM), the neurons of which respond predominantly to noxious stimuli (Kawakita et al., 1993), may contribute to descending inhibition of nociception. This is suggested by the findings that the heat-evoked spinal withdrawal reflex was suppressed by SM microinjection of a cannabinoid agonist (Martin et al., 1999) and that electrical stimulation of some parts of the SM nucleus suppressed responses of nociceptive neurons in the spinal cord, although in most parts of the SM nucleus electrical stimulation had no effect on spinal nociception (Okada et al., 1999). Lesion of the SM nucleus had no influence on either baseline nociception or 5.8% saline intramuscularly induced mechanical hyperalgesia and heat hypoalgesia, indicating that the SM nucleus is probably not involved in descending modulation (You et al., 2013). Habenula that is located in the posterior-medial part of the thalamus has also been shown to play a role in processing and modulation of pain (Shelton et al., 2012). Electrical stimulation of the habenula induced descending antinociceptive action (Mahieux and Benabid, 1987). The antinociceptive effect of the habenula is not tonic as shown by the finding that lesions of the habenula had no effect on baseline pain behavior (Cohen and Melzack, 1993).

2.3 Spatiotemporal characteristics of thalamus-organized endogenous descending modulation

In contrast to tonic control of homeostasis, such as observed with control of proprioception and the sympathetic nervous system ‘at rest’ (Guyton & Hall, 2006), an important feature of the endogenous modulation of pain governed by the thalamic MD and VM nuclei is its inactivity or relative ‘silence’ during physiological state and during exposure to an insufficient magnitude of afferent barrage in nociceptive nerve fibers (You et al., 2010, 2013, 2014, 2016). This thalamus induced descending modulation can be triggered and initiated by an afferent barrage of primary afferent C-fibers that is associated with central temporal and spatial summation needed to reach the thalamic triggering threshold (Table 1). While the descending pain control circuits involving thalamic MD or VM nuclei have shown no tonic influence under physiological conditions, some earlier studies assessing the effects of non-selective spinal blocks (such as spinal transections or cold blocks of the spinal cord) have reported about tonic descending modulation of pain (Duggan & Morton, 1988; Ossipov & Porreca, 2006). Among potential explanations for this apparent discrepancy is that in most of the earlier studies reporting about tonic descending inhibition, preparation of the animals required major surgery (such as laminectomy) that *per se* is likely to have induced a significant injury discharge that may have induced a tonic activation of descending controls.

Another important characteristic of the mechanical and thermal 'nociceptive discriminator' of the thalamic MD/VM nuclei in the control of pain is that the triggering thresholds of descending facilitation and inhibition differ significantly (Table 1). The triggering threshold of facilitation is in intact animals lower, whereas the threshold for descending inhibition is significantly higher (panel 'a' in figure 2) (You et al., 2010, 2013; Lei et al., 2011; Lei & You, 2013). Under the pathophysiological state, however, there can be several changes in the endogenous descending facilitation and inhibition of pain. During special conditions (such as simulated weightlessness, formalin or CFA induced inflammatory conditions, and Parkinson's model), endogenous descending facilitation triggered by conditioning stimulation can be significantly enhanced and inhibition weakened when compared with corresponding pain modulatory effects in intact animals. These pronociceptive variations are related to the enhanced and decreased activities of thalamic MD and VM nuclei, respectively (Lei et al., 2015, 2020a,b; Lei & You, 2013) (panel 'b' in figure 2). Likewise, some pharmacolological treatments may have pronociceptive effects on descending pain modulatory circuits involving the thalamic MD and VM nuclei. Exposure to ⍰-opioid receptor treatment induced a state (mimicking antinociceptive opioid tolerance) that was associated with a decrease of the triggering threshold of descending facilitation and an increase of the triggering threshold of descending facilitation. (You et al., 2016) (panel 'b' in figure 2)

Of potential significance for clinical treatment of pain is that non-painful thermal stimulation can selectively activate the descending inhibition mediated by the thalamic VM nucleus, without triggering descending facilitation, and it can even reduce the triggering threshold of descending inhibition (You et al., 2014) ((I) in panel 'c' of figure 2). This phenomenon provides a potential mechanistic explanation for pain suppression by a traditional Chinese treatment method 'moxibustion'. Interestingly, some pharmacological treatments may promote antinociceptive effects of the descending pain modulatory pathways. For example, treatment with dexmedetomidine, a highly-selective ⍰2-adrenoceptor agonist, significantly increased the triggering threshold of descending facilitation and decreased the triggering threshold of descending inhibition so that the threshold of descending inhibition was lower than that of descending facilitation ((II) in panel 'c' of figure 2) (You et al., 2016). In some cases, the triggering threshold of descending facilitation is above the physiological range observed in intact animals, due to which the descending facilitation of mechanical nociception is not easily triggered by noxious conditioning stimulation, such as i.m. administration of 5.8% saline that in intact animals is an effective trigger (You et al., 2016). The above described pharmacological interference provides new insights into the organization of descending pain control circuitries related to the thalamic MD/VM nuclei that may have relevance to pre-emptive analgesic treatment strategies of postoperative pain.

3. Neurotransmitters in the thalamus-organized descending modulation of pain.

Neurotransmitters involved in the thalamic MD nucleus and VM nucleus organized descending control of spinal nociception are summarized in figure 3.

3.1 Opioid receptors

Opioids are among the most important endogenous substances involved in regulation of nociceptive signals from the periphery to the central targeting site. Activation of opioid receptors exerts analgesic effects at multiple levels of the neuraxis, including peripheral and spinal cord levels (Millan, 1986). However, effects of opioid receptors, particularly those of the μ-opioid receptor, can be complicated (Ossipov et al., 2004; Schrepf et al., 2016). For example, long-term use of μ-opioid receptor agonists (such as morphine or fentanyl) will cause analgesia that is later followed by analgesic opioid tolerance and hyperalgesia (Colpaert, 1996).

Effects of opioid receptors on pain processing and modulation have been studied only little in the thalamus when compared with the extensive number of studies focusing e.g. on the spinal cord or midbrain. Concerning opioid receptor effects on thalamic mechanisms of descending pain modulation, a recent study provided evidence that opioids play distinct roles in descending inhibition evoked by different temperatures of conditioning heating-needle stimulation; microinjections of opioidergic compounds into the thalamic VM nucleus revealed that μ-, δ-, and κ-opioid receptors participate in descending inhibition evoked by 46°C heating-needle stimulation, whereas only μ-opioid receptor is involved in the 43°C stimulation induced inhibition (You et al., 2014). Concerning descending facilitation, microinjections of opioidergic compounds into the thalamic MD nucleus revealed that μ-opioid receptor is involved in the 46°C heating-needle stimulation induced descending facilitation (You et al., 2014). It remains to be studied whether some of these opioid receptor evoked effects in the thalamus might have a role in opioid-induced tolerance, addiction or ‘analgesia-hyperalgesia’ phenomena induced by administration of opioids (Colpaert, 1996). Other studies have shown decreased expression of δ-opioid receptor mRNA in thalamic nuclei during the development of chronic inflammatory pain and neuropathic pain (Neto et al., 2008; Rojewska et al., 2018). Taken together, these findings are in line with the hypothesis that δ-opioid receptor might be a promising target for effective treatment of pain, in particular that of intractable pathological pain.

3.2 Dopamine and dopaminergic receptors

Dopamine (DA) is a monoaminergic neurotransmitter that is involved in multiple functions, including processing of pain-related signals (Girault & Greengard, 2004).

There is accumulating experimental evidence showing that the dopaminergic system regulates pain and nociception due to action on various central structures including the insular cortex, basal ganglia, limbic areas, thalamus, periaqueductal gray, and spinal cord (Chudler & Dong, 1995; Burkey et al., 1999; Wood, 2008). It has been reported that D1 receptor agonists may induce pain facilitation (Aira et al., 2016). In contrast, D2 or D2/D3 receptors in the brain are hypothesized to be involved in pain inhibition according to both human and animal studies (Martikainen et al., 2018).

It has been recently demonstrated that i.m. heating needle stimulation at the innocuous temperature of 43°C enhanced the strength of descending inhibition that was weakened by a rat model of Parkinson' disease (Lei et al., 2020b). Striatal administration of 5 µg of dopamine failed to reverse the PD-associated increase in descending facilitation or the decrease in descending inhibition, whereas administration of dopamine into the thalamic MD nucleus and VM nucleus significantly decreased the increase in descending facilitation and reversed the attenuation in descending inhibition in a dopamine D2 receptor antagonist-reversible fashion (Lei et al., 2020b). From clinical perspective, the 43 °C heat therapeutic regime, i.e. i.m. innocuous heating-needle stimulation or moxibustion, rather than simple supplement of dopamine, provides an effective non-pharmacological alternative to attenuate pain in PD by selective enhancement of descending pain inhibition that was accompanied by improvement of motor dysfunction at an early stage of PD (Lei et al., 2020b).

3.3 5-HT and noradrenaline

Numerous studies suggest that serotonergic receptors play bi-directional roles in descending control on pain (Millan, 2002). For example, it has been shown that 5-HT$_{1A}$ and 5-HT$_7$ receptors in the parafascicular nucleus of the medial thalamus suppress affective pain behavior (Harte et al., 2005), while spinal 5-HT$_3$ and 5-HT$_7$ receptors play roles in descending pain facilitation and inhibition, respectively (Dogrul et al., 2009). Complexity of the serotonergic system in pain control is shown by the finding that spinally administration of a 5-HT1A receptor agonist induced a pain facilitatory effect that was later followed by analgesia (Colpaert et al., 2002; You et al., 2005).

Serotonergic mechanisms are involved in a sex-dependent fashion in the descending inhibitory circuit that presumably involves the thalamic VM nucleus. This is indicated by the finding a chemical lesion of the serotonergic pathways resulted in attenuation of the noxious conditioning stimulation induced secondary heat hypoalgesia only in male but not female animals (Lei et al., 2011). Chemical lesion of the noradrenergic system also attenuated secondary heat hyposensitivity induced by noxious conditioning stimulation indicating that noradrenergic pathways contribute to the descending inhibitory effect (Lei et al., 2011). Interestingly, the role of the noradrenergic system, unlike that of the serotonergic system, did not vary with sex, since the noradrenergic lesion attenuated descending inhibition in females as well as males (Lei et al., 2011).

3.4 ATP and purinergic P2X3 receptors

Administration of ATP in the periphery or the spinal cord has been reported to induce nociception through action on its purinergic P2X3 receptor (Burnstock, 2018), whereas supraspinally P2X3 receptor may induce antinociception (Fukui et al., 2006). A recent study showed that microinjection of a P2X3 receptor antagonist into the thalamic VM nucleus attenuated in a dose-dependent fashion innocuous conditioning stimulation induced secondary heat hypoalgesia, while microinjection of the P2X3 receptor antagonist into the thalamic MD nucleus attenuated noxious conditioning stimulation induced secondary mechanical hypersensitivity (Lei et al., 2020a). These findings indicate that the thalamic P2X3 receptor has a bidirectional role in descending pain controls that varies with thalamic subnucleus from nociception-promoting role in the MD nucleus to antinociception-promoting role in the VM nucleus.

4. Conclusion

Plastic changes in bottom-up mechanisms may not alone explain some important characteristics of clinical pain conditions, such as secondary (centrally mediated) pain sensitivity changes; i.e., hyperalgesia or hypoalgesia outside of the injury area. Instead, top-down mechanisms that include descending facilitation and descending inhibition provide plausible explanations for secondary hyperalgesia and hypoalgesia, respectively. A series of experimental studies has shown that one distinct circuitry contributing to secondary hyperalgesia and hypoalgesia consists of the ascending transmission pathway to the thalamic MD and VM nuclei that together function as a 'nociceptive discriminator'. This thalamic discriminator accurately distinguishes different types of nociceptive information and even innocuous heat, and it triggers, through a loop involving the cortex and the midbrain, activation of descending pathways that underlies secondary pain sensitivity changes. Thalamic MD nucleus of the 'nociceptive discriminator' is involved in distinguishing ascending signals evoked by noxious mechanical stimulation and in triggering a descending facilitatory pathway that induces secondary mechanical hyperalgesia, without accompanying heat hypersensitivity. Thalamic VM nucleus of the 'nociceptive discriminator' is involved in distinguishing ascending signals evoked by innocuous and noxious heat and in triggering a descending inhibitory pathway that induces secondary heat hypoalgesia.

Treatments that attenuate the descending facilitatory effect mediated by the thalamic MD nucleus and/or enhance the descending inhibitory effect mediated by the thalamic VM nucleus may bring useful treatment regimes against some pathological pain conditions, such as that following surgery or associated with PD.

Conflict of interest statement

The authors declare no personal or financial conflicts of interest.

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References

Aira, Z., Barrenetxea, T., Buesa, I., Martínez, E., Azkue, J.J., 2016. Spinal D1-like dopamine receptors modulate NMDA receptor-induced hyperexcitability and NR1 subunit phosphorylation at serine 889. Neurosci. Lett. 618, 152-158.

Anderson, W.S., O'Hara, S., Lawson, H.C., Treede, R.D., Lenz, F.A., 2006. Plasticity of pain-related neuronal activity in the human thalamus. Prog. Brain Res. 157, 353-364.

Apkarian, A.V., Shi, T., 1994. Squirrel monkey lateral thalamus.I. Somatic nociresponsive neurons and their relation to spinothalamic terminals. J. Neurosci. 14, 6779-6795.

Berkley, K.J., 1997. Sex differences in pain. Behav. Brain Sci. 20, 371-380.

Berkley, K.J., Guilbaud, G., Benoist, J.M., Gautron, M., 1993. Responses of neurons in and near the thalamic ventrobasal complex of the rat to stimulation of uterus, cervix, vagina, colon, and skin. J. Neurophysiol. 69, 557-568.

Besson, J.M., Chaouch, A., 1987. Peripheral and spinal mechanisms of nociception. Physiol. Rev. 67, 67-186.

Bester, H., Bourgeais, L., Villanueva, L., Besson, J.M., Bernard, J.F., 1999. Differential projections to the intralaminar and gustatory thalamus from the parabrachial area: a PHA-L study in the rat. J. Comp. Neurol. 405, 421-449.

Borghi, B., Addabbo, M., Borghi, R., 2014. Can neural blocks prevent phantom limb pain? Pain Manag. 4, 261-266.

Burkey, A.R., Carstens, E., Jasmin, L., 1999. Dopamine reuptake inhibition in the rostral agranular insular cortex produces antinociception. J. Neurosci. 19, 4169-4179.

Burnstock, G., 2018. The therapeutic potential of purinergic signalling. Biochem. Pharmacol. 151, 157-165.

Campbell, J.N., 2016. The fifth vital sign revisited. Pain 157, 3-4.

Carstens, E., Trevino, D.L., 1978. Laminar origins of spinothalamic projections in the cat as determined by the retrograde transport of horseradish peroxidase. J. Comp. Neurol. 182, 161-165.

Cervero, F., Wolstencroft, J.H., 1984. A positive feedback loop between spinal cord nociceptive pathways and antinociceptive areas of the cat's brain stem. Pain 20, 125-138.

Cervero, F., Lumb, B.M., Tattersall, J.E., 1985. Supraspinal loops that mediate visceral inputs to thoracic spinal cord neurones in the cat: involvement of descending pathways from raphe and reticular formation. Neurosci. Lett. 56, 189-194.

Chen, Y.K., Lei, J., Jin, L., Tan, Y.X., You, H.J., 2013. Dynamic variations of c-Fos expression in the spinal cord exposed to intramuscular hypertonic saline induced muscle nociception. Eur. J. Pain 17, 336-346.

Chudler, E.H., Dong, W.K., 1995. The role of the basal ganglia in nociception and pain. Pain 60, 3-38.

Coderre, T.J., Laferrière, A., 2020. The emergence of animal models of chronic pain and logistical and methodological issues concerning their use. J. Neural. Transm. (Vienna) 127, 393-406.

Coghill, R.C., Talbot, J.D., Evans, A.C., Meyer, E., Gjedde, A., Bushnell, M.C., Duncan, G.H., 1994. Distributed processing of pain and vibration by the human brain. J. Neurosci. 14, 4095-4108.

Cohen, S.R., Melzack, R., 1993. The habenula and pain: repeated electrical stimulation produces prolonged analgesia but lesions have no effect on formalin pain or morphine analgesia. Behav. Brain Res. 54, 171-178

Colpaert, F.C., 1996. System theory of pain and of opiate analgesia: no tolerance to opiates. Pharmacol. Rev. 48, 355-402.

Colpaert, F.C., Tarayre, J.P., Koek, W., Pauwels, P.J., Bardin, L., Xu, X.J., Wiesenfeld-Hallin, Z., Cosi, C., Carilla-Durand, E., Assié, M.B., Vacher, B., 2002. Large-amplitude 5-HT1A receptor activation: a new mechanism of profound, central analgesia. Neuropharmacology 43, 945-958.

Craig, A.D., Bushnell, M.C., Zhang, E.T., Blomqvist, A., 1994. A thalamic nucleus specific for pain and temperature sensation. Nature 372, 770-773.

Davis, K.D., Kiss, Z.H., Luo, L., Tasker, R.R., Lozano, A.M., Dostrovsky, J.O., 1998. Phantom sensations generated by thalamic microstimulation. Nature 391, 385-387.

Descartes, R., 1972. Seventeenth Century - Treatise of Man. Trans. by Thomas Steele Hall. Foreword by I. Bernard Cohen. Cambridge, Mass.: Harvard University Press, and London: Oxford University Press.

Dogrul, A., Ossipov, M.H., Porreca, F., 2009. Differential mediation of descending pain facilitation and inhibition by spinal 5HT-3 and 5HT-7 receptors. Brain Res. 1280, 52-59.

Dostrovsky, J.O., Craig, A.D., 2009. The thalamus and nociceptive processing. In: Basbaum AI, Bushnell MC, editors. Science of pain. San Diego: Academic Press. p. 635-654.

Duggan, A.W., Morton, C.R., 1988. Tonic descending inhibition and spinal nociceptive transmission. Prog. Brain Res. 77, 193-211.

Fernandes, E.C., Pechincha, C., Luz, L.L., Kokai, E., Szucs, P., Safronov, B.V., 2020. Primary afferent-driven presynaptic inhibition of C-fiber inputs to spinal lamina I neurons. Prog. Neurobiol. 188, 101786.

Franz, D.N., Iggo, A., 1968. Dorsal root potentials and ventral root reflexes evoked by nonmyelinated fibers. Science 162, 1140-1142.

Fukui, M., Nakagawa, T., Minami, M., Satoh, M., Kaneko, S., 2006. Inhibitory role of supraspinal P2X3/P2X2/3 subtypes on nociception in rats. Mol. Pain 2, 19.

Gauriau, C., Bernard, J.F., 2004. A comparative reappraisal of projections from the superficial laminae of the dorsal horn in the rats: the forebrain. J. Comp. Neurol. 468, 24-56.

Girault, J.A., Greengard, P., 2004. The neurobiology of dopamine signaling. Arch Neurol. 61, 641-644.

Goldscheider, A., 1894. Über den Schmerz: Physiogischer und Klinischer Hinsicht. Berlin: Hirschwald.

Guilbaud, G., Peschanski, M., Gautron, M., Binder, D., 1980. Neurones responding to noxious stimulation in VB complex and caudal adjacent regions in the thalamus of the rat. Pain 8, 303-318.

Guilbaud, G., Kayser, V., Benoist, J.M., Gautron, M., 1986. Modifications in the responsiveness of rat ventrobasal thalamic neurons at different stages of carrageen in produced inflammation. Brain Res. 385, 86-98.

Guilbaud, G., Benoist, J.M., Jazat, F., Gautron, M., 1990. Neuronal responsiveness in the ventrobasal thalamic complex of rats with an experimental peripheral mononeuropathy. J. Neurophysiol. 64, 1537-1554.

Guyton, A.C., Hall, J.E., 2006. Textbook of Medical Physiology. 11th edn, Elsevier Inc. ISBN: 0-7216-0240-1, Philadelphia.

Hagbarth, K.E., Kerr, D.I., 1954. Central influences on spinal afferent conduction. J. Neurophysiol. 17, 295-307.

Halassa, M.M., Kastner, S., 2017. Thalamic functions in distributed cognitive control. Nat Neurosci. 20, 1669-1679.

Hardy, J.D., Wolff, H.G., Goodel, H., 1952. Pain Sensations and Reactions. The Williams and Wilkins Company, Baltimore, MD.

Harte, S.E., Kender, R.G., Borszcz, G.S., 2005. Activation of 5-HT1A and 5-HT7 receptors in the parafascicular nucleus suppresses the affective reaction of rats to noxious stimulation. Pain 113, 405-415.

Head, H., Holmes, G., 1911. Sensory disturbances from cerebral lesions. Brain 34, 102-254.

Heinricher, M.M., Tavares, I., Leith, J.L., Lumb, B.M., 2009. Descending control of nociception: Specificity, recruitment and plasticity. Brain Res. Rev. 60, 214-225.

Kawakita, K., Dostrovsky, J.O., Tang, J.S., Chiang, C.Y., 1993. Responses of neurons in the rat thalamic nucleus submedius to cutaneous muscle and visceral nociceptive stimuli. Pain 55, 327-338.

Laird, J.M., Cervero, F., 1990. Tonic descending influences on receptive-field properties of nociceptive dorsal horn neurons in sacral spinal cord of rat. J. Neurophysiol. 63, 1022-1032.

Lei, J., You, H.J., 2013. Endogenous descending facilitation and inhibition differ in control of formalin intramuscularly induced persistent muscle nociception. Exp. Neurol. 248, 100-111.

Lei, J., Jin, L., Zhao, Y., Sui, M.Y., Huang, L., Tan, Y.X., Chen, Y.K., You, H.J., 2011. Sex-related differences in descending norepinephrine and serotonin controls of spinal withdrawal reflex during intramuscular saline induced muscle nociception in rats. Exp. Neurol. 228, 206-214.

Lei, J., Pertovaara, A., You, H.J., 2015. Effect of simulated weightlessness on intramuscular hypertonic saline induced muscle pain and spinal Fos expression in rats. Brain Res. 1594, 204-214.

Lei. J., Sun, T., Lumb, B.M., You, H.J., 2014. Roles of the periaqueductal gray in descending facilitatory and inhibitory controls of intramuscular hypertonic saline induced muscle nociception. Exp. Neurol. 257, 88-94.

Lei, J., Ye, G., Wu, J.T., Pertovaara, A., You HJ., 2017. Role of capsaicin- and heat-sensitive afferents in stimulation of acupoint-induced pain and analgesia in humans. Neuroscience 358, 325-335.

Lei, J., Ye, G., Pertovaara, A., You, H.J., 2020a. Effects of intramuscular heating-needle stimulation in controlling adjuvant-induced muscle nociception in rats: differential roles of thalamic purinergic P2X3 receptors. Neuroscience 433, 81-93.

Lei, J., Ye, G., Pertovaara, A., You, H.J., 2020b. Effects of heating-needle stimulation in restoration of weakened descending inhibition of nociception in a rat model of Parkinson's disease. Neuroscience 440, 249-266.

Lewis, T., 1936. Experiments relating to cutaneous hyperalgesia and its spread through somatic nerves. Clin, Sci, 2, 373-423.

Lumb, B.M., 2002. Inescapable and escapable pain is represented in distinct hypothalamic-midbrain circuits: specific roles for A□- and C-nociceptors. Exp. Physiol. 87, 281-286.

Liao, C.C., Yen, C.T., 2008. Functional connectivity of the secondary somatosensory cortex of the rat. Anat. Rec. 291, 960-973.

Liao, C.C., Chen, R.F., Lai, W.S., Lin, R.C., Yen, C.T., 2010. Distribution of large terminal inputs from the primary and secondary somatosensory cortices to the dorsal thalamus in the rodent. J. Comp. Neurol. 518, 2592-2611.

Mahieux, G., Benabid, A.L., 1987. Naloxone-reversible analgesia induced by electrical stimulation of the habenula in the rat. Brain Res. 406, 118-129.

Martikainen, I.K., Hagelberg, N., Jääskeläinen, S.K., Hietala, J., Pertovaara, A., 2018. Dopaminergic and serotonergic mechanisms in the modulation of pain: In vivo studies in human brain. Eur. J. Pharmacol. 834, 337-345.

Martin, W.J., Coffin, P.O., Attias, E., Balinsky, M., Tsou, K., Walker, J.M., 1999. Anatomical basis for cannabinoid-induced antinociception as revealed by intracerebral microinjections. Brain Res. 822, 237-242.

McGaraughty, S., Chu, K.L., Bitner, R.S., Martino, B., El Kouhen, R., Han, P., Nikkel, A.L., Burgard, E.C., Faltynek, C.R., Jarvis, M.F., 2003. Capsaicin infused into the PAG affects rat tail flick responses to noxious heat and alters neuronal firing in the RVM. J. Neurophysiol. 90, 2702-2710.

Melzack, R., Wall, P.D., 1965. Pain mechanisms: A new theory, Science 150, 971-979.

Mendell, L.M., 1966. Physiological properties of non-myelinated fibre projection to the spinal cord. Exp. Neurol. 16, 316–332.

Mendell, L.M., 1970. Positive dorsal root potentials produced by stimulation of small diameter muscle afferents. Brain Res. 18, 375-379.

Miletic, V., Coffield, J.A., 1989. Responses of neurons in the at nucleus submedius to noxious and innocuous echanical cutaneous stimulation. Somatosens. Mot. Res. 6, 567-587.

Millan, M.J., 1986. Multiple opioid systems and pain. Pain 27, 303-349.

Millan, M.J., 1999. The induction of pain: an integrative review. Prog Neurobiol 57, 1-164.

Millan, M.J., 2002. Descending control of pain. Prog. Neurobiol. 66, 355-474.

Mogil, J.S., 2020., Qualitative sex differences in pain processing: emerging evidence of a biased literature. Nat. Rev. Neurosci. 21, 353-365.

Monconduit, L., Bourgeais, L., Bernard, J.F., Villanueva, L., 2003. Convergence of cutaneous, muscular and visceral noxious inputs onto ventromedial thalamic neurons in the rat. Pain 103, 83-91.

Nafe, J.P., 1929. Quantitative theory of feeling. J. Gen. Psychol. 2, 199-210.

Okada, K., Murase, K., Kawakita, K., 1999. Effects of electrical stimulation of thalamic nucleus submedius and periaqueductal gray on the visceral nociceptive responses of spinal dorsal horn neurons in the rat. Brain Res. 834, 112-121.

Olausson, H., Wessberg, J., Morrison, I., McGlone, F., Vallbo, A., 2010. The neurophysiology of unmyelinated tactile afferents. Neurosci. Biobehav. Rev. 34, 185-191.

Ossipov, M.H., Lai, J., King, T., Vanderah, T.W., Malan, Jr., Hruby, V.J., Porreca, F., 2004. Antinociceptive and nociceptive actions of opioids. J. Neurobiol. 61, 126-148.

Ossipov, M.H., Porreca, F., 2006. Descending excitatory systems. Handb. Clin. Neurol. 81, 193-210.

Pertovaara, A., Almeida, A., 2006. Descending inhibitory systems. Handb. Clin. Neurol. 81, 179-192.

Peschanski, M., Guilbaud, G., Gautron, M., 1981. Posterior intralaminar region in rat: neuronal responses to noxious and nonnoxious cutaneous stimuli. Exp. Neurol. 72, 226-238.

Radhakrishnan, R., Sluka, K.A., 2005. Deep tissue afferents, but not cutaneous afferents, mediate transcutaneous electrical nerve stimulation-induced antihyperalgesia. J. Pain 6, 673-680.

Rainville, P., Duncan, G.H., Price, D.D., Carrier, B., Bushnell, M.C., 1997. Pain affect encoded in human anterior cingulated but not somatosensory cortex. Science 277, 968-971.

Raja, S.N., Carr, D.B., Cohen, M., Finnerup, N.B., Flor, H., Gibson, S., Keefe, F.J., Mogil, J.S., Ringkamp, M., Sluka, K.A., Song, X.J., Stevens, B., Sullivan, M.D., Tutelman, P.R., Ushida, T., Vader, K., 2020. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. Pain 161, 1976-1982.

Reynolds, D.V., 1969. Surgery in the rat during electrical analgesia induced by focal brain stimulation. Science 64, 444-445.

Santos, A.R., Calixto, J.B., 1997. Ruthenium red and capsazepine antinociceptive effect in formalin and capsaicin models of pain in mice. Neurosci. Lett. 235, 73-76.

Schmelz, M., Schmidt, R., Bickel, A., Handwerker, H.O., Torebjörk, H.E., 1997. Specific C-receptors for itch in human skin. J. Neurosci. 17, 8003-8008.

Schrepf, A., Harper, D.E., Harte, S.E., Wang, H., Ichesco, E., Hampson, JP, Zubieta, J.K., Clauw, D.J., Harris, R.E., 2016. Endogenous opioidergic dysregulation of pain in fibromyalgia: a PET and fMRI study. Pain 57, 2217-2225.

Shelton, L, Becerra, L, Borsook, D., 2012. Unmasking the mysteries of the habenula in pain and analgesia. Prog. Neurobiol. 96, 208-219.

Silva-Cardoso, G.K., Lazarini-Lopes, W., Hallak, J.E., Crippa, J.A., Zuardi, A.W., Garcia-Cairasco, N., Leite-Panissi, C.R.A., 2021. Cannabidiol effectively reverses mechanical and thermal allodynia, hyperalgesia, and anxious behaviors in a neuropathic pain model: Possible role of CB1 and TRPV1 receptors. Neuropharmacology 197, 108712.

Takata, N., 2020. Thalamic reticular nucleus in the thalamocortical loop. Neurosci. Res. 156, 32-40.

Tjølsen, A., Berge, O.G., Hole, K., 1991. Lesions of bulbo-spinal serotonergic or noradrenergic pathways reduce nociception as measured by the formalin test. Acta Physiol. Scand. 142, 229-236.

Todd, A.J., 2010. Neuronal circuitry for pain processing in the dorsal horn. Nat. Rev. Neurosci. 11, 823-836.

Treede, R.D., 2006. Pain and hyperalgesia: definitions and theories. Handb. Clin. Neurol. 81, 3-10.

Treede, R.D., Meyer, R.A., Raja, S.N., Campbell, J.N., 1992. Peripheral and central mechanisms of cutaneous hyperalgesia. Prog. Neurobiol. 38, 397-421.

Treede, R.D., Kenshalo, D.R., Gracely, R.H., Jones, A.K.P., 1999. The cortical representation of pain. Pain 79, 105-111.

Urban, M.O., Gebhart, G.F., 1999. Supraspinal contributions to hyperalgesia. Proc. Natl. Acad. Sci. USA. 96, 7687-7692.

Villanueva, L., Le Bars, D., 1995. The activation of bulbo-spinal controls by peripheral nociceptive inputs: diffuse noxious inhibitory controls. Biol. Res. 28, 113-125.

Von Frey, M., 1895. Beitrag zur Sinnesphysiologie der Haut. Ber. Verh Sachs. Acad Wisss. Leipzig Math, Phys. Kl 47, 166-184.

Wall, P.D., 1964. Presynaptic control of impulses at the first central synapse in the cutaneous pathway. Prog. Brain Res. 12, 92-118.

Whitt, J.L., Masri, R., Pulimmood, N.S., Keller, A., 2013. Pathological activity in mediodorsal thalamus of rats with spinal cord injury pain. J. Neurosci. 33, 3915-3926.

Wood, P.B., 2008. Role of central dopamine in pain and analgesia. Expert Rev. Neurother. 8, 781-797.

Woolf, C.J., 1983. Evidence for a central component of post-injury pain hypersensitivity. Nature 306, 686-688.

Xiao, Y., Lei, J., Ye, G., Xu, H., You, H.J., 2015. Role of thalamic nuclei in modulation of Fos expression within cerebral cortex during hypertonic saline induced muscle nociception. Neuroscience 304, 36-46.

Yuan, B., Morrow, T.J., Casey, K.L., 1986. Corticofugal influences of S1 cortex on ventrobasal thalamic neurons in the awake rat. J. Neurosci. 6, 3611-3617.

Yen, C.T., Shaw, F.Z., 2003. Reticular thalamic responses to nociceptive inputs in anesthetized rats. Brain Res. 968, 179-191.

You, H.J., Dahl Morch, C., Chen. J., Arendt-Nielsen, L.. 2003. Simultaneous recordings of wind-up of paired spinal dorsal horn nociceptive neuron and nociceptive flexion reflex in rats. Brain Res. 960, 235-245.

You, H.J., Colpaert, F.C., Arendt-Nielsen, L., 2005. The novel analgesic and high-efficacy 5-HT1A receptor agonist F 13640 inhibits nociceptive responses, wind-up, and after-discharges in spinal neurons and withdrawal reflexes. Exp. Neurol. 191, 174-183.

You, H.J., Lei, J., Sui, M.Y., Huang, L., Tan, Y.X., Tjølsen, A., Arendt-Nielsen, L., 2010. Endogenous descending modulation: spatiotemporal effect of dynamic imbalance between descending facilitation and inhibition of nociception. J. Physiol. 588, 4177-4188.

You, H.J., Lei, J., Niu, N., Yang, L., Fan, X.L., Tjølsen A, Li Q. 2013. Specific thalamic nuclei function as novel 'nociceptive discriminators' in the endogenous control of nociception in rats. Neuroscience 232, 53-63.

You, H.J., Lei, J., Ye, G., Fan, X.L., Li, Q., 2014. Influence of intramuscular heat stimulation on modulation of nociception: complex role of central opioid receptors in descending facilitation and inhibition. J. Physiol. 592, 4365-4380.

You, H.J., Lei, J., Xiao, Y., Ye, G., Sun, Z.H., Yang, L., Niu, N., 2016. Pre-emptive analgesia and its supraspinal mechanisms: enhanced descending inhibition and decreased descending facilitation by dexmedetomidine. J. Physiol. 594, 1875-1890.

Zhao, Z.Q., 2008. Neural mechanism underlying acupuncture analgesia. Prog. Neurobiol. 85, 355-375.

Zhu, L.X., Li, C.Y., Yang, B., Ji, C.F., Li, W.M., 1990. The effect of neonatal capsaicin on acupuncture analgesia. Acupunct. Res. 15, 285-291.

Zimmermann, M., 1968. Dorsal root potentials after C-fiber stimulation. Science 160, 896-898.

Legends to figures

Fig. 1. Schematic representation of thalamic mediodorsal (MD) and ventromedial (VM) nuclei organized discrimination system in monitoring ascending afferent information and in exerting different modulatory effects: facilitation and inhibition, *via* descending pathways, on spinally-organized nociception at different spinal layers in rats. For the purpose of illustration, the ascending pathways *via* thalamic MD and VM nuclei are shown on both sides of the drawing, whereas descending tracts from cerebral cortex are shown on the middle part of the diagram. Afferent signals from ascending pathways are discriminated by thalamic MD nucleus and VM nucleus, which are activated by noxious C-fibers (C1) and innocuous/noxious C-fibers (C1+C2) that project to cingulate cortex and insular cortex, respectively. As stated in the text, the descending pathways involved in the control of spinally-organized nociception terminate at different layers of the DH of the spinal cord *via* at least three pathways. The descending facilitation pathway terminates at the superficial layer (Laminae I-II), to which the effect is carried *via* either corticospinal tract (CST) - dorsal column (DF) pathway or *dl*PAG pathway. In contrast, the descending pathway showing inhibitory function terminates at the deep layer of spinal DH, to which the effect is carried *via vl*PAG-DLF (dorsal lateral funiculus) pathway. Note here that CST in rodents terminates in the DH, but not ventral horn, of the spinal cord. It is suggested that the function of corticospinal tract is more likely to control sensory rather than motor components of the response to peripheral stimulation in rats. (C1-afferents represent noxious information mediated by C fibers, whereas C2-afferents represent C-fiber mediated innocuous message evoked by innocuous stimuli, i.e. 43°C non-painful heat stimulation.)

Fig. 2. Conceptual diagram of variations of triggering thresholds of endogenous descending controls of nociception governed by the thalamic ‘nociceptive discriminator’: thalamic MD nucleus and VM nucleus, during the conditions of physiological pain (panel ‘**a**’), pathological pain or condition with ineffective pain treatment (panel ‘**b**’), and with effective pain treatment (panel ‘**c**’), i.e. 43°C non-painful heating stimulation or[illegible]-2 receptor agonist induced pre-emptive analgesia. In physiological conditions, endogenous descending facilitation has a low triggering threshold (red circle), whereas descending inhibition shows a high triggering threshold (green circle). These triggering thresholds of the thalamic ‘nociceptive discriminator’ controlling endogenous descending facilitation and inhibition are not solid, but exhibit plastic characteristics during pathological conditions and conditions associated with pharmacological interference. Opioid [illegible]-receptor agonist, i.e. fentanyl, decreases the triggering threshold of descending facilitation, and elevates the triggering threshold of descending inhibition (panel ‘**b**’). Effective pharmacological treatment can restore or regulate the abnormal triggering thresholds of descending modulation back to the normal range. For instance, non-painful, i.e. 43°C, heating stimulation can bypass the lower triggering thresholds of descending facilitation and decrease the threshold of descending inhibition that results in the possibility to initiate the descending inhibition alone, which

gives a promising avenue to control pain ((I) in panel ‘**c**’). In contrast to ‘analgesia-hyperalgesia’ effects of opioids, dexmedetomidine (Dex, 2-adrenoceptor agonist) reverses the triggering thresholds of descending modulations so that the triggering threshold of descending inhibition is lower that that of descending facilitation ((II) in panel ‘**c**’). In some cases, the triggering threshold of descending facilitation is elevated beyond the physiological range, due to which the descending facilitation is not easily triggered by noxious conditioning stimulation, such as insults from intamuscular 5.8% saline that is enough to trigger descending facilitation in healthy controls. (D.: descending) (Modified from You et al., 2016, with permission)

Fig. 3. Schematic drawing of the involvement of different neurotransmitter receptors in the thalamic MD and VM nuclei mediated endogenous modulation of nociception. As stated in the text, thalamic MD and VM nuclei discriminate between noxious mechanically and heat evoked activities, and then project the modulating information to the cingulate cortex and the insular cortex, respectively. From pharmacological perspective, the role of the opioid -receptor interestingly differs in the control of activities of thalamic MD and VM nuclei. Opioid -receptor participates in both the thalamic MD nucleus mediated facilitation and the thalamic VM nucleus modulated inhibition. An interesting analogy is that long-term use of opioids has bidirectional effects in the clinic varying from early analgesia to late hyperalgesia. Thalamic 5-HT1A receptor first exerts descending facilitatory effects through action on the thalamic MD nucleus followed by descending inhibitory effects through action on the thalamic VM nucleus. Note here, however, that some conclusions, i.e. role of TRPV1 (transient receptor potential vanilloid type 1) receptor, are from our unpublished experimental results. ‘+’ represents excitation; ‘-’ represents inhibition; ‘0’ represent no effects.

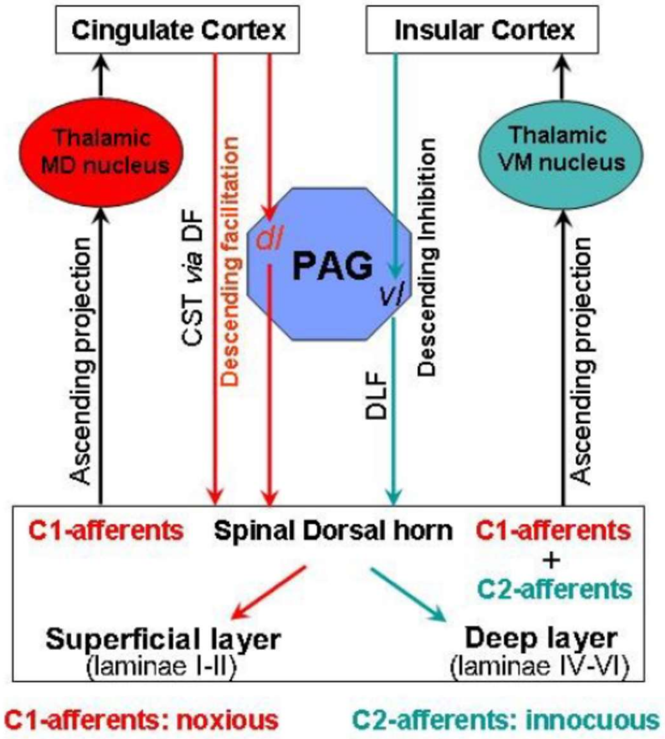


Figure 1 You et al., 2022

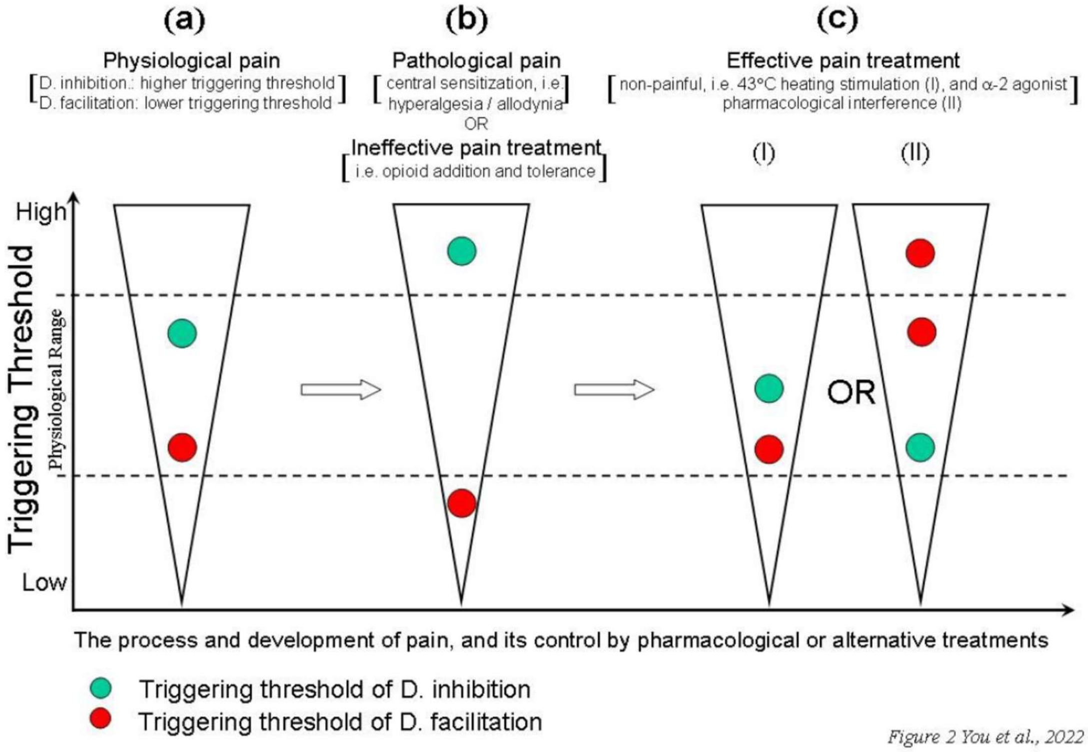


Figure 2 You et al., 2022

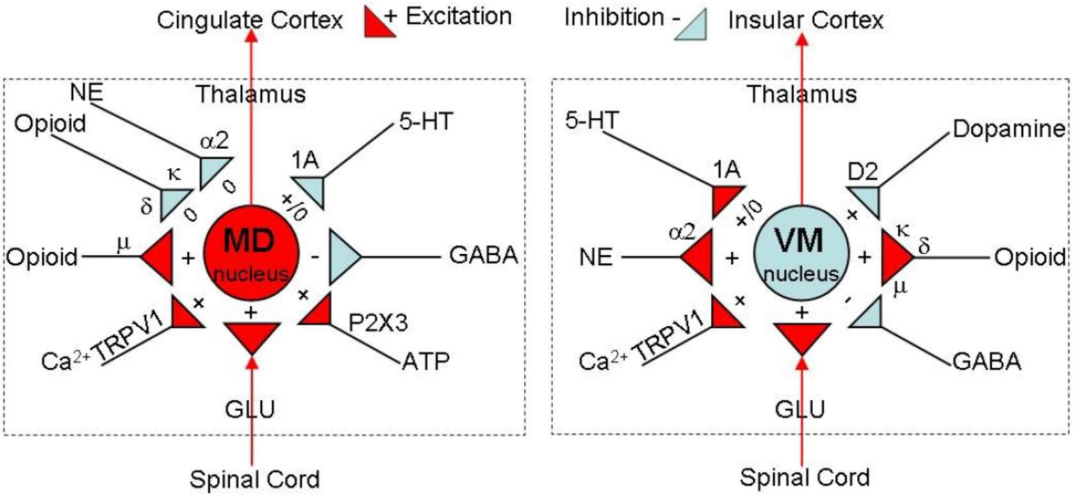
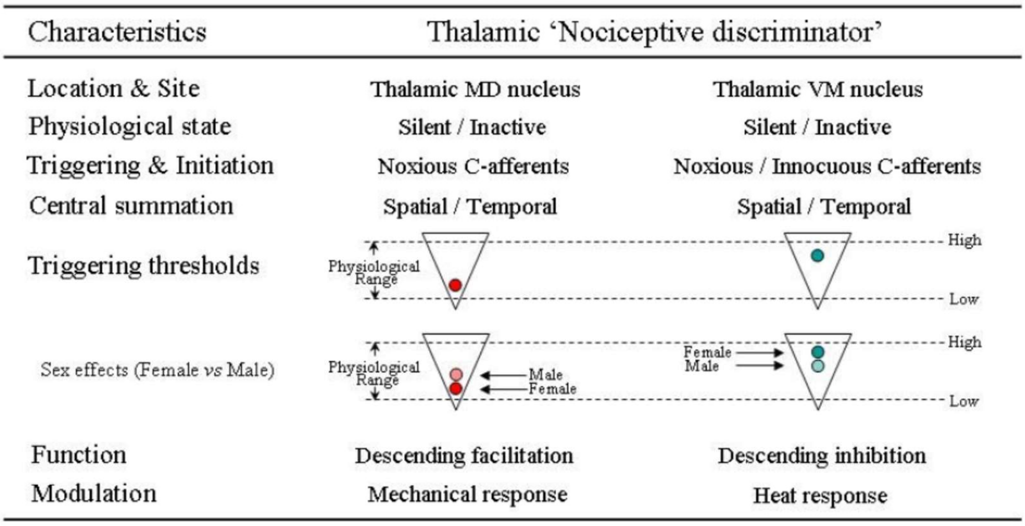


Figure 3 You et al., 2022

Table 1 Function of thalamic ‘nociceptive discriminators’ and its characteristics



Characteristics	Thalamic ‘Nociceptive discriminator’	
Location & Site	Thalamic MD nucleus	Thalamic VM nucleus
Physiological state	Silent / Inactive	Silent / Inactive
Triggering & Initiation	Noxious C-afferents	Noxious / Innocuous C-afferents
Central summation	Spatial / Temporal	Spatial / Temporal
Triggering thresholds	Physiological Range ●	● High Low
Sex effects (Female *vs* Male)	Physiological Range ● Male ● Female	Female ● Male ● High Low
Function	Descending facilitation	Descending inhibition
Modulation	Mechanical response	Heat response

Table 1 You et al., 2022