Anatomy, physiology and pharmacology of pain

Michael J Hudspith

Abstract

Pain is neither a mere sensation nor a simple warning of potential or actual bodily injury: rather it a complex emotional experience arising from integrated processing of nociceptive input subject to inhibitory and excitatory modulatory influences at multiple levels of the neuro-axis. 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 immune cell interactions. There are therefore multiple potential pharmacological targets and the complexity of pain perception necessitates multimodal management.

Keywords Central sensitization; glia; inflammation; 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
- recall the importance of immune cell — nociceptor interactions in acute and chronic pain
- 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* (IASP): it is therefore an integrated conscious experience whose neural correlate is considered to be the integrated activation of a spatially diffuse 'pain matrix' or 'pain connectome'.

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 each synapse from periphery to cortico-thalamic networks. To understand the concepts of pain therefore necessitates an exploration 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 as a stimulus that may be threatening to bodily integrity. Pain therefore arises from a highly plastic neurophysiological process and appears to be necessary to human existence: congenital insensitivity to pain is associated with unrecognized trauma and progressive disability. Acute pain may serve an immediate protective purpose and produce subsequent learned behaviours to avoid future 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. When considering clinical pain scenarios, it must be acknowledged that nociception can take place in the absence of pain, and conversely pain can be experienced in the absence of nociception.

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Pain transduction

Noxious (i.e. actually or potentially tissue damaging) stimuli may be mechanical, chemical or thermal. Transduction defines the conversion of noxious stimuli by a *nociceptor* to a coded electrophysiological neural signal in form of action potentials that are propagated toward the central nervous system.

Nociceptors are primary afferent pseudounipolar neurons whose cell bodies are located in the spinal dorsal root and trigeminal (Gasserian) ganglia. The peripheral processes of such neurons ramify profusely and innervate a wide variety of tissues where they lose their peri-neural sheath. Proximal to the dorsal root ganglion, nociceptor central processes project to the dorsal horn. Nociceptor peripheral terminals are 'free' nerve endings that lack the morphologically 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 ms^{-1}) and may be categorized according to their stimulation threshold. Type I HTM (high threshold mechanoreceptors) 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-fiber polymodal nociceptors (<2 μm diameter with conduction velocity <2 ms^{-1}) 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 *silent nociceptors* may 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.

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 (TRP) channel superfamily. Noxious heat transduction is characterized by capsaicin-sensitive TRPV1 (vanilloid) receptor channel expression, whereas noxious cold transduction is characterized by the expression of the menthol-sensitive TRPM8 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.

Chemical nociception activates TRP channels of a separate class; thus the TRPA1 receptor is activated by a variety of irritant agents. Ischaemia and inflammation producing acidic tissue conditions due to H^+ ion release and accumulation results in concurrent activation of further population of proton-activated cation ionophores categorized as acid sensing (ASIC) channels.

The precise mechanisms of mechanical nociception are less well defined, although a number of candidate channels (classified as mechano-transducting or MeT receptors) have been proposed including: mechanically activated Na^+-channels of the DEG/ENaC class (for example ASIC receptor); certain cation channels of the TRP superfamily such as the TRPV2 and TRPA1 receptors and also mechanically sensitive '2-pore' potassium channels (K_{2P} channels). More recently, the sequencing of structurally unique mechanosensitive piezo channels identifies a potential transducer that plays a key role in low threshold Aβ-fibre mechano-sensation. While recent data indicates that the piezo2 channel underlies NGF-induced mechano-sensitization of silent nociceptors, the role of piezo channels in physiological cutaneous mechanical nociception remains incompletely defined.

In summary, membrane deformation results in 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

Nociceptor ionophore-mediated depolarization, when sufficient to initiate a suprathreshold stimulus, results in sodium channel (Na_V)-mediated action potential propagation along the nociceptor axon to the dorsal horn and thence via multiple ascending pathways from periphery to central nervous system.

Nociceptor electrophysiology

Sodium channels (Na_V)

Action potential generation in primary afferent neurons is dependent upon voltage-operated sodium channel opening. Nine Na_V isoforms exist: $Na_V1.1-1.9$, of which the TTX-sensitive Na_V 1.1, 1.6, 1.7 and the TTX-resistant $Na_V1.8$ and 1.9 are expressed in adult mammalian sensory neurons. Na_V 1.7 and 1.8 are preferentially localized to nociceptors such that $Na_V1.7$ dysfunction is associated with human pathological pain states and $Na_V1.8$ knockout animals have attenuated mechanical nociception.

Potassium channels (K_V)

Resting membrane potential and repolarization following nociceptor action potential generation is modulated by a complex array of voltage-operated potassium channels.

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

K_{2P} (2-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 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.

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 DRG 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 (Ca_V): 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 express α2δ ancillary subunits in association with the pore forming $Ca_V\alpha1$ 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 certain forms 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 1 or 2 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.

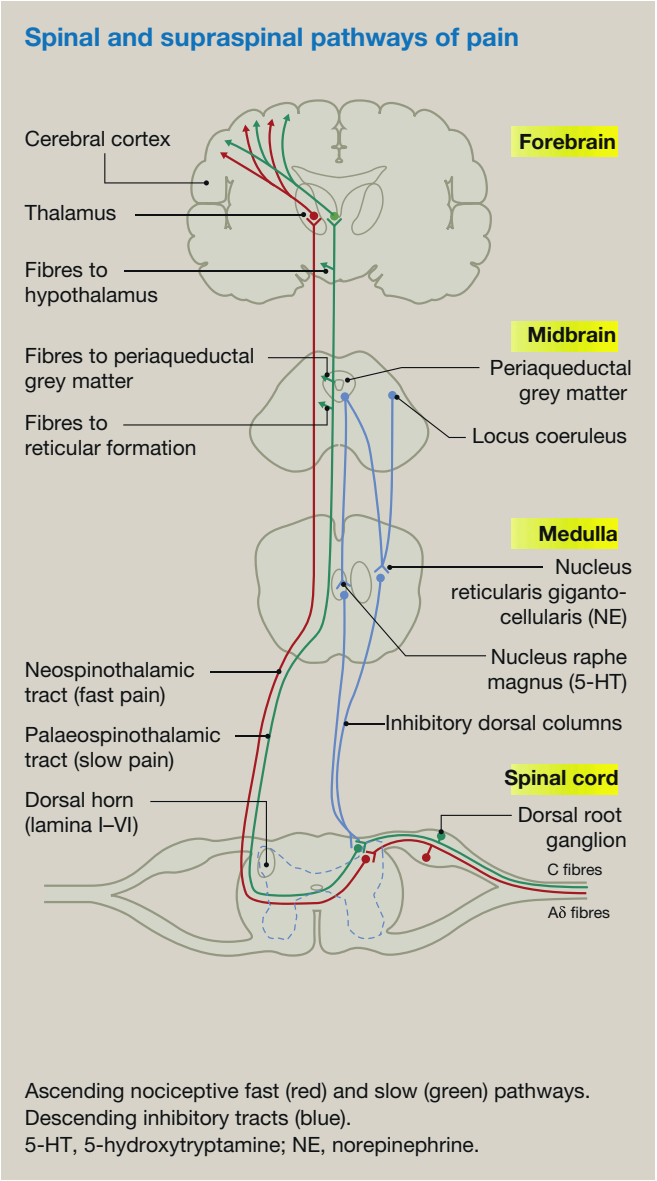


Figure 1

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. Those lamina V projection neurons receiving convergent input from Aδ nociceptors, lamina II interneurons and Aβ fibres (from lamina III and IV) are wide dynamic range (WDR) neurons that may also receive segmental input from visceral afferents.

The major nociceptive output from the dorsal horn comprises laminae I and V second-order neurons that constitute the crossed spinothalamic and spinoreticulothalamic tracts projecting to contralateral thalamic and brainstem nuclei. The majority of ascending spinothalamic neurons synapse with somatotopic arrangement in the ventral posteriorolateral thalamic nucleus (VPL) and provide a rapid oligosynaptic *neothalamic* pathway mediating sensory-discriminative aspects of nociceptive input to higher centres. In contrast, spinoreticulothalamic neurons project via a predominantly crossed polysynaptic pathway with less precise somatotopic organization. In the brainstem, these spinoreticulothalamic neurons synapse in close apposition to autonomic centres and have collateral input to regions involved in descending modulation of pain before projecting to medial thalamic nuclei. This *palaeothalamic* pathway contributes to the negative affective component of pain. Other polysynaptic pathways critical to the aversive and emotional component of pain include spinoparabrachial projections to the dorsolateral pons from which there is direct output to the amygdala and limbic nuclei.

In contrast to anatomically defined areas such as primary visual or sensory cortical areas, there is no equivalent primary pain or nociceptive cortex to which ascending nociceptive input is directly relayed. Rather, positron emission (PET) and fMRI neuroimaging studies demonstrate that it is synchronized processing of VPL output to somatosensory cortex (and other areas associated with sensory-discriminative processing) integrated with polysynaptic activation of areas involved in emotion (such as anterior cingulate and insular cortex) and fear or anxiety (e.g. amygdala and limbic structures) that correlates with the complex experience of pain. Moreover, co-ordinated activation of areas involved in behavioural planning (such as prefrontal cortex) and motor response (for example basal ganglia and cerebellum) may also have a fundamental role in human pain experience.

Peripheral sensitization

The activation threshold of both polymodal C-fibre nociceptors and HTM Aδ-nociceptors is under dynamic control dependent upon the surrounding cellular milieu. Tissue injury results in release of intracellular contents from cellular disruption, local sympathetic efferent discharge and influx of activated cells such as macrophages, lymphocytes and mast cells resulting in a cascade of events initiating the peripheral inflammatory response and generating an inflammatory sensitizing soup of which key constituents include: bradykinin, H^+ ions, ATP, purines, prostaglandin E2, leukotrienes, cytokines (e.g. TNFα and IL-1β) and nerve growth factor (NGF) (Figure 2).

Upregulation of TRPV1 receptor threshold is a key mechanism underlying thermal hyperalgesia. Proposed mechanisms involve direct positive allosteric modulation of TRPV1 (e.g. by H^+ ions)

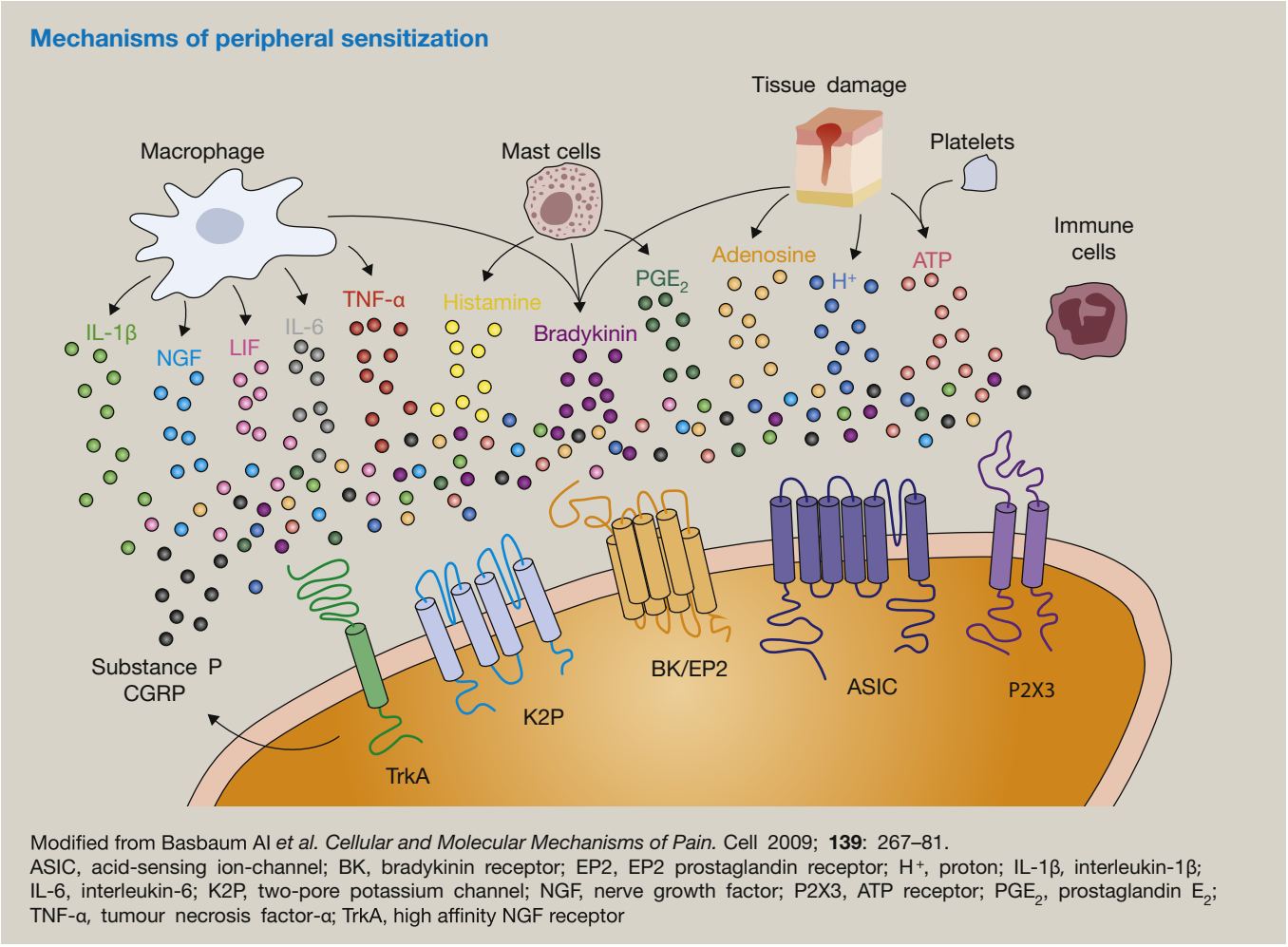


Figure 2

and downstream phosphorylation by intracellular 2nd messenger action (e.g. via the BK or P2X3 receptor).

NGF released by activated macrophages, acts directly upon peptidergic C-fibres expressing the TrkA receptor and is a key component of peripheral sensitization. NGF-TrkA interaction results in intracellular phosphorylation of TRPV1 and rapid development of thermal hyperalgesia. Similar mechanisms involving other nociceptor terminal transducer proteins may contribute to mechanical hyperalgesia.

NGF, once bound to the TrkA receptor, is internalized and translocated by retrograde axonal transport mechanism to the dorsal root ganglion resulting in gene expression with increased or novel synthesis of substance P, TRPV1 and Nav1.8 contributing to a delayed enhancement of peripheral nociceptor function. This phenotypic change underlies the transition of 'silent nociceptor' to mechanically sensitive low threshold nociceptors in inflammatory conditions involving activation or unmasking of piezo2 channels.

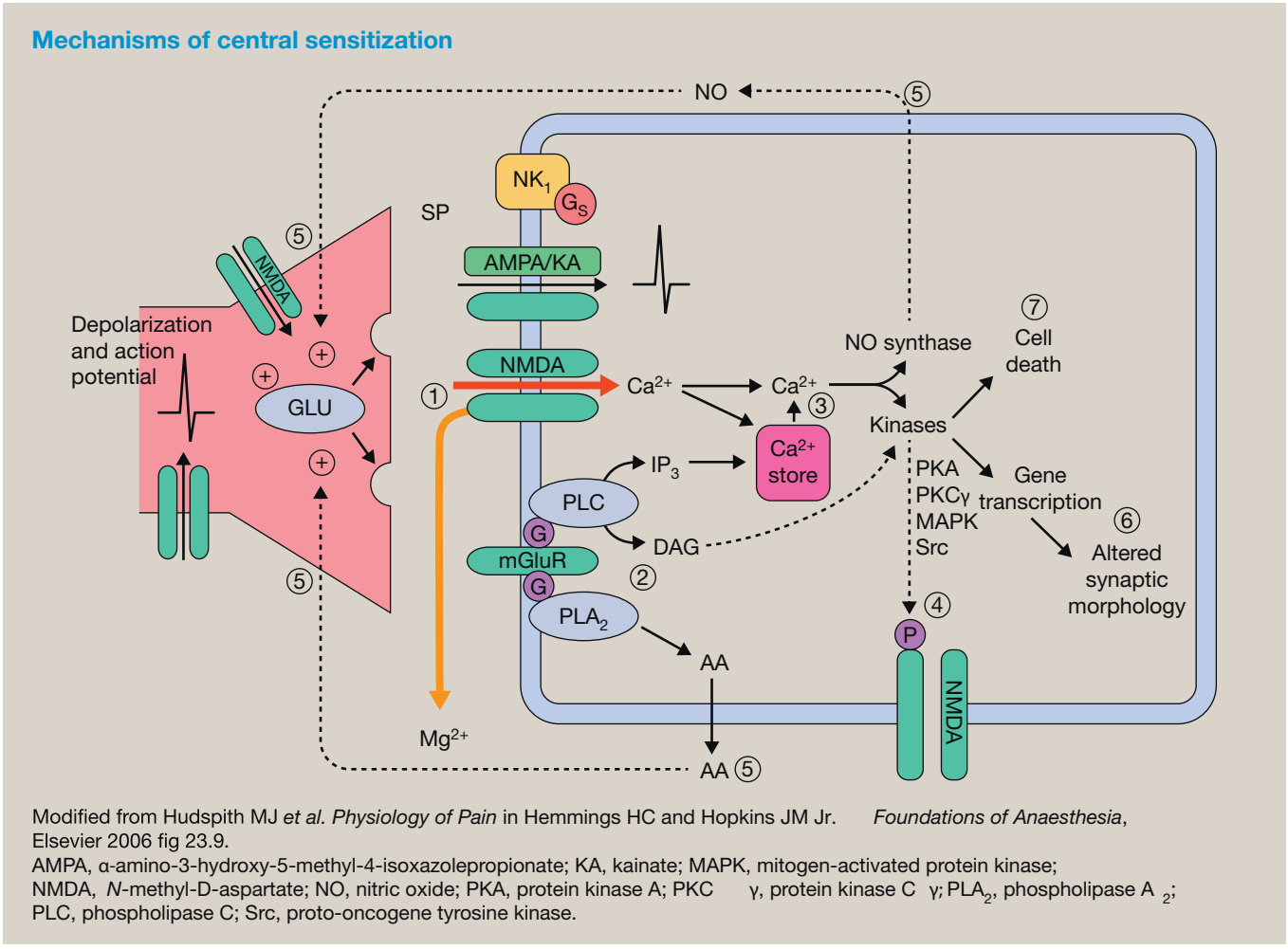
The macrophage response to injury also involves the release of cytokines IL-6, IL-1β, TNF-α. These contribute to peripheral sensitization via increased local production of proalgesic agents including bradykinin, prostaglandins and further release of NGF by inflammatory cells.

Cytokine inhibitors form the basis of rheumatological disease modifying (DMARD) therapy and markedly reduce pain and hyperalgesia in rheumatoid arthritis and inflammatory spondyloarthropathies. Anti-NGF agents remain under development for peripheral inflammatory pain syndromes.

Dorsal horn pharmacology and central sensitization

The central terminals of Aδ and C-nociceptors in common with all sensory afferents, release glutamate as a primary fast neurotransmitter in the dorsal horn. In contrast to peripheral synapses, the concept of a single neuron releasing a single transmitter within a synaptic cleft does not apply: nociceptors co-express excitatory amino acid alongside peptide and neurokinin transmitters (e.g. CGRP and SP) with multiple transmitters being released in response to nerve terminal depolarization. The precise ratio of co-transmitter release is dynamic and dependent upon stimulus parameters. Moreover, both local synaptic cleft transmission and 'volume' transmission (activation of distant receptors) are implicated in dorsal horn nociception.

AMPA/KA receptors: Peripheral nociceptor axonal action potentials result in Ca^{2+}-mediated quantal release of glutamate



Modified from Hudspith MJ *et al. Physiology of Pain* in Hemmings HC and Hopkins JM Jr. *Foundations of Anaesthesia*, Elsevier 2006 fig 23.9.
AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate; KA, kainate; MAPK, mitogen-activated protein kinase; NMDA, *N*-methyl-D-aspartate; NO, nitric oxide; PKA, protein kinase A; PKC γ, protein kinase C γ; PLA_2, phospholipase A $_2$; PLC, phospholipase C; Src, proto-oncogene tyrosine kinase.

Figure 3

from synaptic vesicles in the dorsal horn that generate excitatory post-synaptic currents (EPSC) in second-order neurons. EPSC arise as a consequence of Na^+-ion entry via activation of AMPA and Kainate subtypes of ionotropic glutamate receptors. The second-order neuron will generate a consequent action potential when EPSCs summate to threshold potential, thus initiating the transmission of a nociceptive signal to higher centres. Short lived, low intensity but suprathreshold nociceptor activation (such as associated with 'first pain' phenomenae) results in AMPA/KA mediated action potential generation in the dorsal horn while the NMDA receptor remains quiescent due to channel blockade by Mg^{2+}-ions.

NMDA receptors: High-intensity and/or prolonged nociceptor activation in association with injury and inflammation (and also 'injury discharge' potentials caused by peripheral nerve transection) produce sufficient release of glutamate in conjunction with co-release of neurokinins such as SP to maintain neuronal membrane depolarization above approximately −40 mV such that Mg^{2+} ions dissociate from the NMDA receptor. Ca^{2+} entry through such glutamate-activated NMDA channels initiates the cascade of events (initially reversible) associated with central sensitization (Figure 3).

Central sensitization

Elevation of intraneuronal Ca^{2+}ion concentration in second-order and WDR neurons results in activation of a host of second messenger and cellular signaling pathways. Most notable are the intracellular and cytosolic kinases including MAPK, PKA, PKCγ and Src. Auto-phosphorylation of the NMDA receptor by cytosolic PKCγ results in attenuation of the Mg^{2+} gating of the receptor such that ongoing lower intensity nociceptor input can continue to maintain elevated dorsal horn intraneural Ca^{2+} levels and strengthen synaptic connections. Supra-normal Ca^{2+} entry supplemented by Ca^{2+} release from intraneural stores mediated by metabotropic glutamate receptor and neurokinin receptor activation initiate Ca^{2+}-mediated changes in gene expression and associated phenotypic shifts in dorsal horn nociceptive neurons.

NMDA receptor activation underlies the electrophysiological phenomenon on dorsal horn wind-up and clinically manifests as a broadening of sensory fields and allodynia associated with secondary hyperalgesia. Central sensitization similarly occurs at higher CNS synapses in nociceptive pathways and has much in common with long term potentiation (LTP) that underlies memory formation in hippocampal networks. Such strengthened nociceptive networks may persist after healing of peripheral injury and Apkarian has commented that *one could define*

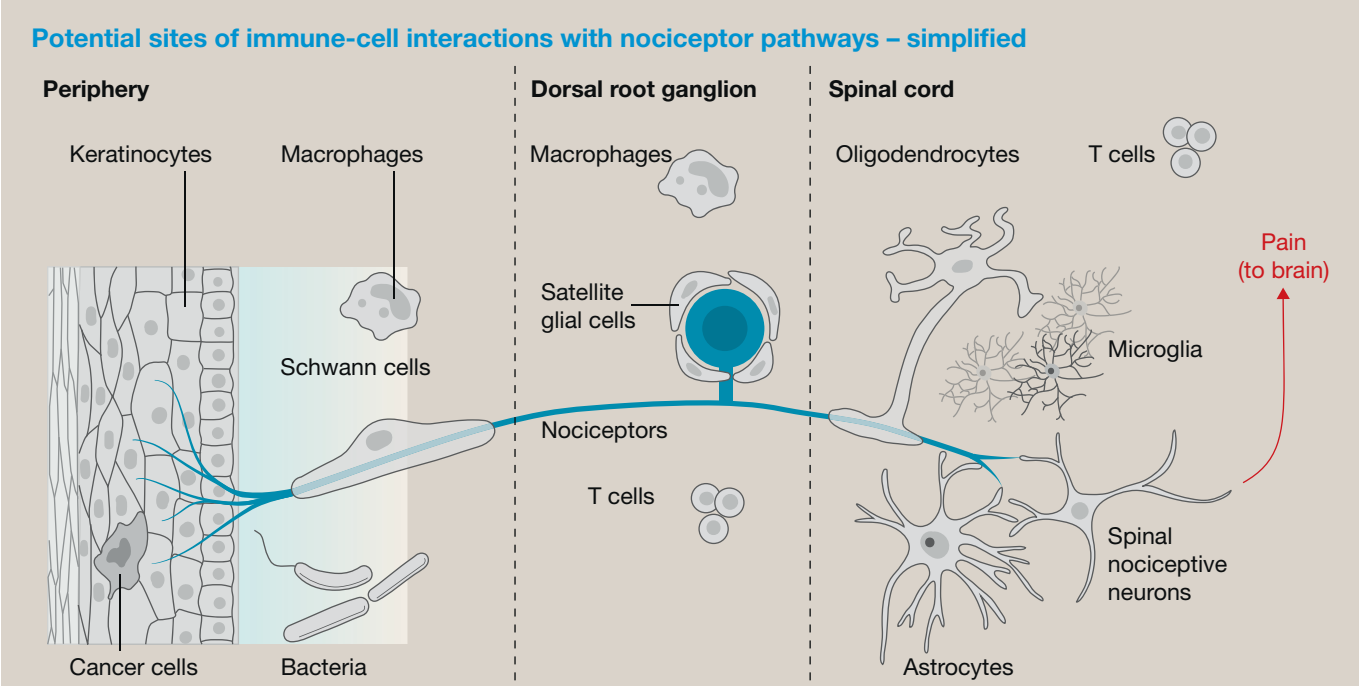


Figure 4

chronic pain as a persistence of the memory of pain and/or the inability to extinguish the memory of pain evoked by an initial inciting injury.

NMDA receptor antagonists such as ketamine clearly attenuate central sensitization but their ultimate efficacy may be limited by inhibition of higher level CNS synapses involved in conscious processing and memory.

Inhibitory mechanisms

In 1965 Melzack and Wall hypothesized an electrophysiological dorsal horn *gating mechanism* whereby nociceptive input could be inhibited by segmental non-nociceptive Aβ input and further modulated by descending spinal and supraspinal influences. Such a mechanism necessitates a population of inhibitory interneurons within the dorsal horn and the presence of inhibitory neurotransmission from supraspinal centres.

The superficial dorsal horn has a dense glycinergic and GABAergic intrinsic innervation mediating a resting inhibitory tone through hyperpolarizing Cl^- currents. Potentiation of these mechanisms (e.g. spinal administration of $GABA_A$ agonists such as midazolam) produce analgesia whereas, spinal administration of $GABA_A$ antagonists (such as Bicuculline) or glycine antagonists produce experimental hyperalgesia and pain behaviour.

Peripheral nerve injury may both reduce absolute GABA interneuron density (involving apoptosis) and also alter K^+—Cl^- membrane transporter function resulting in a shift of Cl^- reversal potential and functional loss of $GABA_A$—Cl^-- mediated inhibitory dorsal horn tone. Central disinhibition thereby contributes to peripheral neuropathic pain mechanisms following peripheral nerve injury.

Descending modulation

Supraspinal modulation of dorsal horn nociceptive transmission is complex and involves both descending inhibitory (i.e. analgesic) and excitatory (i.e. proalgesic) mechanisms. Descending inhibitory signaling of cortical and thalamic origin is relayed via the rostral ventromedial medulla (RVM) involving serotonergic neurons of the nucleus raphe magnus and noradrenergic neurons of the nucleus reticularis gigantocellularis, each of which receive input from the opioid receptor rich periaqueductal grey area of the midbrain (PAG). Significantly, the RVM is characterized by high levels of expression of opioid (and also cannabinoid) receptors that modulate the firing of RVM 'ON' and 'OFF' neurons, the balance of activity of which contributes to resting facilitatory or inhibitory tone. PAG and RVM receptors are the primary central sites of action following systemic administration of opioids and cannabinoids. The noradrenergic locus coeruleus (LC) also receives inputs from the PAG and communicates with the RVM mediating both direct and indirect caerulospinal inhibitory input to the dorsal horn.

At the dorsal horn, descending supraspinal inhibition results in the activation of opioid receptors and α2 adrenergic receptors that hyperpolarize presynaptic C-fibre and Aδ-nociceptor terminals, post synaptic interneurons and projection neuron dendrites. Approximately 70% of dorsal horn opioid receptors are pre- rather than post-synaptic, whereas the distribution of α2 receptors shows high densities on post-synaptic dendrites. Spinal opioid and α2 agonists are therefore analgesic by attenuation of nociceptor glutamate and neurokinin release and a reduction of the magnitude and spread of post-synaptic EPSCs. The response of dorsal horn neurons to descending serotonergic input from the nucleus raphe magnus is variable dependent upon 5HT-receptor

populations and 5HT can mediate both analgesic and proalgesic responses.

This underlies the observation that SNRI agents demonstrate higher efficacy than SSRI antidepressants as analgesic agents in chronic pain. Tricyclic agents in addition to potentiation of noradrenergic pathways manifest additional efficacy through sodium channel (and possibly NMDA channel) binding.

Glial and non-neuronal contributions to pain (Figure 4)

It is increasingly clear that considering nociceptive neuronal-neuronal interactions in isolation provides an incomplete picture of the initiation and maintenance of pathological pain states.

Peripheral inflammatory cells including monocytes, macrophages, T-cells and keratinocytes can directly upregulate nociceptor sensitivity through cytokine and other inflammatory mediator interactions; moreover, bacteria such as *Staphylococcus aureus* may directly activate nociceptor terminals through pore-forming toxins.

In the central nervous system, glial cells including astrocytes and microglia express a variety of receptors including P2X3 ATP, ionotropic and metabotropic glutamate receptors, neurokinin receptors, CB2 cannabinoid and opioid receptors for agents hitherto considered as neuronal neurotransmitters. Rather than playing a passive supportive role in the CNS, emerging evidence indicates that pathological glial activation and CNS neuroinflammation contributes to the maintenance of neuropathic and (perhaps to a lesser extent) inflammatory pain states. Glial cells express Toll-like receptors (TLR) that may initiate and maintain neuroinflammatory states; moreover TLR may be directly activated by viral infections – e.g. herpes zoster with resultant initiation and maintenance of neuropathic pain manifesting as post-herpetic neuralgia.

Overall, a bidirectional communication between glia (and other immune cells) and nociceptors modulates neuroinflammation in both the peripheral and central nervous system and is increasingly considered to play a key role in maintaining pathological pain. Pharmacological agents that suppress neuroinflammation – for example low dose naltrexone inhibiting the TLR4 receptor may therefore have promising analgesic and antineuropathic potential.

Summary

Detailed understanding of pain anatomy, physiology and pharmacology may ultimately enable a mechanism-based classification of pain states and permit optimal analgesic drug therapy with selective targets that include nociceptor transduction, transmission and central modulatory mechanisms. ◆

FURTHER READING

Basbaum AI, Bautista DM, Scherrer G, Julius D. Cellular and molecular mechanisms of pain. *Cell* 2009; **139: 2**67–81.

IUPHAR/BPS Guide to pharmacology. Jan 2019, http://www.guidetopharmacology.org.

Ji R-R, Chamessian A, Zhang Y-Q. Pain regulation by non-neuronal cells and inflammation. *Science* 2016; **354:** 572–7.

West SJ, Bannister K, Dickenson AH, Bennett DL. Circuitry and plasticity of the dorsal horn. *Neuroscience* 2015; **300:** 254–75.