

The importance of the descending monoamine system for the pain experience and its treatment

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Abstract

Brainstem and midbrain areas engage descending facilitatory and inhibitory neurones to potentiate or suppress the passage of sensory inputs from spinal loci to the brain. The balance between descending controls, both excitatory and inhibitory, can be altered in various pain states and can critically determine the efficacy of certain analgesic drugs. There is good evidence for a prominent α_2 adrenoceptor-mediated inhibitory system and for 5-HT₃ receptor-mediated excitatory control of spinal cord activity that originates in supraspinal areas. Given the multiple roles of these transmitters in pain and functions such as sleep, depression, and anxiety, the link between spinal and supraspinal processing of noxious inputs (via the monoamine transmitters) could be pivotal for linking the sensory and affective components of pain and their common co-morbidities, and also may potentially explain differences in pain scores and treatment outcomes in the patient population.

Introduction and context

Descending controls – pathways originating in midbrain and brainstem regions that project onto the spinal cord – have long been recognised as key links in the multiple neuronal networks that interact to produce the overall pain experience. The potential for higher cognitive function through cortical controls that project to the cells of origin of descending controls to influence spinal function allows for ‘top-down’ processing of pain. The major transmitter systems implicated in the descending controls are the monoamines, noradrenaline (NA) and 5-hydroxytryptamine (5-HT), and so the comorbidities of sleep problems, anxiety, and depression result from the dual roles of NA and 5-HT in these functions and also in pain. A number of analgesic drugs interact with descending controls, including opioids, which have direct supraspinal interactions with these systems, pregabalin and gabapentin, whose actions are regulated by descending pathways, and also the tricyclic antidepressants (TCAs) and serotonin and noradrenaline reuptake inhibitors (SNRIs), which alter synaptic levels of NA and 5-HT. Tramadol and the newer tapentadol

have mixed mu-opioid receptor and reuptake inhibition actions, the former with dual NA/5-HT actions and the latter with NA only. TCAs and SNRIs have greater efficacy than selective serotonin reuptake inhibitors (SSRIs) in neuropathic pain, and tapentadol is more powerful than tramadol. Thus, the potential pronociceptive effects of increasing levels of 5-HT may counter the analgesic effects of various molecules. Preclinical data can explain this on the basis that descending NA actions clearly mediate inhibitions through spinal α_2 adrenoceptor, whereas 5-HT, via 5-HT₂ and 5-HT₃ receptors, is a key transmitter in descending facilitations.

Research has moved on significantly from the early idea that pain is the product of nociceptive signals linearly impacting on an alert and responsive brain. Our current understanding is of a plastic, integrative, and highly individualised nociceptive system that is subject to many internal and external influences. Because considerable processing of nociceptive signals occurs in the spinal cord, it was reasonably assumed that plasticity (which enables sensitisation) was an intrinsic function of the

dorsal horn, yet when seminal experiments in rodents showed that electrically stimulating an area of the midbrain, the periaqueductal grey (PAG), resulted in no overt behavioural signs of distress to an otherwise painful procedure [1], it became apparent that the brain could influence pain. It was further shown that stimulation-produced analgesia could be triggered downstream of the PAG in the rostral ventromedial medulla (RVM) [2], an area of the brainstem that integrates information that passes from limbic areas of the brain to the spinal cord. The PAG and the RVM are therefore key components of the descending modulatory repertoire, a system of neuronal pathways that enables the brain (and thus cognitive and emotional states) to control pain processing at the first relays within the spinal cord.

Descending systems depend on feedback circuitry that relays between the spinal cord and supraspinal areas [3]. Hence, nociceptive signals that arrive in the dorsal horn from the periphery synapse with spinal neurones that project to thalamic and parabrachial areas that respectively attach sensory-discriminative (that is, the quality, intensity, and location of the stimulus) and emotional/contextual meaning to the signal. Partly on the basis of this received information, limbic, cognitive, and somatic areas in turn send out signals that converge and feed into descending pathways to either increase or decrease the influence of further incoming input into the dorsal horn, causing the feedback cycle to continue. The neural bases for this bidirectional modulation from the brainstem are the 'On' and 'Off' cells; On cells burst-fire in response to peripheral noxious stimuli, enhance nociception, and are implicated in the hypersensitivities associated with a range of pain states, whereas Off cells undergo a pause in firing in response to peripheral noxious stimuli and are involved in inhibiting spinal neuronal activity [4]. Incidentally, and importantly, the responses of these RVM neurones to noxious stimuli are inversely predictive of their responses to systemic or brainstem opioid administration, and hence On cells are inhibited by morphine whereas Off cells are disinhibited [5].

Recent advances

The original notion of descending controls was that they were predominantly inhibitory in nature, but this has been broadened and refined so that we now know that the brainstem's output (likely via the On cells) can be predominantly facilitatory (particularly with respect to high-intensity stimuli) and that this may be the main physiological function [6]. This 'gain control' ensures the detection of (and appropriate response to) noxious inputs. The balance between supraspinal inhibition and facilitation can, however, be altered, either transiently or durably (for example, in some cases of chronic pain).

With respect to the former, descending inhibitory pathways can be activated and endogenous analgesia recruited so that nociception and protective responses to noxious stimuli are temporarily suppressed in situations of threat and danger. In terms of longer-lasting alterations in descending output, the RVM may serve a protective, or 'masking', role during some pain states by increasing its inhibitory output (for example, during inflammatory pain and potentially during the early stages of cancer). The descending system may, however, become maladaptive so that pain outlasts its biological usefulness; after neuropathy, aberrant neuronal activity can increase the descending facilitatory drive to maintain the pain state, yet after the injury is healed, descending facilitatory neurones may fail to disengage, which means that they continue to enhance the transmission of sensory input. These mechanisms not only contribute to the neuropathic pain state but also are permissive for the efficacy of gabapentinoid drugs [7,8]. Because one mechanism by which descending neurones achieve this is through enhancing the evoked transmitter release from peripheral nerves [9], the feed-forward compensatory circuit between the periphery, spinal cord, and supraspinal structures becomes self-sustaining and therefore could give rise to chronic pain. Indeed, these supraspinal influences appear to be prominent in the maintenance of persistent pains but not in their induction, suggesting that at first the pain states are driven by peripheral processes but that with time the pain drive moves higher up the neuraxis. In addition to providing insight into neuropathic pain, abnormal activity in this loop may shed some mechanistic light on diffuse pain states that lack simple peripheral causal explanations, such as fibromyalgia [10].

The specialised role of midbrain and brainstem areas in pain processing has been demonstrated not only in animal studies but in human subjects too; human imaging studies have shown that supraspinal activations during painful stimulation significantly localised in regions consistent with the nucleus cuneiformis and PAG [11], areas that collectively form the major source of input to the RVM. Furthermore, when the pattern of brain activity evoked by cold pain versus cold allodynia is compared in human volunteers, areas within the dorsolateral pons (that are consistent with the parabrachial area) are recruited in the processing of the latter, which verifies the role of the brainstem during central sensitisation [12]. This is consistent with analyses of brainstem activity during dynamic mechanical allodynia, which highlighted neuronal changes and increased activity in the ipsilateral dorsal medulla/upper cervical cord in an area consistent with the location of the RVM [13]. Thus, together with diffusion tractography

techniques that confirm anatomical pathways mediating top-down control of nociceptive processing in humans [14], these imaging studies provide a clear picture of the brainstem's representation of pain and central sensitisation in humans and reinforce the importance of descending modulatory systems, first mapped out in animals, to human correlates of the pain experience.

Implications for clinical practice

Pain doctors should therefore be aware that descending controls can have a major impact on the patient's pain experience where top-down modulation can be influenced by mood, fear, or sleep, for example. Plausibly, the balance between facilitatory and inhibitory controls could be influenced by coping or catastrophising. Preclinical data show descending facilitations dominating inhibitions in disparate models that include peripheral neuropathy, spinal cord injury, cancer-induced bone pain, and opioid-induced hyperalgesia. Currently, the role of descending facilitations in clinical pains can be surmised by human imaging studies (as discussed above) in which activation of midbrain and brainstem structures in situations in which the pain rating is high is indicative of their facilitatory roles. On the other hand, the functional status of inhibitions can be evinced in some clinical situations, such as in their failure in patients with fibromyalgia [15]. Even here, the reduction in inhibition could be secondary to enhanced facilitations [10]. Some diffuse pain conditions may therefore be underscored by a malfunction of central neuronal systems that control mood, sleep, and pain such that a generalised pain state could be generated in the absence of overt peripheral pathology. In pains of peripheral origins, descending facilitations act alongside spinal mechanisms of hypersensitivity to further shift the pain score upwards.

Clinicians should also be aware that descending controls do not just modulate the pain state but are permissive for the actions of several important drug classes. The analgesic effects of TCAs, SNRIs, and the new mu-opioid receptor agonist and noradrenaline reuptake inhibitor tapentadol, for example, rely on altering activity at monoamine synapses and therefore are dependent on activity in the descending circuits (the weaker analgesic efficacy of SSRIs is explicable in terms of the established noradrenergic inhibitory tone that contrasts with certain pronociceptive effects of 5-HT). Furthermore, because gabapentin and pregabalin have efficacies that are dependent on activity within descending circuits [7,8], individual variations in pain comorbidities may explain why there are variable responses to treatments such as gabapentin and pregabalin in seemingly uniform pain groups [16]. Indeed, despite consistent efficacy in most animal models of neuropathic pain in which these

co-morbid factors and societal influences may have less of an impact than in chronic pain patients, there is an ill-defined link between the presence of nervous system lesions or abnormal sensory phenomena and the responsiveness to gabapentinoid drugs in the clinic [17]. Clinical investigations relating the analgesic efficacy of TCAs, SNRIs, and gabapentinoids with affective measures may therefore be a step toward predicting treatment responsiveness in patients.

Abbreviations

5-HT, 5-hydroxytryptamine; NA, noradrenaline; NRI, noradrenaline reuptake inhibitor; PAG, periaqueductal grey; RVM, rostral ventromedial medulla; SNRI, serotonin and noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Competing interests

The authors declare that they have no competing interests.

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