The Veterinary Journal 237 (2018) 55–62

Contents lists available at ScienceDirect

The Veterinary Journal

journal homepage: www.elsevier.com/locate/tvjl

Review

The neurobiology of acute pain

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ARTICLE INFO

Article history:
Accepted 15 May 2018

Keywords:
Analgesia
Neurobiology
Nociception
Pain
Spinal cord

ABSTRACT

The mechanisms by which noxious stimuli produce the sensation of pain in animals are complex. Noxious stimuli are transduced at the periphery and transmitted to the CNS, where this information is subject to considerable modulation. Finally, the information is projected to the brain where it is perceived as pain. Additionally, plasticity can develop in the pain pathway and hyperalgesia and allodynia may develop through sensitisation both peripherally and centrally. A large number of different ion channels, receptors, and cell types are involved in pain perception, and it is hoped that through a better understanding of these, new and refined treatments for pain will result.

Introduction

Pain is the subjective experience of harm in a part of one's body, and is currently more strictly defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (Williams and Craig, 2016). By this definition it is an experience, which therefore requires activity of structures in the brain to be perceived. This is in contrast to nociception which is defined as the encoding and processing of noxious stimuli in the nervous system. Pain has a fundamentally important protective role, alerting us to threats and providing an impetus for the preservation of the integrity of the body. However, in the context of veterinary treatment of illness or injury, acute pain may become an unwanted consequence that compromises the welfare of animals in our care. The implications of chronic pain, which is generally defined as pain that extends beyond the normal duration of healing, can be even more detrimental to wellbeing and is covered in another article within this issue.

A wide variety of thermal, chemical, mechanical and inflammatory stimuli can trigger pain and the experience of clinical pain is likely a complex amalgam of these stimuli perceived after significant modulation in the central nervous system. Pain may also result from a lesion or disease of the nervous system itself. However, the complex mechanisms of this so-called neuropathic pain, which have received significant attention from pain researchers, are not covered in detail in this review.

The nociceptive pathway that carries signals from the periphery to the brain where pain is perceived can be broken into components: *Transduction* of noxious stimuli at the periphery, *transmission* of those stimuli to the central nervous system (CNS), *central integration and modulation* of the signals at the CNS level, and finally *projection* to the brain followed by *perception*. This article aims to detail the important cellular and molecular mechanisms of each of these stages.

Transducing the stimulus at the periphery; the role of the nociceptor

Nociceptors are primary afferent neurons which project from tissues including skin, muscle, joints and viscera to the spinal cord or its trigeminal equivalent in the brainstem. Unlike other classes of primary afferents, e.g. those that convey touch, nociceptors preferentially transduce stimuli with intensities in the noxious range allowing them to respond to injurious stimuli (Basbaum et al., 2009). Anatomically, the cell bodies of nociceptors are located in the dorsal root ganglia (DRG) adjacent to the spinal cord or in the trigeminal ganglia in the case of sensory information arising from the face. Their axons arise from these cell bodies and have both a peripheral branch that innervates the tissues where stimuli are transduced, and central branch innervating the spinal cord. While other classes of sensory primary afferents may have complex peripheral apparatus for the detection of stimuli, e.g. Meissner's corpuscles for low threshold touch, nociceptors are present at the periphery as simple branched free nerve endings (Lumpkin and Caterina, 2007). Despite this apparently simple anatomical arrangement, nociceptors have a complex array of cellular and molecular machinery that enables stimulus transduction, as detailed below.

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https://doi.org/10.1016/j.tvjl.2018.05.004
1090-0233/

Classifying nociceptors

Primary afferent neurons are classically characterised by their diameter and degree of myelination which both determine their conduction velocity (Table 1). Most large myelinated afferents (termed Aβ fibres) are low frequency mechanoreceptors which respond to touch or hair movement (Abraira and Ginty, 2013). Two major classes of nociceptor exist. The first are medium diameter, myelinated afferents (Aδ) and these are responsible for the transmission of well-localised 'fast' or 'first' pain (Ringkamp et al., 2013). The second are unmyelinated, small C-fibre nociceptors which convey poorly localised 'slow' pain. The Aδ nociceptors can be further subdivided into two functional groups (Treede et al., 1998). Type I Aδ nociceptors respond to mechanical and chemical stimuli but have high heat thresholds but will sensitise in the context of tissue injury. These fibres are probably responsible for 'first' pain from mechanical stimuli such as a pin prick. Type II fibres have a much lower heat threshold and a high mechanical threshold and are involved in 'fast' pain responses to heat.

Mammalian C-fibre nociceptors can be further classified, not by their functional or conduction properties but on a molecular basis based on receptors and neurochemicals that they express. A wide range of markers has been studied with the aim of defining neuronal subpopulations and correlating these with the response properties of the nociceptors. It is common practice to divide the nociceptive C-fibres into two groups; the peptidergic fibres marked by the expression of calcitonin gene-related peptide (CGRP) and substance P, and the non-peptidergic group identified by their binding of isolectin B4 (IB4) (Snider and McMahon, 1998). A plethora of other single markers, such as the transient receptor potential channels (TRP channels) and the Mrg family of G-protein linked receptors, have been suggested to define functional populations (Zhang et al., 2013) but recent unbiased molecular strategies aiming to define classes within all sensory primary afferents indicate the situation is clearly more complex (Usoskin et al., 2014; Li et al., 2016). These studies have sought to define primary afferent heterogeneity using modern molecular techniques to analyse mRNA transcripts in the cell bodies of DRG neurons. Individual cells can then be classified, not by a single marker, but by the constellation of genes that they express. The result is that primary afferents are grouped on a molecular basis into ten or eleven subgroups and in one study the functional significance of these groups has been interrogated (Li et al., 2016).

It is of interest that not all sensory C-fibres are nociceptive. Small subgroups of C fibres appear to be specifically responsible for itch transduction and are termed pruritoceptors (Han et al., 2013; Mishra and Hoon, 2013). Additionally, two small classes of C-fibres are low threshold afferents (termed C low threshold mechanoreceptors, (C-LTMR)) that are involved in the transduction of pleasant or gentle touch sensations (Seal et al., 2009; Vrontou et al., 2013).

Much of the knowledge about nociceptors is derived from those that innervate the skin, so called cutaneous nociceptors, rather than those that innervate the viscera and convey the impulses that can lead to the sensation of visceral pain. As such, much of what is presented in this section is relevant only to cutaneous nociceptors. In some respects, visceral sensory neurons with the capacity to convey nociceptive information are similar to cutaneous nociceptors; their cell bodies are present in the DRG (or nodose ganglia in the case of vagal visceral afferents), and they generally possess thinly myelinated or unmyelinated axons and small to medium sized cell bodies (i.e. Aδ and C fibres). Some visceral afferents, however, traverse pre- and paravertebral ganglia en route to the spinal cord (Gebhart and Bielefeldt, 2011). Importantly, the viscera are sparsely innervated compared to the non-visceral tissues, and visceral nociceptors have markedly different response properties. Specifically, visceral nociception and hence pain does not arise from cutting or burning of organs, rather it arises from distension, traction, ischaemia and through release of chemical mediators of inflammation. While our knowledge of the biochemical differences underlying these functional differences is incomplete, it is safe to say that the make-up of receptors and ion channels present on visceral nociceptors is unique, and several notable differences have been reported (Robinson and Gebhart, 2008).

Mechanisms of stimulus transduction

Acute noxious stimuli may be thermal, mechanical or chemical and specific ion channels and G-protein linked receptors are involved in conversion of the stimulus into electrical signals in the primary afferents. These channels generate an electrical current through either opening, hence allowing the influx of Na^+ or Ca^{2+}, or closing if the channel is responsible for a hyperpolarising current (e.g. a K^+ channel) (Gold, 2013). Many chemical stimuli act via G-protein linked receptors and in these cases intracellular signalling pathways indirectly modify ion channel activity.

The specific channels and receptors that transduce stimuli have been studied extensively with the transient receptor potential channels (TRP channels) being of importance. In the case of heat sensation the TRP Vanilloid 1 (TRPV1) channel would appear to play a prominent role (Cavanaugh et al., 2009). This is of particular interest as TRPV1 is the receptor for capsaicin, the active ingredient in chilli peppers, and there has been significant attention paid to developing drugs acting here (Brown, 2016). TRPV1 is one of some 30 or so members of the transient receptor potential family with other channels also important for stimulus transduction. TRP Melastatin 8 (TRPM8), the receptor for menthol, is proposed to have major roles in the transduction of cold stimuli (Bautista et al., 2007). Other thermotransducers also contribute to temperature sensation and these include two-pore potassium channels (K2P) (Noël et al., 2009) and voltage gated sodium channels (Zimmermann et al., 2007). A number of candidate proteins have also emerged as important contributors to noxious mechanosensation. These include the acid-sensitive ion channels (ASICs) (Omerbašić et al., 2015), Piezo channels (Coste et al., 2010), TRP Ankyrin 1 (TRPA1) (Corey et al., 2004), and K2P channels, although the molecular basis for mechanotransduction requires further clarification (Basbaum et al., 2009).

The ability to detect chemical signals is an important requirement for an organism for avoiding both environmental noxious chemicals and also to detect endogenous irritants that may be produced as a result of injury and inflammation. The TRP channels are particularly important here acting as the receptors for capsaicin (TRPV1), mustards and garlic (TRPA1), and a wide array of

Table 1
The classification of primary afferents by fibre diameter and conduction velocity.

Classification	Diameter	Myelin	Conduction velocity	Sensory function
Aβ	Large (6–12 μm)	Yes	>35 m/s	Touch
Aδ	Medium (1–5 μm)	Thin	5–35 m/s	'Fast' pain
C	Small (0.2–1.5 μm)	No	<2.0 m/s	'Slow' pain