

# Transition from acute to chronic pain

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## Key points

Physiology of pain involves activation and complex interactions of autonomic, peripheral and central nervous systems, endocrine and immune systems.

Persistent nociceptive stimulation may cause various changes in pain physiology leading to pain sensitization.

Cellular changes in the periphery and central nervous system result in peripheral and central sensitization.

Cerebral disorganization, pathophysiological changes in neurones are associated with a hyper-excitabile neuronal state.

Transition of acute to chronic pain may be minimized by early recognition of risk factors and early biopsychosocial pain management.

Pain is commonly classified into acute and chronic. Acute pain implies a painful condition with a rapid onset or of a short course whereas chronic pain is referred to as a painful condition persisting beyond the normal time of healing. Transition of acute pain to chronic pain is an observed entity associated with enormous burden on the healthcare system. Minimization of this transition has been a challenge for decades. Numerous studies have investigated different factors that increase susceptibility in transition of acute to chronic pain. This article focuses on the basic science and pathophysiological changes during pain processing and clinical modalities aiming to minimize the risk of transition from acute to chronic pain.

## Pain physiology during acute tissue injury

### In the periphery

Acute tissue insults such as heat, cold, chemical or mechanical injury, cause disturbance in homeostasis, and stimulate the pain receptors, called nociceptors. Homeostasis can be restored by activation and complex interaction among autonomic, endocrine, immune, and nervous systems.<sup>1</sup> After an injury, a wide range of inflammatory mediators are released locally either from damaged tissue or by activated mast cells and neutrophils. These mediators are adenosine-5-triphosphate (ATP), bradykinin, prostaglandin E<sub>2</sub>, sodium (Na<sup>+</sup>), hydrogen (H<sup>+</sup>), potassium (K<sup>+</sup>), histamine, and serotonin. The released substances interact with their corresponding receptors located on the peripheral nociceptive neurones leading to depolarization of cell membrane and impulse generation within A $\delta$  and C fibres.

After tissue injury, cyclo-oxygenase-2 enzyme is activated and macrophages release pro-inflammatory substances such as interleukin-1B, interleukin-6, nerve growth factor, and tumour necrosis factor-alpha (TNF- $\alpha$ ). Peripheral inflammation at the site of tissue injury activates C-fibres, which release substance P, calcitonin gene-related peptide (CGRP), neurokinin A and nitric oxide (NO) in a retrograde fashion called 'neurogenic

inflammation'. This amplifies the whole process resulting in an 'inflammatory soup'. The end result is further activation of 'silent' C fibres with a reduction of pain threshold and increased excitability.<sup>1</sup>

Systemic inflammation is also activated along with the process of tissue injury. This activates the sympathetic system, releasing noradrenaline. Noradrenaline by itself further activates peripheral nociceptors. In summary, an acute nociceptive stimulation induces complex biochemical peripheral changes. These changes include:

- Up-regulation of substance P,
- phosphorylation of various enzymes (e.g. protein kinase A and C),
- activation of transient receptor potential vanilloid (TRPV) receptor and purinergic receptor,
- increased responsiveness of the nociceptors, and
- activation of silent nociceptors. All these changes potentiate nociception; leading to a state of 'peripheral hypersensitivity' and hyperalgesia.<sup>2</sup>

These changes are usually reversible once the tissue healing is completed.

### Within the spinal cord

Generated action potential is transmitted from the injury site to the spinal cord via primary afferent sensory fibres with their cell bodies located at the dorsal root ganglion (DRG). The sensory fibres (except those arising from the face) form synapses in the dorsal horn of the spinal cord. The fibres arising from the face synapse at the nucleus caudalis.

Primary afferent C and A $\delta$  fibres enter the spinal cord through the dorsal horn and synapse with the secondary afferent neurones at Rexed laminae I and II. A $\beta$  fibres that carry touch and pressure sensation, synapse at the laminae III–VI.<sup>3</sup>

In the laminae I–V, there are three groups of second-order neurones. The first group is involved in proprioception. The second group includes nociceptive specific cells that synapse at laminae I and II. The third group of

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second-order neurones comprises wide dynamic range (WDR) neurones that synapse at lamina V. WDR neurones are usually in a dormant state until sensitization occurs.<sup>3</sup>

Transmission of a nociceptive impulse from the primary afferent to the secondary afferent is facilitated by the secretion of excitatory substances such as glutamate, substance P, CGRP, and neurotrophic factors. Glutamate, the chief excitatory neurotransmitter in the central nervous system, is able to bind onto three different receptors located on the post-synaptic end. These are alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), N-methyl-D-aspartate (NMDA) and G-protein coupled metabotropic receptors. Among these, AMPA is the main receptor activated during acute nociception.<sup>3,4</sup> The NMDA receptor is not activated under acute noxious circumstances and it will be discussed further later.

The second important excitatory substance is substance P working closely with glutamate generating nociceptive transmission. It is a neuropeptide functioning as a neurotransmitter or neuromodulator. Physically it is closely related to neurokinin A; hence substance P binds onto neurokinin receptors, which are abundant in spinoparabrachial pathway at lamina I. Apart from nociceptive transmission, the release of substance P has a positive influence on activation of glial cells.<sup>5</sup> The importance of glial cells will be explained later.

While excitatory mechanisms facilitate the transmission of nociception to the brain, inhibitory mechanisms within the spinal cord dampen and impede the transmission. These inhibitory mechanisms consist of:

- inhibitory gamma-aminobutyric acidergic and glycinergic interneurons,
- descending inhibitory pathways from the brain,
- production of endogenous opioids, and
- higher order brain functions responsible for distraction and cognitive function.

The balance between excitatory and inhibitory functions determines the overall transmission of noxious stimuli to the brain.

### Ascending and descending pathways to the brain and pain matrix

Ascending pathways or secondary afferent neurones from dorsal horn terminate at the thalamus and cerebral cortex. Spinothalamic tract is an important ascending pathway originating from lamina I, II, and V. Via the thalamus, it ends at the somatosensory cortex with an important role for sensory discrimination. Other important ascending pathways are the spinoparabrachial and spinomesencephalic tracts. They synapse at lamina I and project to the brainstem and medulla, and transmit the nociception.<sup>2</sup>

Pain matrix is the brain network responding to nociceptive processing. It incorporates multiple cortical areas collaboratively activated by nociception and is divided into two parts. The first part is the *nociceptive cortical matrix*, consisting of posterior insula, medial parietal operculum and mid-cingulate cortex. These areas are responsible for the earliest response to a nociceptive input from spinothalamic tract.<sup>6</sup> Fine distinction, inter-individual variability of

pain experience and consciousness are clinical interpretations managed by the second part of the pain matrix called the *second-order perceptual matrix*. This area determines and reflects different individual responses when exposed to a similar nociception. The second-order matrix contains: (i) the mid/anterior insula, anterior cingulate cortex and prefrontal cortex, (ii) the periaqueductal gray matter (PAG) and rostroventromedial medulla (RVM), and (iii) reticular formation.<sup>2,6</sup>

Descending pathways arise from PAG, RVM, and adjacent reticular formation secreting either noradrenaline or serotonin. Noradrenaline stimulates  $\alpha_2$ -adrenoceptors inhibiting release of neurotransmitters from primary afferent neurones.<sup>3,7</sup> The aim is to minimize the nociceptive transmission.

### Pathophysiological changes during the transition of acute to chronic pain

Termination of acute nociception and full tissue recovery would result in restoration of normal homeostasis and end the pain process. However, continuous or repetitive nociceptive stimulation leads to a series of pathophysiological changes in pain processing. Complex changes are observed at all levels from the periphery to the brain resulting in persistent pain.

#### In the periphery

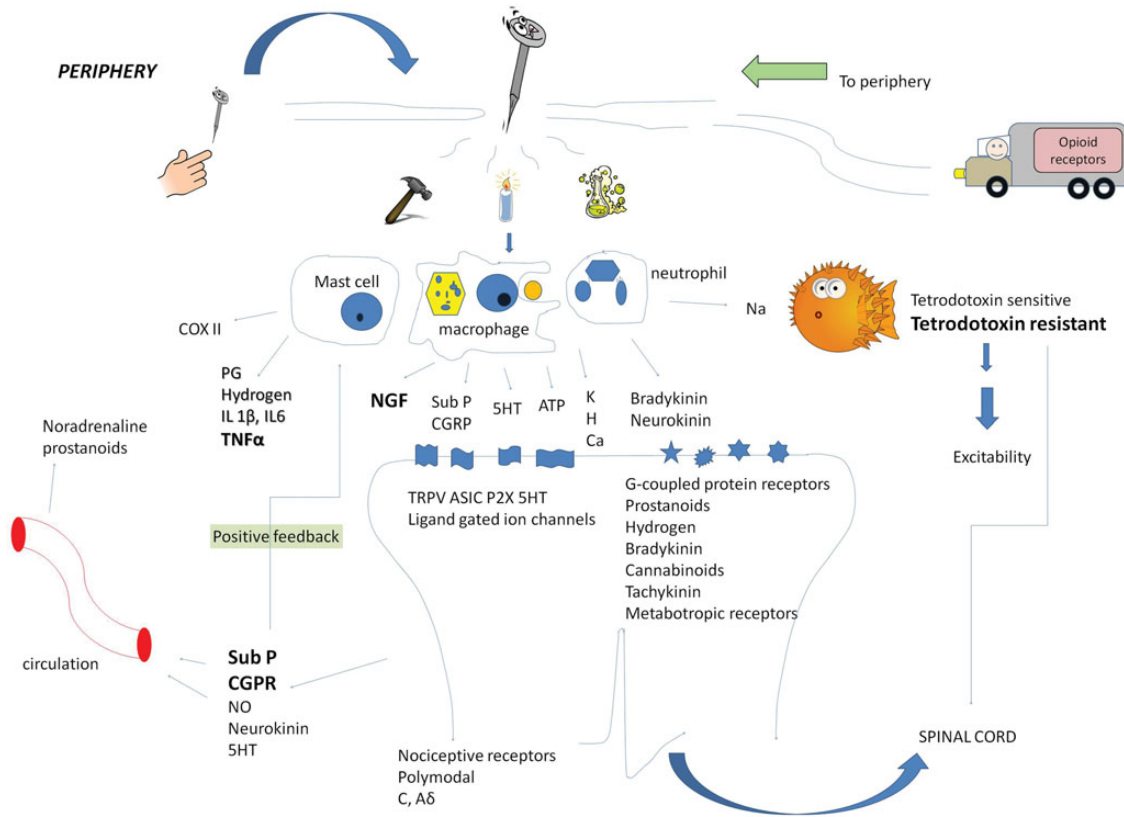
Repetitive nociceptive stimulation may result in a prolonged inflammatory process through activation of lymphocytes and release of TNF- $\alpha$  and interleukins such as IL1, IL6, and IL1 $\beta$ . Chronic inflammation leads to a series of changes in the periphery such as:

- reduction of pain threshold in the primary afferent neurones,
- phosphorylation of protein kinases A and C,
- activation of TRPV1 receptors,
- up-regulation of voltage-gated sodium channels and TRPV1 receptors in DRG, and
- increased production of substance P and CGRP in the periphery and the spinal cord.<sup>1,3,8-10</sup> This mechanism is known as 'peripheral sensitization' secondary to a prolonged inflammatory state (Fig. 1).

#### Within the spinal cord

Continuous nociception stimulation leads to a number of changes in gene and protein expression in both DRG and dorsal horn neurones. The most prominent change is an increase in the mRNA coding for the production of various receptors and ion channels such as Na and TRPV1 receptors.<sup>2</sup> Changes in receptor kinetics lead to the hyperexcitable state of chronic pain.

Another important receptor type in the spinal cord is the NMDA. This receptor remains inactive during acute noxious stimulation because of the tightly bound Mg plug. Continuous nociceptive stimulation causes prolonged slow depolarization of the neurones in the dorsal horn. This leads to massive influx of calcium which removes the Mg plug from NMDA receptors allowing glutamate to



**Fig 1** Pain physiology in periphery: neurogenic inflammation, reduced nociceptive threshold and up-regulation of receptors, and ion channels cause peripheral sensitization.

bind onto NMDA receptors. Activation of NMDA receptors leads to the ‘wind-up’ phenomenon (Fig. 2).

Once wind-up has developed, it induces and potentiates a WDR neuronal response to each stimulus. Subsequent sensory stimulation via Aβ fibre (touch) ends up with exaggerated WDR neuronal output. Clinically, this manifests as allodynia. The end result of the wind-up process is ‘neuroplasticity,’ which is a change in neuronal structure with potential enhancement of signal transduction.

Prolonged nociceptive transmission to the spinal cord causes release of neuronal chemokines (fractalkine and monocyte chemoattractant protein-1), neurotransmitters (substance P, CGRP, glutamate, and ATP) and neuromodulators (prostaglandins and NO); and produces endogenous danger signals (heat shock proteins and the nuclear protein HMGB1). All these substances activate glial cells in the central nervous system.

Glial cells are non-neuronal cells and are important in homeostasis and protection of neurones by means of myelin formation. Once glial cells are activated, they release various substances (IL-1, IL-6, TNF, chemokines, prostaglandins, excitatory amino acids, reactive oxygen species, and NO) into the central nervous system. The cumulative interactions result in enhanced neuronal excitability, up-regulation of AMPA and NMDA receptors, activation of tetrodotoxin-resistant sodium channels, and down-regulation of GABA receptors. These changes tip the balance towards an exaggerated excitable sensitized

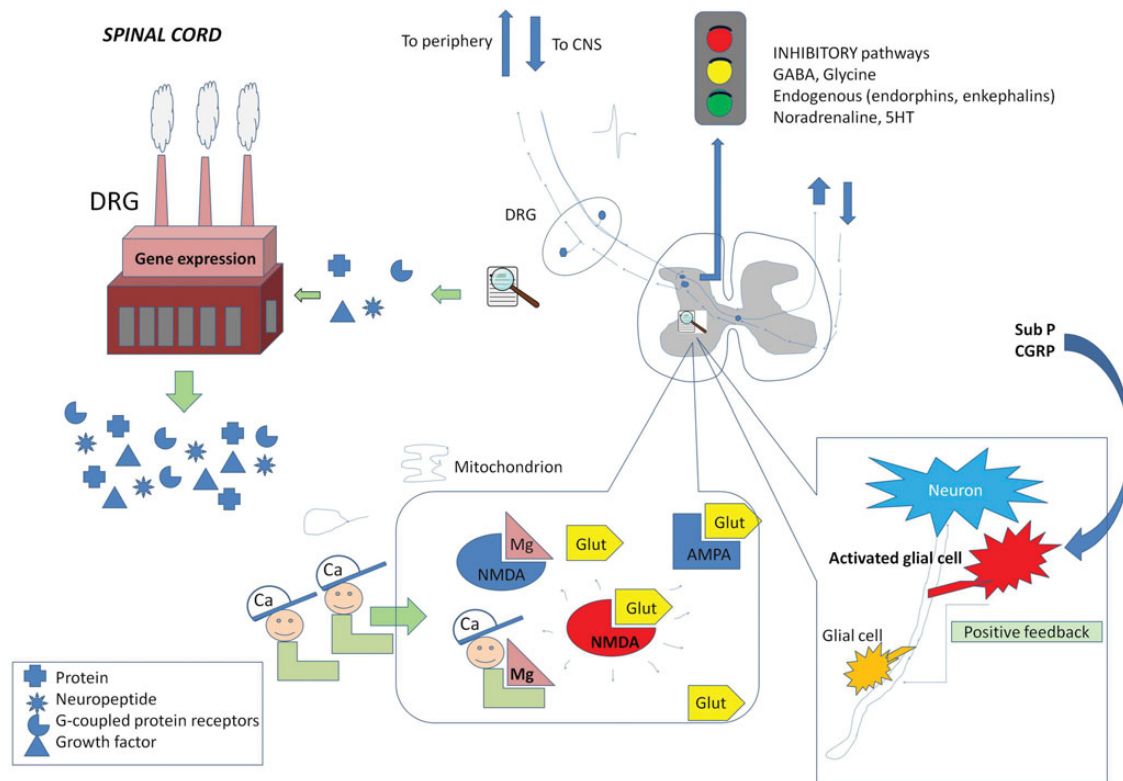
condition.<sup>4 5</sup> All these changes cause ‘central sensitization’, which are a state of reduced thresholds to stimulations associated with escalated neuronal activity response in the dorsal horn.<sup>3</sup>

### In the brain

Pain matrix has been identified by radiological evidence. Imagings such as functional magnetic resonance imaging and positron emission tomography scans have identified five important pain centres and various changes in the pain matrix when sensitization occurs. The identified regions (and their associated clinical roles) are as follows:

- Thalamus where spinothalamic tract terminates (somatosensory discrimination),
- mid/anterior insula, anterior cingulate cortex and prefrontal cortex (affective and motivational components of pain),
- PAG and RVM (fight-or-flight responses and stress-induced analgesia),
- reticular formation (regulating descending pathways), and
- spinoparabrachial pathway to the hypothalamus and amygdala (autonomic and sensory coordination).

Pathophysiological changes in the pain matrix reflect strong correlation between chronic pain and mental status. Mental issues vary



**Fig 2** Pain physiology in spinal cord. Increased production of various substances in the DRG, activation of NMDA receptors, and glial cells cause central sensitization.

from maladaptive pain coping ability to anxiety and depression. Substance misuse and addiction are not uncommon. Psychological stressors tend to accentuate pain intensity and compromise an individual's ability to cope with pain. Therefore, biopsychosocial evaluation is a critical component of chronic pain management.<sup>3 6</sup>

### Approach to minimize the transition from acute to chronic pain-clinical application of basic science

Physiological changes during the transition of acute to chronic pain are observed at various levels, from the peripheral to the central nervous system. Theoretically, if the pathophysiological changes during this transition could be prevented or reversed, we would be able to prevent or minimize the development of chronic pain in practice. Numerous studies have attempted to formulate analgesic approach to prevent this transition, but so far, there has been very limited promising evidence.

Apart from ethical and humanitarian reasons, early management of patients with acute pain is paramount in minimizing the risk of chronic pain development. Early recognition of patients with a high risk of developing chronic pain is imperative in reducing chronic pain development (Table 1).<sup>4 11</sup> Upon risk stratification, appropriate preventative analgesia aiming at various levels of pain pathways would reduce the potential risk of developing chronic pain.

**Table 1** Risk factors for developing chronic pain (post-surgical)

Patient factors	Medical factors
Psychology vulnerability	Preoperative moderate-to-severe pain lasting more than 1 month
Preoperative anxiety	Repeat surgery
Female gender (higher reported pain score)	Radiotherapy to the area
Younger age (adult)	Nerve damage
Worker's compensation	Chemotherapy
Genetic factors	Types of surgery (amputation, breast surgery, thoracotomy, herniorrhaphy, coronary artery bypass, and Caesarean section)
Depression	Operations longer than 3 h
Unpleasant past experience with pain	Surgical technique, experience of surgeon, Prolonged postoperative pain/inflammation
Social environment	Duration of postoperative pain treatment

### In the periphery

The extent of tissue damage determines the severity of nociceptive stimulation, length of tissue healing process, and magnitude of inflammation. These factors affect the risk of chronic pain development. Careful tissue handling, avoidance of nerve damage and minimal invasive surgical techniques during surgery minimize tissue damage and potentially reduce the risk of chronic pain.

Reduction of an inflammatory process may reduce the risk of sensitization in both the periphery and central nervous system.

COX-2 inhibitors and NSAIDs have been proved to reduce inflammation. COX-2 inhibitors also prevent the breakdown of endocannabinoids, neuromodulatory substances, which reduces the release of neurostimulators (e.g. glutamate).<sup>11</sup> A long-term use of these two classes of medications leads to unwanted medical complications; which are not discussed in this article. Local anaesthetic infiltration of the surgical field is another effective technique to reduce the intensity of immediate postoperative pain.

### Within the spinal cord

During the transition of acute to chronic pain, the activation of NMDA receptors and wind-up phenomenon are important changes in the spinal cord. Blocking the NMDA receptors with antagonist such as ketamine, nitrous oxide, and methadone would be effective in reducing the pain intensity and wind-up.<sup>11</sup> In the presence of intractable pain, particularly ketamine can be used as an adjunct of multimodal pharmacological treatment. However, because of its side-effect profile and highly addictive potential the treatment course should be limited to a short period. Adjuvants such as  $\alpha$ -2- $\delta$  ligands binding to voltage dependent calcium channels (gabapentin and pregabalin) are anti-neuropathic agents with the probable preventative effect.<sup>4,11</sup>

The principle of utilizing multimodal analgesic approach is to provide synergistic pain control. This technique targets receptors at different levels of the pain pathway aiming to reduce neuronal excitability. Local and regional anaesthesia is another technique aiming to block the afferent transmission of pain signals reducing pain sensitivity. In theory, reduction of acute pain should reduce central neuroplasticity and minimize the risk of development of chronic pain, yet available evidence is limited.<sup>11</sup>

### In the brain matrix

There is a strong link between individual preoperative expectation, psychological status, and postoperative pain intensity.<sup>11</sup> Functional MRI studies have demonstrated changes in the centres of the brain matrix of patients with chronic pain. These centres are mainly responsible for mood, affect, and behaviour. It seems reasonable to predict patients with significant psychosocial stressors being more prone to chronic pain development. Therefore, a biopsychosocial approach should be utilized in treating patients with a high risk of developing chronic pain.

### Conclusion

Pain physiology involves complex immune, sensory, hormonal and inflammatory processes in the periphery, spinal cord, and brain.

Repetitive nociceptive stimulation induces pathophysiological changes in the pain pathways leading to peripheral or central sensitization; hence, resulting in chronic pain in susceptible patients. Although evidence is limited, identifying risk factors and early multimodal approach and biopsychosocial assessment are reasonable steps to reduce the risk of developing chronic pain.

Application of the basic science of pain pathways to clinical practice would improve the clinician's ability to deal with those patients at risk of chronic pain development. This may lead to more enthusiastic and exciting studies offering more robust evidence in preventing chronic pain. Advances and development of drugs preventing activation of glial cells, pharmacological agents aiming at the Na channel subtypes specific to nociceptors, and purinergic and TRPV receptor antagonists are ongoing with potential near-future innovations in the prevention of this transition.

### Declaration of interest

None declared.

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