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Review

Gainfully employing descending controls in acute and chronic pain management

K. White[a,*], M. Targett[a], J. Harris[b]

[a] School of Veterinary Medicine and Science, University of Nottingham, Sutton Bonington, Loughborough LE12 5RD, UK
[b] School of Biosciences, University of Nottingham, Sutton Bonington, Loughborough LE12 5RD, UK

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ABSTRACT

Specific primary afferent fibres termed nociceptors are responsible for transmitting nociceptive information. Centrally the axonal terminals of these fibres synapse with secondary projection neurones in the spinal dorsal horn to transmit nociceptive information to the higher centres in the brain. Irrespective of the presence or absence of nociceptive inflow the activity of dorsal horn neurones is modulated by, amongst other things, local interneurones and descending midbrain and brainstem networks which can inhibit or facilitate dorsal horn transmission. These pathways therefore set the threshold for information inflow to the CNS. This review article summarises the anatomy, physiology and pharmacology particularly of these descending inhibitory and facilitatory pathways and explains why the study of descending modulation is essential if we are to develop more efficacious interventions for treating pain and relieving suffering.

Introduction

Much of what we know about pain to date has been discovered utilising various pharmacological and neurophysiological techniques in animal models and these discoveries have more recently been confirmed with genomics and advanced imaging. Nociceptors transmit information from the periphery to the dorsal horn of the spinal cord. Here the axonal terminals synapse with secondary projection neurones which then transmit nociceptive information to higher centres in the brain. The activity of these dorsal horn neurones is modulated by, amongst other things, local interneurones and descending midbrain and brainstem networks which can inhibit or facilitate dorsal horn transmission. These pathways therefore set the threshold for information inflow to the CNS. Neurophysiological modalities, such as electroencephalography (EEG), bispectral index (BIS), nociceptive withdrawal reflexes (NWRs) and somatosensory evoked potentials (SEP) have been used to study both afferent ascending and descending pain pathways and cortical representation of pain (Murrell and Johnson, 2006). Whilst some may argue that it is preferable to use behavioural outcome measures in conscious animals in order to better capture behavioural/learned and homeostatic mechanisms in response to a noxious insult, anaesthetized animal models can reduce the subjectivity and bias associated for example with quantifying a withdrawal response. Nonetheless, the emphasis in both anaesthetized and conscious patients, particularly in the study of chronic pain, should be that an appropriate parameter is measured (Mogil and Crager, 2004), but we are still some way off having a validated set of tools for testing all components of the pain experience. This review focuses particularly on the anatomy, physiology and pharmacology of the descending inhibitory and facilitatory pathways highlighting potential targets for pain modulation in animals and man.

Studying pain electrophysiologically

Electroencephalography provides a unique insight into how the nociceptive pathways contribute to pain perception. This technique utilises electrodes placed at various locations on the head producing the summated electrical activity of populations of neurones and glial cells (Murrell et al., 2005, 2008). Electroencephalography has numerous research and clinical applications (Teplan, 2002). The technique can be used in humans and animals to measure anaesthetic depth and antinociceptive effect of different drugs during anaesthesia (Rampil and Matteo, 1987; Johnson and Taylor, 1998). For example in ponies undergoing halothane anaesthesia, lidocaine obtunded the EEG median frequency (F_{50}) change, which is the frequency below which 50% of the power of the EEG is located, that occurred with surgical castration illustrating the use of intraoperative EEG monitoring

* Corresponding author.
E-mail address: kate.white@nottingham.ac.uk (K. White).

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and examination of F_{50} during application of a noxious surgical stimulus as a tool to investigate the antinociceptive action of different agents (Murrell et al., 2003, 2005). Direct recording of the activity of individual neurones during application of a noxious or non-noxious stimulus can provide information about the intensity, quality, duration and velocity of the stimulus and may involve recording from peripheral afferent sensory fibres or from dorsal horn wide dynamic range (also known as convergent) neurones (Dickenson and Le Bars, 1983; Bee and Dickenson, 2007; Kelly et al., 2012). Recording of NWRs is also an established neurophysiological technique consisting of applying a noxious stimulus, for example to the limb of an animal, and measurement of electromyographic (EMG) activity in muscles contributing to limb withdrawal (Levinsson et al., 1999; Clarke et al., 1992; Clarke and Harris, 2004). The withdrawal response, far from being a simplistic monolithic reflex, is a modular combination of reflexes to individual muscles arranged in a matrix to best withdraw or remove the limb from the inciting injury (Harris and Clarke, 2003, 2007). NWRs can be used as a direct measure of spinal cord hyperexcitability and thus a biomarker of central sensitization (Harris and Clarke, 2007). Central sensitization is defined as an increase in excitability of neurones in the central nociceptive pathways to normal or subthreshold input (Loeser and Treede, 2008), and is manifest as altered pain sensitivity (Woolf, 2011). In models of persistent pain, central sensitization causes a decrease in the threshold required to elicit an EMG response and is also characterized by enhanced temporal summation of NWRs, which describes an increased perception of pain in response to repetitive painful stimuli; both measures are used to evaluate changes in spinal cord nociceptive processing (Kelly et al., 2013). These techniques are used in rodents during anaesthesia, but NWR thresholds and temporal summation have also been measured in awake and anaesthetized dogs and horses using electrical stimuli to evaluate central sensitization, study the pharmacology of descending controls and characterise antinociceptive effects of analgesic drugs (Peterbauer et al. 2008; Bergadano et al. 2009; Levionnois et al. 2010; Hunt et al. 2016).

The spino-bulbo-spinal loop

A pain experience consists of both a somatosensory component and a psychological, affective component. The term nociception refers to the neural activity in the peripheral and central nervous system caused by a painful stimulus and the term pain itself is used to describe both this and the emotional and autonomic responses to the insult. These different components of pain are processed in separate, discrete areas of the brain. In most cases the nociceptive insult is the cause of pain, but this insult may be absent and its magnitude is not linearly related to the pain that is reported or behaviours that are displayed (Loeser and Treede, 2008). This is, in part, a consequence of a feedback loop between the brain and spinal cord. This spino-bulbo-spinal loop can alter the extent to which pain signals are amplified or inhibited within the spinal cord (Fig. 1).

Painful stimuli are sensed by a diverse range of nociceptor terminals, and initiate action potentials that travel along nociceptive afferents (non-myelinated C fibres or small diameter myelinated A delta fibres) which synapse with nociceptive specific (NS) cells in laminae I–II of the superficial dorsal horn, with a small number terminating deeper in the spinal cord. In contrast transmission of innocuous stimuli is predominantly through large diameter, myelinated A beta fibres which terminate predominately in laminae III–VI, hence within these laminae are proprioceptive neurones responding exclusively to touch. A third class of neurone, known as wide dynamic-range (WDR), can receive input from A delta, A beta or C fibres and responds in a graded manner (i.e. frequency of action potentials) from low through to high threshold noxious input. It is within the spinal cord that substantial transformation and modulation of the nociceptive signal can occur before it ascends to higher centres (Kayalioglu, 2009), due to discrete populations of intrinsic interneurones that can alter responses of NS and WDRs neurones, and astrocytes and microglia are also modulatory, particularly in disease states (Hains and Waxman, 2006; Scholz and Woolf, 2007; Ji et al., 2013). The ascending tracts are usually defined according to where they terminate in the brain (Dostrovsky and Craig, 2013). Briefly, the spinothalamic tract (terminating in the thalamus) integrates the thalamic traffic (and other signals) and is responsible for the discriminative/localisation component of pain via projections to the sensorimotor cortex, insular cortex and the anterior cingulate (Purves et al., 2001; Dum et al., 2009). The other major ascending partner tract is the spinobulbar tract (terminating in both the hindbrain and midbrain regions associated with pain processing) and this conveys the affective/intensity component, and projects to the amygdala and hypothalamus via the parabrachial nucleus (Craig, 2003). This spinobulbar pathway can influence and recruit descending pathways via the periaqueductal grey, pontine locus coeruleus and rostroventromedial medulla, thereby dictating the output passing through the spinal cord (Benarroch, 2008; Waters and Lumb, 2008).

Anatomy of the descending pathways

One of the most important structures associated with the descending pain control system is the region located around the aqueduct of Sylvius known as the periaqueductal grey matter (PAG) (Behbehani, 1995; Keay and Bandler, 2015). The PAG assimilates information from the somatosensory and cingulate cortices, the thalamus, amygdala and hypothalamus as well as directly receiving nociceptive input from the ascending pathways. However, although there is evidence for the PAG having direct projections to the spinal cord (Mantyh and Peschanski, 1982) spinal analgesia following its stimulation is considered to be due to its projections to the nucleus raphe magnus (NRM) and neighbouring structures of the rostral ventromedial medulla (RVM) (Vanegas and Schaible, 2004; Heinricher et al., 2009). In general, the descending pathways ascendancy can be considered to originate at the periaqueductal grey-rostral ventromedial medulla (PAG-RVM) and the ventrolateral medulla (Basbaum and Fields, 1979). Within the spinal cord the descending inhibitory influences are arranged in the dorsolateral funiculi with the facilitatory influences tending to be centred in the ventral/ventrolateral cord (Zhuo and Gebhart, 1997, 1990a, 1990b). The PAG-RVM exerts a degree of selective inhibition of C fibre mediated nociceptive impulses, but preserves A fibre messages coding sensory and discriminatory information (Lu et al., 2004; McMullan and Lumb, 2006a; Heinricher et al., 2009) and the RVM can be considered the final relay point through which facilitation or inhibition of the nociceptive message passes (Villanueva and Le Bars, 1995; Calejesan et al., 2000). The degree of inhibition or facilitation of the pain signals in some part is controlled in the RVM by at least two different types of neurones known as ON-cells and OFF-cells and these cells are inextricably connected to the higher brain centres involved in a large number of emotions, psychological states, stresses, and pathologies. The role of these cells may be more complicated than previously thought (Cleary et al., 2008; Lau and Vaughan, 2014; Salas et al., 2016). Despite the overwhelming evidence for the major role of the RVM as a relay station, it is without doubt that the descending pathways also require a forebrain loop (Millan, 2002). There is also evidence for anterior cingulate cortex (ACC) projections regulating spinal neurones (Gu et al., 2015; Kang et al., 2015) and being able to selectively