Topical Review

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One size does not fit all: towards optimising the therapeutic potential of endogenous pain modulatory systems

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1. Introduction

Top–down processing pathways modulate neuronal transmission at the level of the spinal cord dorsal horn and thus govern, in part, the percept of pain. In health, these descending control systems can give rise to a naturally occurring form of pain inhibition. Despite a high therapeutic potential, the clinical applicability of harnessing such endogenous systems has not been fully realised. We propose that this is due to several complicating issues. First, the descending pain modulatory system (DPMS) is influenced by sensory as well as affective brain circuits. Thus, because of the bidirectional nature of the DPMS, pain may be facilitated or inhibited in a manner that corresponds not only to the degree of injury but also to the emotional status of the individual. This relates to the second issue; the DPMS, traditionally viewed as an encompassed "whole" for top–down processing, is in fact comprised of distinct neuronal networks. Emerging data highlight that a blanket pharmacological approach does not consider that diverse circuits, despite overlapping functionality and neurochemistry, require unique intervention. Meaning that, for DPMS-targeted analgesia, activity must be altered in the *relevant* pathway where cortical influences must also be considered.

Here, we review what is known about the neuroanatomical framework by which distinct descending pathways are subserved, citing evidence from both preclinical (animal) and clinical (human) studies. This is timely because movement towards selective therapeutic intervention (ie, relevant to specific features of pathological pain conditions and their comorbidities) will depend on recognition of top–down controls within the DPMS as functionally unique systems that are engaged by specific environmental or affective "drivers." For this to occur, studies that define the anatomical and pharmacological nature of the circuits therein, and translational delineation of the mechanisms underlying key descending control pathways, are key.

2. The descending pain modulatory system

Dissecting the functionality of discrete descending modulatory pathways, where each mechanism likely represents a distinct system, would allow identification of precise and disease-specific novel targets. This has implications for patient stratification (eg, based on correlation or relationships between cognitive or affective processes and pain modulatory pathway efficiency) and related mechanistic therapeutic approaches. Toward this notion, we begin by evidencing the known relationship between "drivers" and neurophysiological systems that affect activity in the DPMS.

2.1. Modulators, integrators, and effectors

Endogenous analgesic circuitry can be modulated by pharmacological[3,8,25,30,35,40,72] or psychological interventions.[10,16,19,36,42,49] Emotional changes,[23] mindfulness therapy,[73] exercise,[22] and cognitive status[43,68] may affect brain–spinal cord nociceptive transmission[4] where convoluted underlying mechanisms influence the centrifugal descending modulation of spinal nociceptive transmission. Take noradrenaline as an example. Opposing alpha 2 adrenoreceptor-mediated facilitatory signalling in the brainstem has been demonstrated,[70] and the locus coeruleus (LC), a traditionally viewed inhibitory component of the DPMS,[18] evokes a bidirectional change in thermal nociception in rats when optogenetically activated.[33] Its modular functional organisation lends the LC to multiple pain-modulatory influences.[9,34,50] Recently, its propain mechanism has been linked to a regulatory role on noncoerulean noradrenergic cell group(s),[45] highlighting the functional nuance of seemingly comparable brainstem with spinal cord projection circuits.

Serotonergic, opioidergic, and GABAergic mechanisms are also recruited by descending pathways, in which distinct (even if overlapping) governance of specific circuits occurs. For example, the caudal raphe sends descending projections to the dorsal horn,[37] and the rostral ventromedial medulla (RVM) harbours neuronal populations involved in antinociceptive and pronociceptive behavioural responses. Most of the transmission is dual GABA and opioidergic.[21] Interestingly, this unique circuit integrates stress information to limit the presynaptic inhibition of afferent neurons terminating in the same region, representing a network whereby endogenous analgesic processes are influenced by environmental factors. Mechanistically, this links with the influence of higher brain centres on final modulatory output.

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For example, the forebrain targets caudal medullary regions, and emotional and cognitive processing is implicated in the control of pain transmission through a direct impact on brainstem loci.[51,74] The dorsal reticular nucleus (DRt) can enhance nociceptive responses,[52] and circuitry between brainstem sites including the DRt, RVM, and midbrain periaqueductal grey (PAG) provides a substrate for emotional and cognitive modulation of pain, where the targeting of afferent neurons links the "dynamic pain connectome" to integrated pain responses.[53] Thus, although defining discrete nucleus–spinal cord projection sites is an important first hurdle, identifying their cortical control is crucial for movement towards selective therapeutic interventions.

The rostral anterior cingulate cortex (ACC) explicitly regulates spinal nociceptive processing whereby separable effects on sensory and affective components of the pain descriptive axes are evident,[25,61] while a basolateral amygdala–prefrontal cortex–PAG–spinal cord pathway that ordinarily drives feed-forward inhibitions contributes to sensory hypersensitivity in animal models of disease.[38] Amygdala activity influences nocifensive behaviours by projections that affect activity in the pain neuraxis[55,64] and lateralised outputs from the amygdala and brainstem modulate spinal nociceptive processing by opioidergic mechanisms differentially in health and disease.[60] This is also evident when considering ACC–spinal cord, right central nucleus of the amygdala–spinal cord, and RVM–spinal cord circuits.[14] Identifying affective influences on brainstem–spinal cord pathway functionality is complicated; activity in key nuclei may operate as "brake on" or "brake off" systems for the expression of specific circuits. Nonetheless, since defining the top–down regulation of brainstem origin spinally projecting pathways becomes clinically relevant when the anatomical and pharmacological underpinning of those pathways is known, the process is crucial.

3. Discrete circuits

External factors can manipulate descending pathway functionality, and yet, there remains an untapped source of clinically relevant targets (linked to mechanisms involved in descending control expression) that could be exploited for improved analgesia. Functional delineation of endogenous pain modulatory systems would allow the development of mechanism-driven therapeutic approaches (for a variety of chronic pain conditions) to be expedited. This is only beneficial, for optimal analgesic prescription, if (1) the circuitry of the pathways being targeted is known and (2) the descending pathways comprising the DPMS have distinct governance.

3.1. Descending pain modulatory system pathway governance

Naturally occurring mechanisms by which external factors can manipulate modulatory control expression are exemplified by the application of paradigms that seek to evoke stress-induced analgesia (SIA), diffuse noxious inhibitory controls (DNICs), and offset analgesia (OA), among others. The separable nature of the paradigms evidences the nuanced nature of top–down control activation within the DPMS.

Mechanistically, psychological stress recruits RVM-mediated modulatory mechanisms.[67] This, coupled with the fact that RVM-driven circuits integrate stress information to limit the presynaptic inhibition of afferent neurons terminating in the same region hints at the functionality (anatomy and pharmacology) of an "SIA descending control pathway." SIA, a pain suppression system instigated on exposure to unconditioned or conditioned stressful stimuli,[11] is governed by an interplay between endocannabinoid and endogenous opioid systems in a manner that is specific to the paradigm applied.[2] More research is required in order that therapeutic targeting strategies for stress and pain-related disease may be finessed. Meanwhile, the noradrenergic DNIC pathway inhibits the spinal neuronal activity when activated by a conditioning stimulus.[7,48] Conditioned pain modulation (CPM), the proposed human counterpart of DNIC, is dysfunctional in patients with chronic pain [27,72] and its maladaptive expression is associated with increased postoperative pain and persistent pain.[71] Underlying noradrenergic mechanisms explain the relationship between dysfunctional CPM and the beneficial use of tapentadol (μ-opioid receptor agonist and noradrenaline reuptake inhibitor) and duloxetine (serotonin noradrenaline reuptake inhibitor)[62,72] in a manner that back translates.[6,7] However, the fact that noradrenergic brainstem–spinal cord pathways are distinctly governed in a "one mechanism does not fit all" manner,[45] argues that the functionality of discrete pathways is crucial for understanding sensorimotor modulation in health and disease.

The separable nature of specific DPMS-encompassed pathways can also be considered according to those pharmacological mechanisms *not* involved in key circuits. Opioid-independent mechanisms underlie the phenomenon whereby lowered pain scores accompany a small decrease in temperature during noxious thermal stimulation,[54,59] a paradigm used to evoke OA. Such as SIA and DNIC, OA is a potent example of a situation in which stimulus manipulation induces an adaptive change in sensory processing. Previously, the reduction in pain experience evoked by application of the OA paradigm was correlated with DPMS activity originating in the PAG and RVM in a human fMRI study.[13] However, the precise mechanistic underpinning is unknown. Onset hyperalgesia (OH) meanwhile describes a situation whereby a disproportionate increase in pain intensity is experienced at a given stimulus intensity when this intensity is preceded by a rise from a lower temperature.[1] Despite the paradoxical to OA outcome, we hypothesise that OH is a phenomenon of the same pathway but with some separable governance. Indeed, these latest investigations provide evidence for the separable nature of descending modulatory circuits, even those as closely related (for the paradigm applied) as OA and OH.

The clinical benefit of defining DPMS controls will rely in part on optimally prescribing currently available pharmacotherapies according to the dysfunction in question. While mu-opioid receptor expression in the DPMS underlies opioid antinociception[65] neither morphine nor naloxone impact CPM expression in humans.[20,32] Previously, pain facilitative CPM observed in patients with fibromyalgia was mechanistically linked to attenuation of pain inhibitory as well as amplification of pain facilitative processes in the central nervous system.[28] Meanwhile, tapentadol's analgesic mechanism was shown not to extend to an impact on the magnitude of the OA response in diabetic polyneuropathy patients, indicative of a preferential top–down effect for CPM alone.[62] Cumulatively, the data indicate distinct yet intertwined descending analgesic mechanisms, which are differentially modulated according to the pain state; it is likely the case that multiple endogenous analgesic systems could be dysfunctional in nociplastic patient groups. For example, since CPM is associated with a distinct pharmacological and functional pathway within the DPMS, where wakefulness affects the overall expression status of the mechanistic DNIC underpinning,[5] it is highly probable that a chronic pain patient with a normal CPM response may have alterations within a separate analgesic system. Thus, optimal analgesic strategies could encompass

pharmacological and nonpharmacological interventions that are specific to 1 or 2 cortical and brainstem circuits. This kind of precision medicine requires further translational research efforts; the advent of bedside tests that allow rapid delineation of functionality in key pain processing pathways will first rely on delineation of the pathways in question.

So far, the influence of SIA or DNIC or OA on DPMS functionality and the nature of the underlying mechanisms that lead to dysregulation of DPMS-encompassed vs the specified pathways in chronic pain (where environmental influences on endogenous analgesic processes are likely) are unknown. If, for example, there is a switch in the dominant brainstem noradrenergic nucleus influencing spinal nociceptive processing in chronic pain (or indeed the functionality of reciprocal connection), then the pharmacotherapeutic target has changed. This has implications for age and disease-associated decrements in endogenous analgesic responses, where there is a need to compare pain measures (including activity in discrete modulatory pathways) across the adult lifespan and disease course.[15,44,47] Plasticity in the pathways comprising the DPMS is a key factor in the transition from acute to chronic pain. Although this topic is outside the scope of the present review, we emphasise that, following the identification of distinct circuits that comprise the DPMS, understanding the nature of the plasticity therein in chronicity (where each circuit, as in health, is likely to undergo changes that are unique to the pathway itself) is going to be a key factor in the eventual optimisation of therapeutically targeting endogenous pain modulatory systems.

4. Psychological and environmental influences

Endogenous analgesic circuits may be influenced by psychological and environmental factors; understanding the biomedical mechanisms requires consideration of psychological social theories, further complicating the process of untangling singular controls. Recent NICE guidelines have suggested that nonpharmacological approaches including cognitive behavioural therapy, mindfulness, exercise, and acupuncture should be encouraged even as blanket treatment options for chronic pain conditions driven by centrally mediated changes in the absence of obvious injury (ie, nociplastic pain). Pain catastrophizing is often linked to a vicious cycle of fear avoidance, pain hypervigilance, disability, depression, and ultimately a worsening of chronic pain.[12,69] Patients with fibromyalgia with high pain catastrophizing scores also showed stronger activation of the ACC suggesting an increased affective processing of their pain,[26] and patients with knee osteoarthritis with high levels of pain hypervigilance show facilitated temporal summation of pain[31]. Interestingly, mindfulness therapy has been linked with reduced pain catastrophizing in a heterogeneous group of patients with chronic pain,[66] and a neuroimaging study in healthy volunteers has demonstrated changes in the ACC during a mindfulness paradigm, which was related to a reduction in pain-intensity ratings.[73] Similar cortical regions have been implicated in pain relief mediated through physical exercise in patients with fibromyalgia, with more activity reported in the dorsolateral PFC following exercise.[17] Acupuncture has also been shown to cause increased opioid binding in the ACC, which was associated with clinically relevant reduction in pain in patients with fibromyalgia.[29] Even the ability to mind wander is affiliated with changes in top–down antinociceptive systems and the PAG.[46] Activation of CPM-dependent mechanisms are also believed to occur during exposure to immersive virtual reality environments, which can also work to attenuate experimentally induced secondary hyperalgesia in human pain models.[43,58] Taken together, these findings have helped shape our understanding of how psychological therapies known to improve clinical pain symptoms interact with cortical regions implicated in the DPMS. Linking mechanisms of pain relief with activity in a specific circuit is still lacking. However, from these data, an outline therapeutic strategy is formed, whereby application of specific modulatory control–activating paradigms in carefully stratified patient cohorts may, for example, reveal those top–down influences that act as a gatekeeper to the expression of a specific control. This would inform the tools required for back translational studies, where, ideally, patient observations are recapitulated with faithful paradigms at the bench.

5. Harnessing cortical influences over descending pain modulatory system pathways

There is a growing body of evidence that suggests harnessing top–down cortical influences over brainstem endogenous analgesic systems could provide a feasible route to precision manipulation of descending control circuits and, thus, precision medicine. Through effective screening for dysfunction in discrete cortically driven cognitive or affective pathways, psychological interventions which target specific DPMS pathways can be tailored to the correct patient. The future of neurotechnology for the treatment of chronic pain also holds promise. Despite the overall poor clinical evidence for transcranial direct current stimulation (tDCS) as a treatment for chronic pain,[63] it is increasingly apparent that analgesic effect sizes are bigger during dynamic sensory testing paradigms or when sensitisation is present, having minimal effects over acute pain thresholds.[24] A number of experimental "healthy human" studies have shown that tDCS applied over the primary motor cortex can exert an influence on brainstem regions involved in endogenous pain control,[57] directly boost CPM efficiency,[19] and attenuate facilitated spinal pain mechanisms.[39,41,42] Indeed, baseline CPM efficiency was related to the analgesic effects of tDCS applied over the DLPFC in patients with chronic low back pain,[56] which others have linked to changes in activity within the posterior insula cortex.[49] A systems-based approach, whereby screening for specific endogenous analgesic mechanisms (eg, CPM dysfunction), may lead to improved efficacy in future randomised controlled trials. Clinically speaking, optimising the therapeutic potential of these endogenous inhibitory systems through improved patient profiling, and centrally acting targeted interventions, is within reach.

Conflict of interest statement

The authors have no conflict of interest to declare.

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