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REVIEW

Physiology and pathophysiology of chronic pain (Part II): how does pain become chronic?

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Chronic pain occurs when pain transitions from an acute to a chronic state, especially when acute pain is not effectively managed. In the presence of continuous acute pain, pain processing and pathways gradually undergo several structural and functional modifications in a process known as sensitisation. These modifications may occur in the peripheral or central nervous system. The consequences of these modifications include decreased pain threshold, increased excitability and increased responsiveness to pain. A combination of all of these changes result in the conversion of acute to chronic pain. This review summarises the pathophysiological alterations that are involved in pain chronification. However, these changes and mechanisms are not as simplistic as presented here, as the mechanisms involved are far more complex. The presentation adopted is for the benefit of a basic understanding and not a comprehensive treatise on chronic pain mechanisms.

Keywords: pain, chronic pain, physiology

Introduction

Pain chronification describes the process of transient pain progressing to persistent pain. Pain processing changes as a result of an imbalance between pain amplification and pain inhibition. Genetic, environmental and biopsychosocial factors determine the risk, degree and time-course of chronification[1] – a term that has become increasingly popular within the pain community. Chronification simply refers to the gradual transition of acute pain to chronic pain. There are gradual modifications in the anatomical and physiological architecture of the pain pathways.[1] It involves pathophysiological changes in pain processing that result in sensitisation, which plays a critical role in the development of chronic pain.[2,3] Sensitisation is characterised by a decreased pain threshold, together with heightened and exaggerated responses to noxious stimuli. Sensitisation can be categorised into peripheral sensitisation and central sensitisation.

The processes that underlie peripheral and central sensitisation can be categorised into two: post-translational changes and altered gene expression.[4] Post-translational modification are the changes that occur as a result of modification of proteins after messenger RNA (mRNA) has been translated into proteins and it affects the activity and function of the proteins. These changes include phosphorylation of protein kinase A and C, increased expression of calcium and sodium channels, and downregulation of potassium ion channels. All these changes prolong depolarisation, leading to amplified responses as a result of decreased threshold and prolonged opening time of the channels.[4,5] The alteration in gene expression of many proteins modifies their activities, for example, an increase in gene expression of transient potential vanilloid-1 (TRPV1) will lead to the upregulation of TRPV1 receptors. TRPV1 is a member of a family of proteins that represent more than thirty receptors which are implicated in pain processing. An increase in expression in TRPV1 will therefore translate to increased pain signals. These two categories of events primarily account for the changes seen in peripheral and central sensitisation.

Peripheral sensitisation

Peripheral sensitisation is defined as the 'increased responsiveness and reduced threshold of nociceptive neurons in the periphery to the stimulation of their receptive fields'.[6] This is caused by the continuous firing of pain signals which is usually preceded by the initiation of inflammation.[1,7] Peripheral sensitisation is a response in primary afferent nerves to a noxious event, such as tissue injury and inflammation, which causes changes in the nerves. After nerve damage within the periphery, an inflammatory response is activated which results in the release of a host of endogenous inflammatory mediators, including serotonin, bradykinin, substance P, histamine, adenosine triphosphate (ATP), prostaglandins (PGE2), thromboxanes, leukotrienes, endocannabinoids, nerve growth factor (NGF), cytokines (IL6, IL1β, TNFα), chemokines and calcitonin gene-related peptide (CGRP). These substances sensitise nociceptors in the periphery to subsequent input resulting in increased responsiveness to thermal and mechanical stimuli at the site of injury.[8,9] These inflammatory mediators activate and sensitise nociceptors, resulting in either post-translational changes in proteins (in the short-term) or alteration in gene expression of proteins (in the long-term). This consequently leads to changes as described below.

Alterations in ion channels

These are alterations that occur in the sodium, calcium or potassium ion channels. The interaction among these ion channels is such that the potassium and calcium ion channels regulate the activity of the sodium ion channels. This may lead to

either excessive activity or loss of function. Some analgesic drugs act on these ion channels to relieve pain.

Voltage-gated sodium channels are critical for pain transduction, as they are primarily responsible for action potential generation. They therefore play a crucial role in pain processing. Of the nine types of voltage sodium channels, the most commonly implicated in pain are Nav1.7, Nav1.8 and Nav1.9.[10] Inflammatory mediators can cause an alteration of sodium gene expression resulting in upregulation or downregulation in sodium channels. An upregulation will promote generation of pain signals, while a downregulation will decrease it.

Calcium influx also contributes prominently to the processing of pain signals (transduction, transmission, processing and modulation).[11] Some receptors are intricately associated with calcium channels, for example, the TRPV1 receptors. They contain cation permeable channels that activate in response to noxious stimulus. Therefore, an overexpression of calcium channels will cause excessive activation of the TRP channels. Calcium influx is required for the release of neurotransmitters from nociceptive terminals. An overexpression of Ca^{2+} channels in the dorsal ganglia can cause an excessive release of pro-nociceptive neurotransmitters like glutamate. The increase in expression and distribution of calcium and sodium ions on the afferent neurons will correspond to an increase in excitability and ectopic activity that will be perceived by patients as spontaneous pain, hyperalgesia or allodynia in various pain conditions.[12]

Potassium channels play an important role in pain signalling, although their role differs from that of calcium and sodium channels. The opening of potassium channels causes a potassium efflux which influences the generation of the action potential (depolarisation) by causing repolarisation or hyperpolarisation of the nerve.[13] These channels help to suppress action potential and sensory neuron excitability, limiting receptor excitability. Impairment or malfunction by downregulation of these potassium channels will diminish the role they play in decreasing excitability, thus contributing to the development and maintenance of chronic pain. Potassium ion channels have great potential as therapeutic targets in the management of chronic pain.

Ectopic discharges in injured fibres

This is the spontaneous production of action potentials within the injured axon due to an overexpression of voltage-gated sodium and calcium channels, and a decrease in potassium ion channels. These alterations may lead to membrane instability causing spontaneous and excessive activity of the nociceptors.[12,14]

Abnormal activity in axons not directly affected by lesions

This occurs when nerve fibres that normally convey non-nociceptive sensory signals (tactile sensations) begin to convey pain signals. This phenomenon is referred to as 'phenotypic switch', a mechanism mostly associated with chronic neuropathic pain.[7] Lesions in the distal part of the primary nociceptive afferent nerve leads to Wallerian degeneration, which develops into inflammation, activation of macrophages and oedema in the axon separated from the cell body. All these changes encourage abnormal activities in the non-nociceptive neuron which are not affected by the lesion.[15] These changes may involve overexpression of TRPV1, neurochemicals, neurotrophic factors (e.g. BDNF, NGF), pro-nociceptive neurotransmitters (CGRP) and abnormal discharges from neurons.[14]

Neuroimmune interactions

The interaction between nerves and the immune system can result in enhanced production of inflammatory signalling molecules. Nerve injury has been reported, with increasing frequency, to be associated with activation of the peripheral immune system altering sensory processing. Pro-inflammatory cytokines such as interleukins or TNFα released from immune cells can cause sensitisation of channels resulting in spontaneous firing of nociceptors.[16]

Central sensitisation

The International Association for the Study of Pain (IASP) defines central sensitisation as 'increased responsiveness of nociceptive neurons in the central nervous system (CNS) to their normal or subthreshold afferent input'.[6] This is a state where hyperexcitability is developed and maintained by the excessive bombarding of pain signals within the CNS, leading to a phenomenon referred to as 'wind up'. Pain signals are amplified, and it is characterised by a decreased pain threshold and an increased pain sensitivity.[17] Hyperexcitability of neurons, neuronal loss, disinhibitory mechanisms and structural reorganisation are some of the causes of central sensitisation and development of pain chronicity (Figure 1).

The role of the inflammatory system

Microglia and astrocytes are non-neural immune cells in the brain that carry out supportive functions and maintain brain homeostasis, among other functions. Microglia act primarily via phagocytosis during injury and disease,[18,19] while astroglia function in ion homeostasis, synapse formation and elimination.[20] Microglia and astrocytes are potent pain modulators and are contributors to central sensitisation.[21] Microglia, which are normally found in the grey matter of the spinal cord, are activated in the presence of injury. They are immediately mobilised to the site on the dorsal horn of peripheral nerves that have been injured as a central response to peripheral injury. The activated microglia release a number of inflammatory molecules, for example, TNF-α, IL-1β, IL-6, nitric oxide (NO) and prostaglandin E_2,[3,21,22] which exacerbate hypersensitivity by decreasing pain threshold and facilitating chronification of acute pain.[22]

Microglia are not activated directly but via molecules released by physically damaged nerves. Most notable among them is ATP, acting via purinergic receptors. Microglial activation is also implicated in disinhibition. ATP activation of purinergic receptors provoke the release of brain-derived neurotrophic factor (BDNF) from microglia. BDNF reacts with tropomyosin kinase B receptor (TrkB) altering the Cl^- gradient, causing depolarisation rather

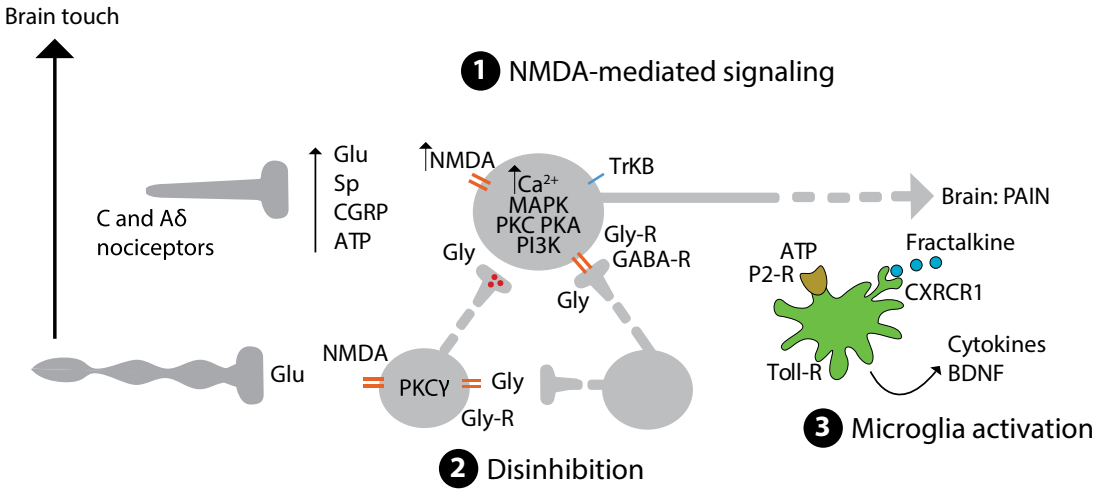

Figure 1: Central sensitisation mechanisms[3]
(1) NMDA-mediated receptor signalling: Silent NMDA receptors (which are normally inactive) are activated by repeated stimulation (caused by injury) of Aδ and C nociceptor resulting in the release of neurotransmitters such as glutamate, substance P (SP), calcitonin-gene related peptide (CGRP) and ATP. These neurotransmitters act on the NMDA glutamate receptors located in the postsynaptic neuron leading to increased intracellular calcium and release of several calcium dependent second messengers that includes mitogen-activated protein kinase (MAPK), protein kinase C (PKC), protein kinase A (PKA) and Src. These molecules cause heightened excitability of the neuron and facilitate the pain transmission signals to the brain.
(2) Disinhibition: The release of GABA and/or glycine (Gly) modulate pain transmission by decreasing the excitability of neurones and pain transmission. In the presence of injury, this inhibition is lost, resulting in hyperalgesia.
(3) Microglial activation: Peripheral nerve injury causes the release of several molecules such as ATP and fractalkine that activates purinergic (P2-R), chemokine (CX3CR1) and Toll-like receptors (Toll-R) on microglial cells. This results in the release of brain-derived neurotrophic factor (BDNF), which enhances excitability and pain response to both noxious and innocuous stimulation (hyperalgesia and allodynia respectively). Cytokines, such as tumour necrosis factor α (TNFα), interleukin-1β and 6 (IL-1β, IL-6) released by microglia can also contribute to central sensitisation.

than hyperpolarisation in GABAergic neurons. Other than BDNF, many other mediators, such as chemokines (fractalkine, etc.) and Toll-like receptors (TLR), are also involved in the development of central sensitisation.

The role of astrocytes in the central sensitisation process is not clear. What is known, however, is that they require a longer period for activation and their activity lasts longer. It is postulated that astrocytes are crucial for the maintenance, rather than development, of central sensitisation. Glial cell activation also contributes to an imbalance of the pain modulation process by enhancing descending facilitatory effects in pain processing in the spinal cord.

The role of central neurotransmitters

Pain signalling involves the release of a number of neurotransmitters from the terminals of nociceptors, which excites the post synaptic neuron of second-order neurons in the dorsal horn of the spinal cord. The activation of these receptors is done by stimulating α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and kainate subtypes of ionotropic glutamate receptors.[3,22] Action potential is generated and transmitted to the higher centres for further processing and interpretation.

The N-methyl D aspartate (NMDA) receptors are not normally activated during normal physiological processing of acute pain. They usually only participate when nerve injury occurs. After nerve injury, there is an increase in the release of glutamate which is sufficient to activate NMDA receptors, thus facilitating pain transmission and leading to hyperexcitability.

This also explains neuronal plasticity that occurs as a result of long-term potentiation (LTP). LTP is a process by which synaptic connections are strengthened, leading to a long-lasting increase in signal transmission between neurons.[23] This mechanism not only accounts for hyperalgesia but is also responsible for the development of allodynia which is common in some chronic pain conditions.

Substance P is also released in addition to glutamate in chronic pain states. Substance P binds to postsynaptic receptors and causes the release of calcitonin gene-related peptide (this is usually the case in neuroinflammatory pain, pain that occurs in response to tissue or nerve damage and inflammation). All these neurotransmitters act synergistically to trigger a cascade of events that contribute to the development of chronic pain.[2,3]

Disinhibition

Disinhibition refers to the loss of or decrease in the inhibition of pain signals by GABAergic and glycinergic interneurons. These form a crucial part of the descending inhibitory control of pain. GABAergic and glycinergic inhibitory interneurons are present in the dorsal horn of the spinal cord and they exert their inhibitory effects at the junction of presynaptic and postsynaptic neurons. A decrease in the function of these interneurons leads to enhanced pain transmission.[3]

Peripheral nerve injury has been demonstrated to cause a decrease in the functioning of the inhibitory interneurons by reducing the K^+-Cl^- cotransporter (KCC2), which is crucial in maintaining K^+ and Cl^- gradients across plasma membranes. In summary, when KCC2 is downregulated, it causes a shift in the Cl^- gradient which leads to activation of γ-aminobutyric acid (GABA) causing it to depolarise rather than hyperpolarise. This causes decreased pain threshold, increased pain excitability

and enhanced pain transmission. Disinhibition may also occur when excitatory neurons become unresponsive to the glycine inhibitory effects, via a prostaglandin mechanism.[3]

Neuroplastic changes in the central nervous system

Neural plasticity refers to the ability of the brain and its neurons to form and reorganise synaptic connections in response to learning or experience or following injury,[24] allowing the brain to compensate and adapt its activities in response to changes in the environment.

The presence of ongoing pain states and the persistent discharge of pain signals initiates neuroplasticity which responds by facilitating pain processing, thus creating a vicious cycle. The process of neuroplasticity begins with the over-firing of the inhibitory interneurons and their subsequent death (this is associated with decreased grey matter as observed in chronic pain sufferers).[25] This leads to plastic changes in the components involved in pain processing (nociceptors, sensory pathways, cortical and subcortical centres).

Changes in the function and structure of the brain have also been reported. Studies have shown that areas involved in cognitive and emotional aspects of pain processing, for example, the anterior cingulate cortex (ACC), show increased activity in chronic pain patients.[2]

Conclusion

The role of anaesthesiologists goes beyond the administration of anaesthesia. It also involves the efficient and effective management of pain and critical care services. However, this is only possible with a sound understanding of the physiological basis of the pain condition to be managed. Comprehension of the anatomical structures, sensory processing, targets of modulation and the subjective nature of pain will enhance the pain management role of the anaesthesiologist. This review emphasises the interplay of several mechanisms involved in development and maintenance of chronic pain. The balance between the facilitatory and inhibitory pain control systems is critical in contributing to the transition of acute to chronic pain. A thorough comprehension of these various components will improve the knowledge base of the anaesthesiologist in effectively managing chronic pain and improving the quality of lives of individuals.

Most importantly, it emphasises that effective management of acute pain is important as a measure in preventing development of chronic pain.

Conflict of interest

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