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What do monoamines do in pain modulation?

Kirsty Bannister* and **Anthony H. Dickenson**
Neuroscience, Physiology and Pharmacology Department, G35 Medical Sciences building, University College London, Gower Street, London. WC1E 6BT

Abstract

Purpose of review—Here we give a topical overview of the ways in which brain processing can alter spinal pain transmission through descending control pathways, and how these change in pain states. We link preclinical findings on the transmitter systems involved and discuss how the monoamines, noradrenaline (NA), 5-hydroxytryptamine (5-HT) and dopamine, can interact through inhibitory and excitatory pathways.

Recent findings—Descending pathways control sensory events and the actions of the neurotransmitters NA and 5-HT in the dorsal horn of the spinal cord are chiefly implicated in nociception or anti-nociception according to the receptor that is activated. Abnormalities in descending controls effect central pain processing. Following nerve injury a NA-mediated control of spinal excitability is lost while its restoration reduces neuropathic hypersensitivity. The story with 5-HT remains more complex due to the myriad of receptors that it can act upon; however the most recent findings support that facilitations may dominate over inhibitions.

Summary—The monoaminergic system can be manipulated to great effect in the clinic resulting in improved treatment outcomes and is the basis for the actions of the anti-depressant drugs in pain. Looking to the future, prediction of treatment responses will possible by monitoring a form of inhibitory descending control for optimised pain-relief.

Keywords

Monoamines; descending controls; noradrenergic pain inhibition; serotonergic pain facilitation; conditioned pain modulation

Introduction

It is well established that the monoamines noradrenaline (NA) and 5-hydroxytryptamine (5-HT) have complex modulatory roles in pain signalling. Top-down processing pathways arise in midbrain and brainstem structures and exert powerful inhibitory or excitatory control over dorsal horn neuronal responses; this is predominantly via the actions of the neurotransmitters NA and 5-HT acting at specific receptor subtypes. Here we discuss the mechanisms underlying the bi-directional role of the monoamines on pain processing as we consider, in part, their opposing receptor-mediated actions. Compelling evidence attributes

*Corresponding author: Neuroscience, Physiology and Pharmacology Department, G35 Medical Sciences building, University College London, Gower Street, London. WC1E 6BT. Telephone: 0207 679 3733. kirsty.bannister@ucl.ac.uk.

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pain inhibitions to α2-adrenoceptor activation and pain facilitations to 5-HT_3-receptor activation. We highlight recent research regarding analgesics that have monoamine-based mechanisms of action and that interact with descending controls.

Pain Perception

Following injury and subsequent tissue and/or nerve damage peripheral mechanisms are likely subjected to a filtering process through central mechanisms so that the relation between the peripheral damage to nerve or tissue can become dissociated from the amount of pain reported. In most pain syndromes there are multiple pain-signalling mechanisms residing at peripheral sites. Transmission within peripheral nerves follows, and signals are passed to the spinal cord and onwards to the brain. Specifically the pain message is relayed to the thalamus and cortex where the sensory components of pain are generated, thus allowing us to locate the pain and describe its intensity, while parallel pathways transmit the pain message to the limbic brain. This latter part of the brain is where the affective components of pain are produced, which is why chronic pain often goes hand in hand with comorbidities including depression and anxiety. Importantly, pain perception doesn't result from activation of these ascending pathways alone but rather from a dialogue between the higher centers of the brain and the spinal cord, so called top-down processing via long pathways that descend from the brain back to the spinal cord. As well as controlling sensory events in the spinal cord, descending controls also influence autonomic and motor events. For the sake of this review we shall focus only on the former role.

Descending controls

Descending control pathways originate in midbrain and brainstem regions and project to the dorsal horn of the spinal cord. They represent a mechanism through which the transmitted pain signal may be facilitated – this enhances the pain that we are experiencing, or inhibited – thus reducing pain. They have a clear anatomical basis. From the periaquaductal grey (PAG) in the midbrain (an area which integrates forebrain influences) pathways run to a number of brain stem areas. Succinctly, ensuing projections to the locus coeruleus (LC) and to the rostromedial ventral medulla (RVM) are the main sources of descending controls. A major component of the inhibitory bulbo-spinal loop for example is mediated by fibers running in the dorsolateral funiculi (DLF) [1]. The RVM exerts inhibitory and facilitatory controls over deep dorsal horn neuronal responses via two opposing systems that originate from RVM pain-modulating neurons. There are 3 classes of cells that have clear sensitivities to mu opioid receptor (MOR) agonists and are also grouped according to their distinct responses to noxious somatic stimulation prior to a nocifensive reflex withdrawal. Whereas ON cells will start firing rapidly in response to noxious stimuli, OFF cells will cease firing just before a tail flick for example, and are activated by MOR agonists. Thus the RVM possesses neuronal substrates to enhance or to inhibit pain messages. Neutral cells do not change their firing rate in the presence of noxious input nor according to MOR agonist activity. Given the above it is of interest that MOR-expressing neurons in the RVM are shown not to be required for analgesia produced by either direct or indirect activation of neurons in the RVM [2].

Monoamines: NA

The monoamines NA and 5-HT are the neurotransmitters chiefly implicated in the descending control pain modulatory pathway. Descending noradrenergic projections terminating in the dorsal horn of the spinal cord derive almost entirely from nuclei within the dorsolateral pontine tegmentum, in particular the aforementioned LC. It is telling that micro-stimulation of these areas is known to be anti-nociceptive through activation of the α2-adrenoceptor [3] which can be activated by drugs such as clonidine and dexmedetomidine. Fast forward 30 years and a plethora of evidence supports that NA plays a prominent role in inhibition of spinal cord activity that originates in supraspinal areas. Further, research now suggests that an interaction with the noradrenergic system via release of NA and activation of α1, α2C and β-adrenoceptors is in actual fact an essential mechanism underlying the peripheral anti-nociception induced by the non-steroidal anti-inflammatory drugs (NSAIDs) [4].

Mechanisms underlying other central inhibitory effects of NA include activation of α1 adrenoceptors on GABA-ergic and glycinergic inhibitory interneurons, increasing inhibitory drive to projection neurons [5]. Interestingly, whilst it is true that there is significant engagement of noradrenergic inhibitory pathways during extended period of noxious nociceptive drive [6] there is also evidence for the existence of a tonic noradrenergic control of spinal excitability since there is an ongoing alpha-2 adrenceptor control of spinal excitability that is lost after nerve injury [7]. More recently restoration of this diminished noradrenergic control through use of a NA reuptake inhibitor (NRI) was shown to reduce neuropathic hypersensitivity [8].

Monoamines: 5-HT

Electrical stimulation of the RVM, which receives substantial projections from mid brain regions, evokes the spinal release of 5-HT and supports an overall inhibitory influence on dorsal horn neuronal responses to noxious stimulation. It is clear however that parallel inhibitory and excitatory pathways originate from the RVM with the latter appearing to be predominant [9]. The story with 5-HT in terms of its role in pain modulation initially appears complex due to the myriad of spinal cord receptors that it can act upon. Via 5-HT_2 and 5-HT_3 receptors, 5-HT is a key transmitter in descending facilitations. In contrast spinal cord 5-HT_7 and 5-HT_{2A} receptors are classified as inhibitory. Overall a recent study shows that selective activation of RVM 5-HT neurons enhances pain sensitivity [10] supporting the idea that facilitations may dominate over inhibitions. However the anti-depressant Tianeptine increases 5-HT uptake in the brain and is reported to have anti-nociceptive effects; its efficacy in spinal nerve ligated rats is proposed to be in part dependent on modulation of inhibitory 5-HT_7 receptors [11]. Thus the particular 5-HT receptor activated under different circumstances will determine the direction of effect.

Monoamines: Dopamine

The dopaminergic system represents another potential chronic pain treatment target. Dopaminergic agonists were recently shown to promote recovery of locomotor function following spinal cord injury [12] serving as a reminder that, following spinal cord injury at least, a complementary monoaminergic multi-therapy strategy could be employed to great

effect. Indeed NA, 5-HT and DA are shown to adjust actions of the nociceptive machinery via modulation of pre-synaptic inhibition in the mouse spinal cord [13]. The mechanism of nefopam is proposed to involve inhibition of NA, 5-HT and DA reuptake. Recently spinal noradrenergic modulation alone (via the α2-adrenoceptor) was shown to play an important role in the anti-nociceptive effect of nefopam against inflammatory acute pain but not facilitated pain [14]. Studies manipulating DA with the aim of translation to clinical therapy will be hampered by the important roles of DA in movement and reward systems.

Pain Modulation

Abnormalities in the central processing of pain are commonly believed to underlie refractory chronic pain; alterations in those descending control systems that act to enhance or reduce the pain that we are experiencing can contribute to pain chronification (as recently discussed by Ossipov and colleagues, [15]). The clinical relevance and implication of the monoaminergic neurotransmitters involved in the descending control pain pathways continues to be at the forefront of research concerning many varied pathological conditions [16].

The modulatory feedback loop for the control of spinal neuronal excitability during prolonged noxious stimulation is dynamic. Signalling circuits change following physio-pathological events such as those seen in the two broad major types of pain, neuropathic and inflammatory pain where, respectively, nerves or tissue are damaged. Low back pain and cancer pain can be one or the other or a combination, and may be termed mixed pains. The peripheral processes of these types of pain are very different. With neuropathy, nerves are lesioned or diseased and so ion channels drive the pain whereas with inflammatory pains, chemicals from the damaged tissues are at the origins. As a consequence, treatments aimed at the source of pain differ. However, within the central nervous system the mechanisms of pain and pain control appear to be more common. In pains such as fibromyalgia or opioid induced hyperalgesia the underlying mechanisms are more likely to be central than peripheral. A pivotal central common mechanism would appear to be the descending controls, alterations in which have been seen following neuropathy, inflammation and in cancer pain models.

Central mechanisms of pain modulation

Although the periphery provides a level of painful input into the CNS, central mechanisms transform this into a personal pain experience with emotional content. The periphery provides the basic ingredients but then the spinal cord can amplify the messages enormously and on the other hand, it is proposed that descending inhibitions can switch pain down, illustrated by placebo. Recently placebo analgesia was shown to enhance descending pain-related effective connectivity [17] although some claim this may not always stretch to inhibition of the nociceptive input at the spinal level [18]. However it is agreed that both spinal and higher order sensory processes are modulated during placebo analgesia.

Analgesics

The analgesic effects of many drugs are dependent on activity in the descending circuits. The FDA approves drugs that target the descending pain facilitatory and inhibitory systems for use in chronic pain [19].

Neuropathic pain

Following nerve injury there is plasticity in descending noradrenergic pathways as evidenced by the increased potency of α2-adrenoceptor agonists in this particular pain state. In chronic neuropathy it has been shown that there is a transient excess of descending monoaminergic drive when that pathway has been previously primed using a tonic pain paradigm such as the formalin test. This results in inhibition of subsequent nociceptive behaviours. Here the authors propose that earlier activation of those descending pain pathways could then contribute to the establishment of chronic neuropathic pain [20]. In rats subjected to spinal nerve injury it has been shown that activation of 5HT5A and 5HT1A/1B/1D receptors reduces pain processing, stressing the importance of these receptors in the descending pain inhibitory circuit [21].

Contributory mechanisms in neuropathic pain include aberrant ectopic activity in nociceptive nerves as well as central sensitization and impaired inhibitory modulation. First line treatments include the tri-cyclic anti-depressants (TCA's), serotonin, NA reuptake inhibitors (SNRI's) and anticonvulsants such as pregabalin (PGB) and gabapentin (GBP), although it is recognized that individualized, multi-disciplinary rehabilitation approaches will be crucial for the optimal outcome of patient treatment [22]. It is frustrating that only a minority of patients with neuropathic pain have an adequate response to drug therapy; clinical trial modifications could help reduce therapeutic failures [23].

Antidepressants

It is possible to monitor a form of descending inhibition in patients and this allows prediction of treatment responses. Pre-clinically α2-adrenoceptor mediated mechanisms are shown to underlie a unique kind of descending inhibitory control, so called diffuse noxious inhibitory controls (DNIC). DNIC are spinal inhibitory mechanisms utilising descending controls where one pain can inhibit another from elsewhere in the body. In nerve-injured animals DNIC are restored either by blocking 5-HT_3 receptor mediated descending facilitations or by enhancing NA modulation through use of NRI's with or without MOR activity [24]. In the clinic the same phenomenon, termed conditioned pain modulation (CPM), is reduced in chronic pain patients, indicative of altered descending modulation and predictive of the actions of duloxetine, a SNRI [25,26]. Likewise tapentadol, a MOR-NRI, restores CPM in patients with a painful diabetic neuropathy [27].

Altering activity at monoamine synapses is the proposed mechanism underlying the analgesic effects of the aforementioned TCA's and SNRI's. The clinical success of drugs that enhance, for example, spinal NA activity, suggests that a strong descending inhibitory system may normally be engaged aiding protection against the development of chronic pain. The monoamines and their spinal cord concentration also play a key role in terms of the

analgesic efficacy of SNRI's and TCA's. The NA/5HT increase in the spinal cord following use of reuptake inhibitors is considered the main mechanism of action of the therapeutic benefit of anti-depressants in neuropathic pain. This increase is crucial to the anti-hyperalgesic efficacy of duloxetine – SNRI, and amitriptyline – TCA, although the plastic change of the descending NA system that occurs for example at certain time points following a nerve injury, does not obviously effect the analgesic efficacy of either drug [28]. The TCA's and SNRI's have greater efficacy than the serotonin reuptake inhibitors (SRI's) in neuropathic pain, perhaps explicable in terms of the discussed and well-established inhibitory NA tone and the widely pro-nociceptive action of 5-HT.

A recent study looked at the effect of a NRI versus a SRI on the anti-nociceptive action of morphine in mice under a stress condition. Pre-treatment with the NRI but not the SRI improved the anti-nociceptive action of morphine suggesting that under conditions of chronic stress the actions of morphine would be improved by activation of the NA but not serotonergic system [29].

Milnacipran inhibits the reuptake of the monoamines and also inhibits neuronal glutamatergic NMDA receptor activity in the dorsal horn of the spinal cord, revealing a shared mechanism of action regarding the analgesia induced by this anti-depressant [30]. Milnacipran is also prescribed for fibromyalgia where the beneficial effects observed are proposed to be due to effects on central pain modulation. Whether this efficacy depends on the performance of pain inhibitory controls is being investigated; in the clinic new trials are being developed that would allow estimation of the beneficial effect of milnacipran on pain and on descending pain pathways, as well as evaluating whether the performance of the modulatory system could be predictive of its efficacy in reducing pain [31].

NSAID's, anticonvulsants and opioid-based drugs

It is universally agreed that the mechanism of action of PGB and GBP is dependent on activity within functioning descending pathways [32]. Because there can be individual variations in pain comorbidities, variations in limbic function and consequently descending controls may explain why there are variable responses to such treatments in otherwise apparently uniform pain groups.

Tramadol and tapentadol have MOR activity as well as reuptake inhibitory action (SNRI and NRI respectively). The analgesic effects of tapentadol clearly rely on altering activity at monoamine synapses and therefore are dependent on activity in the descending circuits, with which the opioids interact also to produce direct supraspinal interactions. In addition, the interactive components of tapentadol are observed at supra-spinal sites including the right central nucleus of the amygdala, where there is a dose-dependent reduction in neuronal activity after nerve injury [33].

The synergistic relationship between opioid and α2-adrenoceptor agonists as analgesics is complex when considering that α2-adrenoceptor antagonists can inhibit opioid-based analgesia. It is suggested in fact that the α2-adrenoceptor has bi-directional modulatory effects on opioid anti-nociception since NA action at the α2-adrenoceptor facilitates morphine anti-nociception and ligand free α2-adrenoceptors inhibit opioid analgesia.

Clearly there is a complex interplay of sometimes opposing actions therefore between the opioid receptor and the α2-adrenoceptor [34].

As mentioned the NSAIDs induce peripheral anti-nociception by interaction with the adrenergic system [4]. The central analgesic effect of ibuprofen in the human brain includes activation of descending modulatory circuits in the post-surgical state [35].

Conclusion

Altering the synaptic levels of NA and 5-HT works to great effect in terms of pain scores and treatment outcomes in the clinic. We recognize the need for continued preclinical and clinical research to further advance the successful manipulation of the monoaminergic system in pain modulation.

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Key Points

- The monoamines have complex modulatory roles in pain signalling
- Descending controls can enhance or reduce the transmitted pain signal
- Pain inhibitions are attributed to α2-adrenoceptor activation and pain facilitations to 5-HT_3 receptor activation
- 5-HT has a bi-directional role in pain processing via inhibitory actions at the 5-HT_7 receptor
- Following injury there is plasticity in descending noradrenergic and serotonergic pathways