Anatomy, physiology and pharmacology of pain

Michael J Hudspith

Abstract

Pain is a complex emotional experience arising from integrated processing of nociceptive input subject to inhibitory and excitatory modulatory influences at multiple levels of the neuraxis. Transmembrane protein ion channels transduce mechanical, thermal and chemical tissue injury into electrophysiological signals that are transmitted to supraspinal structures via multiple synapses that exhibit neuroplasticity dependent upon coincident neuronal and glial activation. There are therefore multiple potential pharmacological targets and the complexity of pain perception necessitates multimodal management.

Keywords Central sensitization; glia; nociceptor; pain; peripheral sensitization

Royal College of Anaesthetists CPD Matrix: 1A01 1A02 3E00

Learning objectives

After reading this article, you should be able to:

- draw and review the major ascending and descending pathways associated with nociception and pain processing
- understand the excitatory and modulatory processes involved in nociceptive signal transduction and neurotransmission
- explain the contribution of peripheral and central sensitization to nociception and pain perception
- synthesize a basic mechanism-based approach to pharmacological management of pain

Pain is a complex *sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage* (International Association for the Study of Pain): it is therefore an integrated conscious experience. Pain differs from nociception, a phenomenon defined as the neural process of encoding noxious stimuli. Multiple ascending and descending pathways enable modulation of nociceptive input at multiple levels from periphery to CNS. Exploration of the concepts of pain therefore necessitates an understanding of the transduction of physicochemical stimuli into neural signals that are transmitted, subject to modulatory influences and ultimately processed by cortico-thalamic networks to enable conscious perception and interpretation as an unpleasant experience. Pain is a highly plastic neurophysiological process that appears to be necessary to human existence as congenital insensitivity to pain is associated with unrecognized trauma and progressive disability. Acute pain therefore serves an immediate protective purpose and may produce subsequent learned behaviours to avoid trauma and injury. However, pathological pain, where frequently the relationship between ongoing nociception and the subjective perception of pain can be obscure, is a major cause of human suffering with UK population studies indicating that 11% of adults and 8% children report ongoing severe pain.

Pain transduction

Noxious (i.e. actually or potentially tissue damaging) stimuli may be mechanical, chemical or thermal: transduction defines the conversion of such noxious stimuli by a *nociceptor* to a coded electrophysiological neural signal in form of an action potential that is propagated towards the CNS.

Nociceptors are primary afferent pseudounipolar neurons whose cell bodies are located in the dorsal root ganglia and Gasserian ganglia (for trigeminal afferents). The peripheral processes of nociceptor neurons ramify profusely and innervate a wide variety of tissues where they lose their peri-neural sheath: their central processes project to the dorsal horn. Nociceptive afferent peripheral terminals are morphologically 'free' nerve endings that lack the specialized terminal structures associated with low-intensity transducers (c.f. Pacinian or Meissner corpuscles). Approximately 10% of mammalian cutaneous myelinated fibres and 90% of unmyelinated fibres are nociceptors.

Acute injury is associated with a well-localized *first pain* sensation transduced and transmitted by Aδ nociceptors followed by a dull and more diffuse *second pain* sensation mediated by C-fibre nociceptor activation.

Aδ nociceptors are thinly myelinated fibres (2–5 μm diameter with conduction velocity 6–30 m/second) and are categorized according to their stimulation threshold. Type I high-threshold mechanoreceptors (HTM) are activated by heat (>50°C) and noxious mechanical stimuli. These type 1 HTM sensitize with injury and are responsible for first pain pinprick sensation. Type II HTM have a significantly lower thermal threshold (45°C heat) but a much higher mechanical threshold and underlie first pain heat responses.

The majority of cutaneous and somatic nociceptors that initiate second pain sensation are C-fibre polymodal nociceptors (<2 μm diameter with conduction velocity <2 m/second) responsive to a wide range of stimuli that include noxious thermal (>45°C), noxious mechanical and noxious chemical stimuli. A further population of C-nociceptors that are heat-responsive but (under normal conditions) mechanically insensitive can also be identified. In the presence of inflammation these *silent nociceptors* develop mechanical sensitivity.

Pharmacologically, C polymodal nociceptors can be subdivided into peptidergic C-fibres, expressing SP, CGRP and the TrkA high-affinity receptor for NGF and non-peptidergic C-fibres expressing P2X3 and the c-Ret receptor for GDNF. In addition, nociceptor expression of tyrosine hydroxylase defines low-threshold C-fibre mechanoreceptors.

It should be noted that not all C-fibres are nociceptors, with certain subsets of C-fibres responsible for sensations of cooling, itch and even some forms of pleasant touch sensation.

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Nociceptor transduction mechanisms

The peripheral terminal axonal membranes of Aδ and C nociceptors are populated with ionophores that enable specific transduction of noxious stimuli.

Thermal nociception is subserved by non-selective cation channels of the transient receptor potential channel superfamily (TRP). Noxious heat transduction is characterized by TRPV1 (vanilloid or capsaicin sensitive) receptor channel expression, whereas noxious cold transduction is characterized by the expression of the TRPM8 (menthol-sensitive) receptor. Knockout studies in rodents indicate that non-TRP mechanisms of thermal nociception may also exist such as those involving K_{2P} potassium channel ionophores.

TRP channels are also important in chemical nociception with the TRPA1 receptor activated by a variety of irritant agents. Ischaemia and inflammation producing acidic tissue conditions due to H^+ ion release and accumulation results in the activation of separate population of acid-sensing (ASIC) channels in nociceptor terminals that are proton-activated cation ionophores.

The mechanisms of mechanical nociception are less well characterized although a number of candidate channels (classified as MeT receptors) have been proposed including: mechanically activated Na^+-channels of the DEG/ENaC class which includes the ASIC receptor; certain cation channels of the TRP superfamily such as the TRPV2 and TRPA1 receptors and also mechanically sensitive 'two-pore' potassium channels (K_{2P} channels).

Membrane deformation results in the altered gating of cation ionophores and there is clear overlap between classes of mechano-receptors, thermoreceptors and chemoreceptors that define the response characteristics of polymodal nociceptors.

Nociceptor transmission

Transmission defines the communication of an electrophysiological signal in the form of action potentials, initiated through nociceptor ionophore opening via the nociceptor axon to multiple ascending pathways from periphery to CNS via the spinal cord dorsal horn.

Nociceptor electrophysiology

Sodium channels: action potential generation in primary afferent neurons is dependent upon voltage-operated sodium channel (NaV) opening. Multiple NaV isoforms exist: NaV 1.1 −1.9, of which the TTX-sensitive NaV 1.1, 1.6, 1.7 and the TTX-resistant NaV 1.8 and 1.9 are expressed in adult mammalian sensory neurons. NaV 1.7 and 1.8 are preferentially localized to nociceptors such that NaV 1.7 dysfunction is associated with human pathological pain states and NaV 1.8 knockout animals have attenuated mechanical nociception.

Potassium channels: resting membrane potential and repolarization following nociceptor action potential generation is determined by a complex array of voltage-operated potassium channels.

Kv (delayed rectifier channels) − channel opening by the Kv family inhibits nociceptor excitation and modulates nociceptor repolarization and firing frequency. Reduced Kv activity contributes to neural hyperexcitability in certain forms of peripheral neuropathic pain (NeP). Agents potentiating Kv channel opening (such as retigabine) have potential analgesic and anticonvulsant activity.

K_{2P} (two-pore channels) − the K_{2P} channel family determine K^+ leak currents and contribute to setting of resting membrane potential and baseline excitability of sensory afferents. Multiple members of the family including TREK1 and TRAAK channels are expressed in nociceptors. As discussed above, these channels may also play roles in both thermal and mechanical nociception.

Bidirectional transmission: the pseudounipolar neuronal structure of the nociceptor (a dorsal root ganglion cell body with a short axon branching into long peripheral and short central components) enables bidirectional action potential signal transmission.

Antegrade transmission from peripheral nociceptor terminal to central terminals results in Ca^{2+}-dependent release of the excitatory amino acid glutamate in conjunction with neuropeptides such as SP and CGRP. Retrograde transmission from dorsal root ganglion to periphery enables peripheral terminal Ca^{2+}-dependent release of neuropeptides SP, CGRP that contribute to neurogenic inflammation and peripheral sensitization.

Nociceptor Ca^{2+}-channels: there are three major classes of neuronal voltage operated Ca^{2+} channels (Ca_v1, Ca_v2 and Ca_v3) of which the Ca_V2 members $Ca_V2.1$ (P- and Q-channels) and $Ca_V2.2$ (N-channels) are the mediators of synaptic vesicle release associated with fast synaptic transmission mediated by axonal action potential transmission at the dorsal horn. Dorsal horn neuronal threshold excitability is modulated by low voltage-activated Ca_v3 (T-channels) that also contribute to low threshold exocytosis and 'volume transmission' of neurotransmitters and neuromodulators.

Although Ca_V1 high voltage-activated Ca^{2+}-channels (L-channels) do not contribute to fast synaptic transmission, they comprise α2δ ancillary subunits in association with the pore-forming Cavα1 subunit and play a modulatory role in dorsal horn (and possible peripheral) excitation. Up-regulation of the α2δ subunit is causal to the development of neuropathic pain and is the target for gabapentinoid drugs.

Anatomical considerations (Figure 1)

Proximal to the dorsal root ganglia, the central processes of sensory afferents terminate in the dorsal horn where they may penetrate the grey matter directly or (predominantly in the cervical region) form collateral branches ascending or descending one or two spinal segments as Lissauer's dorsolateral tract before terminating. The dorsal horn has a laminar cytoarchitecture (Rexed laminae I − X) with electrophysiologically discrete characteristics and the termination site of nociceptors is determined by their structural and pharmacological characteristics. Thus, peptidergic C-fibres terminate in lamina I and the more superficial layer of lamina II, whereas non-peptidergic C-fibres terminate more deeply in lamina II. Aδ fibres terminate both in lamina I and lamina V.

The synaptic targets of nociceptors in lamina I and lamina V are second-order neurons forming the origin of the multiple ascending pathways. However, the output of lamina II synapses is predominately via interneurons projecting deeper to lamina V.