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Descending pain modulation: influence and impact

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A myriad of complex processes marry to drive pain perception in health and chronicity. A final step in proceedings involves the activation of top-down modulatory pathways that can act directly to attenuate or enhance perceived pain via descending inhibitions or facilitations, respectively. There remains uncertainty regarding the precise and complete peripheral/central nervous system circuitry that drives the full pain experience. But while results gathered over the last decade from research laboratories all over the world have revealed as many new questions as they have answered, our understanding of the descending modulation of pain perception has never been better. Here, a sharp focus on the most relevant and recent articles published in the field shapes our current understanding of brain-spinal cord nociceptive transmission.

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Introduction

Pain perception

Following peripheral injury, the pain message is transmitted to the dorsal horn of the spinal cord along primary afferent fibres with ensuing projections to the cortex (somatosensory and frontal) and limbic brain. Following, descending modulatory controls, originating in central structures of the nervous system, project to the dorsal horn of the spinal cord where they facilitate or inhibit, and thus regulate, spinal nociceptive processing and the final percept of pain. In total, the multi-dimensional nature of pain comprises sensory discriminative and affective motivational elements resulting in an individualised and unique experience. This review summarises the most recent findings in the field relating to the influence and impact of descending modulatory controls on pain perception.

Bottom-up nociceptive drive

There is a weight of influence of primary afferent activation on descending pathway activity. These sensory neurons use glutamate as their major fast (and excitatory) neurotransmitter, and they terminate in the dorsal horn (DH) of the spinal cord with an ordered pattern of distribution that relates to the stimulus transduced. Activity throughout is influenced by excitatory and inhibitory interneurons and the rodent intricacies of this complex region have been beautifully described [1,2]. It is clear that the central terminals form synaptic arrangements that ultimately impact the neuronal circuitry involved in pain processing, in particular descending modulation, to differing degrees of immediacy [3].

Originating in the superficial DH, NK1-expressing projection neurons innervate various brainstem and thalamic nuclei. The lateral parabrachial area is a major target, and the majority of rodent lamina I anterolateral tract projection neurons are retrogradely labelled from this region [4]. Unsurprisingly this translates to an impact on spinal nociceptive processing, and the ascending arm of the spinal-parabrachial-spinal loop was previously shown to directly influence the expression of a unique descending inhibitory control pathway. Specifically, intrathecal administration of NK1 receptor antagonist, or inactivation of the lateral parabrachial area using GABA(A) agonist muscimol, attenuated the inhibitory effect of diffuse noxious inhibitory controls (DNIC) in the presence of a conditioning stimulus [5]. Supporting this, distinct nociceptive input to the brainstem was recently shown to be relayed through the parabrachial complex. Retrograde tracing revealed parabrachial projection neuron termination in the rostral ventromedial medulla (RVM), a brainstem region with a dual function in descending pain modulation, exerting anti-nociceptive and pro-nociceptive effects. Research demonstrating that a recurrent spino-parabrachial circuit directly influences the RVM (and thus ensuing descending control pathways) provides evidence of a direct functional connection between superficial DH ascending projections and descending modulatory controls [6].

In the deep DH, equally complex circuits relay information to several higher brain regions. Lateral spinothalamic tract neurons, typically located deep in the lumbar DH, ascend to the thalamus. The immediacy of impact on descending modulatory controls following activation of this pathway is predictably less than that described above if only considering simple anatomy. However clearly, given that somatosensory and nociceptive inputs are integrated in the thalamus, descending modulatory

output is heavily influenced following processing of nociceptive signals that travel along the spinothalamic tract. In more convoluted terms, a dynamic modulation of ascending sensory information, when considering the ventral posterolateral thalamus, is permitted by descending regulation from the brainstem, and this impacts spinal nociceptive processing and thus ascending information. This modulation is plastic in chronicity [7].

Plasticity in the spinal cord is evidenced by a recent study demonstrating the 'un-silencing' of mechanoinsensitive nociceptors that terminate in the superficial DH; a mechanism for the contribution to the development of mechanical hyperalgesia in inflammation was proposed [8•]. Dysfunctional inhibitory interneurons and hyperactive glial cells are hypothesised to contribute to aberrant excitability of superficial DH neurons leading to altered somatosensory input from the superficial DH to higher brain centres including the anterior cingulate cortex [9,10••]. In turn, the anterior cingulate cortex (ACC) is an origin of descending projection pathways that may directly terminate in the superficial DH and thus regulate nociceptive sensory transmission by explicit regulation of spinal neuronal activity [11,12].

Key nodes in the descending pain modulatory system

The periaqueductal grey (PAG), locus coeruleus (LC) and RVM are key nuclei driving the final throughput of nociceptive information to the DH; the RVM is traditionally considered the last relay point by which modulatory (facilitatory or inhibitory) influences pass to the spinal cord. The majority of RVM-derived descending inputs are dual GABAergic and opioidergic, projecting through the dorsolateral funiculus and innervating the DH [13]. More recently, RVM GABAergic neurons were implicated in the facilitation of mechanical pain via inhibition of DH enkephalinergic/GABAergic interneurons [14••]. This highly relevant piece of research highlights the targeted therapeutic potential of descending disynaptic inhibitory circuits in terms of influencing pain thresholds.

Higher brain centre to spinal cord projection pathways can impact top-down processing by recruiting descending modulatory controls via the brainstem nuclei listed. Because of limbic and thalamic brain region connectivity, an individual's emotional state and sensory experience will modulate, and directly impact, the final output of the top-down controls in terms of pain perception. When considering ACC modulation of the pain experience in terms of top-down processing, it is vital to consider the differential control of sensory versus affective pain responses since there are separable effects [15,16]. Meanwhile the central nucleus of the amygdala also influences the descending pain pathway via medullary mechanisms [17,18••]. Changes in nociceptive processing in terms of alterations in mechanical allodynia are evident following central nucleus of the amygdala (CeA) manipulations [19,20] while opioidergic targeting of the right CeA inhibits stress-induced pain [21,22]. Questions remain regarding the intricacies of medullospinal loops mediating anti-nociception and a direct relay from the CeA. Further, 'analgesic' effects mediated at synaptic inputs onto the PAG from CeA projection neurons are not confirmed. However, it is clear that there is a strong role for limbic influence over descending pain modulation.

Neuroimaging the neuraxis

Human brain imaging techniques and the clinical use of brain stimulation, mirror therapy, virtual reality and, where ethically viable, placebo for analgesia highlight the vital role that the brain plays in descending modulatory drive and pain perception. Neuroimaging data, suggestive of supraspinally mediated reductions in inhibitions and increases in facilitation of nociceptive signalling in pain states such as osteoarthritis [23•], can be used to predict post-surgical outcomes. The descending pain modulatory system is influenced by widely distributed brain regions, and the puzzle of connectivity is under investigation.

In infants, greater functional connectivity across the brain regions associated with the control of descending modulation is indicative of lowered noxious-evoked brain activity [24]. Complimenting, a recent study showed that plasticity in the strength of PAG to caudal pons/rostral medulla resting functional connectivity is associated with pain facilitation in fibromyalgia patients [25••]. Specifically in this latter study the authors used conditioned pain modulation (CPM) as a surrogate measure of a unique endogenous descending control pathway, the integral expression of which, measured as diffuse noxious inhibitory controls (DNIC) in animals, is predictive of the efficacy of drugs that modulate descending monoaminergic neurotransmission [26]. The pathophysiological diversity of the plethora of underlying mechanisms that can result in chronic pain means that brain activity, and therefore the descending modulation of pain when measured in humans using, for example, foot immersion in cold water as a conditioning stimulus, is variable [27]. Other valid ways to evoke CPM and thus measure the descending pain modulatory system in awake volunteers/patients include the use of cuff pressure algometry [28].

Ventrolateral PAG connectivity is altered in chronic pain patients, and the magnitude of dysfunction correlates with patients' spontaneous and allodynic pain [29]. A recent study questioned the contribution of the LC in the descending control of innocuous and noxiously perceived thermal stimulation [30], and both ascending and descending LC projections have been shown to influence the behavioural outcome of a painful insult [31]. Descending noradrenergic controls from the LC are traditionally viewed as inhibitory, predominantly acting through the alpha-2 adrenoceptor. However the story is complex

and a modular functional organisation of the LC has been suggested [32].

Increased behavioural pain sensitivity following opioid discontinuation has been shown, using fMRI in healthy male volunteers, to coincide with altered signalling changes along the entire descending pain modulatory pathway. Opioid suspension increased functional coupling between the nucleus cuneiformis and the rostral ACC; increased neuronal responses in the PAG and RVM among others, as well as changes in spinal pain-related patterns demonstrate that such changes in descending pain pathways directly relate to worsened pain perception [33•]. The situation is complex not least because the brain relies on opioid and non-opioid mechanisms to down-regulate pain. Relief-related analgesia relies on endogenous opioid activity while pain reappraisal through mental imagery is shown non-reliant on opioid receptor activations [34]. This is highly relevant if considering clinical strategies for alleviating pain in the absence of a functional opioidergic system.

Targeting descending modulations

The clinical relevance of top-down pain modulatory controls is clear when considering the mechanism of action of certain drugs that are effective in the treatment of prolonged pain. Different chronic pain states are associated with a disruption in descending facilitations and inhibitions such that the pain is maintained and/or amplified [35]. Spinal cord outputs to the brain, when considering the aforementioned thalamic/cortical and parallel limbic projections are plastic; in chronicity, the brain receives altered and abnormal sensory messaging. Projections from limbic brain regions change their output to the brain stem and thus descending control machinery.

The presence of endogenous DNIC/CPM pathways means that we can evoke and quantify descending pathways in animals and man respectively; they are altered in neuropathy both pre-clinically and clinically [36,37]. The monoaminergic system influences the final expression of DNIC [38] and forward and back translational studies reveal the benefit of targeting serotonergic and adrenergic descending modulatory neurotransmission in pain relief. Translational research, which reveals that deficient DNIC/CPM can benefit from/predict the anti-nociceptive effect of drugs including reboxetine/tapentadol/duloxetine in neuropathy, is clinically relevant [26,36]. Personalised analgesic approaches, in terms of descending monoaminergic manipulations, will depend not only on the chronic pain type but also on the phase of the disease in question. Research using a rodent model of osteoarthritis revealed that the functionality of descending controls, as assessed by quantification of DNIC, changed over the course of the pain model. This would therefore impact the targeted pharmacotherapy best suited for anti-nociception in the early stage when DNIC expression is functional, versus the late stage of disease when DNIC expression is abolished for example [39].

Descending inhibitory influences are arranged in the dorsolateral funiculus but subnucleus reticularis dorsalis (SRD) projections are hypothesised to influence DNIC expression [40], and NK1+ SDH projection neurons are proposed necessary to evoke DNIC [5]. The SRD receives modulation from higher brain centres including the neocortex [41], linking the analgesic actions of distraction with cognitive processes. The SRD has not yet been analysed for the presence of noradrenergic cells, a question of interest since a tonic descending noradrenergic tone is crucial for the expression of DNIC.

Monoaminergic regulation of descending controls extends to dopamine, which plays a critical role in nociceptive transmission within supraspinal brain regions. Descending dopaminergic projection to the spinal cord participates in abnormal pain processing [42] and curbed dopaminergic descending inhibition following macrophage migration inhibitory factor (MIF) function exacerbates peripheral nerve injury-induced hypersensitivity. This research highlights a possible a role for MIF as a modulator of descending control pathways when considering top-down inhibitions mediated by dopaminergic neurotransmission [43]. Nicotinic modulation of descending control pain circuitry offers a separate therapeutic avenue. Distinct roles for nicotinic acetylcholine receptors (nAchRs) in pain perception are suggested following the finding that antagonism of PAG populations of homomeric alpha-7 nAchRs mediates anti-nociception [44].

Final comment

The personalised process of pain perception is borne from descending modulation of spinal nociceptive processes that result following distinct brainstem outputs. The reciprocal, unilateral, bilateral, unidirectional connections of the brain that feed into descending pathways are complex and only partially identified. This review reveals that while the field progresses at pace, a huge number of fascinating questions remain for our consideration.

Conflict of interest statement

Nothing declared.

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