PAIN EDUCATION
Module 6:
The chronification of pain
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Learning objectives

Upon completion of this training module you should have gained an increased understanding of:

- Pain pathways and the relative contributions of peripheral and central mechanisms to pain development
- The process leading to the chronification of pain
- Signs and symptoms of chronic pain
- Comorbidities that can develop as a consequence of pain
- The mechanisms by which treatments can modulate chronic pain
- Optimal treatment pathways for patients with chronic pain

For additional information and further educational content related to the chronification of pain, please see Module 6 of the CME-accredited e-learning PAIN EDUCATION modules, available at www.pain-cme.net
Overview of pain signalling

- **Peripheral nerves**
  - Convey information from external stimuli to the spinal cord
- **Spinal cord**
  - Integrates, amplifies and modifies incoming messages
  - Sends messages via ascending pathways to the brain
- **Cortex**
  - Recognizes intensity and location of pain
- **Limbic brain**
  - Conveys affective aspects of pain
  - Can result in changes in mood, state of mind and sleep pattern

References
General principles of pain

- Nociceptors (sensory nerve fibres)
  - $A\delta$ fibres (large, myelinated, fast)
  - C fibres (small, non-myelinated, slow)
- Located in every tissue, including skin, bone and viscera
- Nociceptors transmit signals via chemical messengers via the spinal cord to the brain
  - Excitatory neurotransmitters (e.g. glutamate) enhance pain
  - Inhibitory neurotransmitters (e.g. GABA) modulate pain
- The spinal cord processes the signals from periphery and conveys them to the brain

GABA = $\gamma$-aminobutyric acid.

References
Descending controls

- Signals transmitted to the brain are modulated by
  - Brain stem
  - Descending controls, via neurotransmitters
- Noradrenaline
  - Key inhibitory transmitter
- Serotonin (5-HT)
  - Inhibitory transmitter
  - Stimulatory transmitter

References
Nociceptive or inflammatory pain

Pain caused by inflammation or tissue damage

Chemicals (e.g. prostaglandin, substance P, histamine, bradykinin, CGRP, neurokinin A) are generated in the damaged area and trigger nociceptors.

Nociceptive pain may have multiple causes

CGRP = calcitonin gene-related peptide.

References
Neuropathic pain

Pain caused by a lesion or disease of the somatosensory system

Nerve damage

Surrounding tissues remain intact

Neuropathic pain may have multiple causes

References
Neuropathic pain and ion channels

- **Sodium channels**
  - Act as an accelerator: generate signals and allow them to pass on
- **Calcium channels**
  - Act as a gear box: facilitate
- **Potassium channels**
  - Act as a brake: modulate signals
  - Transmission of pain signals

These mechanisms may be disrupted in neuropathic pain and form targets for therapeutic intervention

References
# Sodium channels and pain syndromes

<table>
<thead>
<tr>
<th>Pain Disorder</th>
<th>Channel involved</th>
<th>Affect on channel</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inherited erythromyalgia</td>
<td>Na(v)1.7</td>
<td>Lower threshold, enhanced responses</td>
<td>Attacks of burning pain and redness in extremities</td>
</tr>
<tr>
<td>Channelopathy associated insensitivity to pain</td>
<td>Na(v)1.7</td>
<td>Loss of function</td>
<td>Inability to sense pain</td>
</tr>
<tr>
<td>Paroxysmal extreme pain disorder</td>
<td>Na(v)1.7</td>
<td>Impaired inactivation, enhanced response</td>
<td>Episodic lower body, ocular and jaw pain</td>
</tr>
</tbody>
</table>

**References**
Nociceptive pain and neuropathic pain can become chronic

Examples of chronic pain are
- Chronic nociceptive pain: osteoarthritis
- Chronic neuropathic pain: diabetic neuropathy
- Chronic nociceptive and neuropathic pain: chronic back pain and cancer

To treat chronic pain effectively, it is important to understand the underlying mechanism of the chronification process

References
Chronification of pain: central sensitization

Spinal cord is key in chronification of pain
- Persistent peripheral stimuli lead to central sensitization

Central sensitization
- Decrease in neuronal threshold
- Receptive fields expand
- Neurons may become spontaneously active

Consequence of central sensitization
- Allodynia
- Hyperalgesia
- Spontaneous pain

References
Mechanism of central sensitization

NMDA receptors
- In dorsal horn spinal cord
- Normally unavailable for stimulation by its excitatory neurotransmitter glutamate

Repeated stimulation of pain pathways results in prolonged activation of NMDA receptors

Activated NMDA receptor
- Enhances pain and central sensitization
- Leads to wind-up and temporal summation

AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; mGluR = metabotropic glutamate receptors; NMDA = N-methyl D-aspartate.

References
Consequences of central sensitization

- Rapidly enhanced and ongoing pain
- Greater area of pain
- Hyperalgesia
- Allodynia

Central sensitization leads to
- Enhanced release of neurotransmitters
- Amplified output to the brain

Disruption of limbic brain function
- Fear, anxiety
- Sleep disturbance
- Depression

References
Consequences of central sensitization in patients

Osteoarthritis
- Continuous nociceptive input from damaged knee
- Central sensitization in brain stem periaqueductal grey matter (PAG)
- Correlation between blood oxygen level dependent (BOLD) response and pain score

Both peripheral and central aspects of pain should be considered for patients who display signs of central sensitization

References

Descending excitatory and inhibitory controls

- Descending pathways
  - Activate facilitatory neurons \(\rightarrow\) increase dorsal horn activity in spinal cord
  - Activate inhibitory neurons \(\rightarrow\) decrease dorsal horn activity in spinal cord

- Central sensitization
  - Less effective descending inhibitory pathways
  - Hyperexcitable state in spinal cord

Failure of descending inhibition plays a role in chronic pain conditions

References
Applying a prognostic risk approach to chronic pain in clinical practice

Defining chronic pain by duration:
- Is unidimensional
- May not be clinically significant
- Is difficult in recurrent pain conditions that are not continuous

Multidimensional approach includes other factors
- Duration of pain
- Concern about pain condition
- Concern about disability
- Depressive symptoms
- The aim of this approach is to reduce the risk of pain chronification
- Comorbidities associated with chronic pain are key to multidimensional management

References
Different formulations can block chemical messages in nociceptive pain

- Triptans can block serotonin
- Local anaesthetics like lidocaine can non-selectively block ion channels
- NSAIDs and COX inhibitors can block the production of prostaglandins

References

COX = cyclooxygenase; NSAIDs = non-steroidal anti-inflammatory drugs.
Chemicals and channels involved in neuropathic processes

Treatment for neuropathic pain relate to abnormalities in the function of ion channels due to damaged nerves

- Carbamazepine and lidocaine target sodium channels
- Gabapentin and pregabalin target calcium channels
- These compounds reduce incoming activity to the spinal cord

References
Opioid analgesia

- The opioid system is the major inhibitory system related to pain, via dampening of excitatory events.
- Activated opioid receptors open potassium channels, thereby acting as a highly effective brake on (abnormal) electrical activity produced by pain.

References
# Opioid receptors

<table>
<thead>
<tr>
<th>Type of receptor</th>
<th>Endogenous opioid peptides</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>µ</td>
<td>Endomorphins</td>
<td>Opens K⁺</td>
</tr>
<tr>
<td>δ</td>
<td>Enkephalins</td>
<td>Opens K⁺</td>
</tr>
<tr>
<td>κ</td>
<td>Dynorphin</td>
<td>Closes Ca²⁺</td>
</tr>
<tr>
<td>ORL-1</td>
<td>Nociceptin</td>
<td>Opens K⁺</td>
</tr>
</tbody>
</table>

**Endogeneous ligand**

**Drugs**
- Morphine
- Codeine
- Fentanyl
- Pethidine
- Heroin
- Oxycodon

**µ-opioid receptor**

**Minimal pain inhibition**

**Significant pain inhibition**

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References
Opioid analgesia

Opioids

Spinal cord C- and Aδ-fibres

Pre-synaptic inhibition
• Transmission of pain to spinal cord is blocked

Post-synaptic inhibition
• Pain signal output of the spinal cord is modulated

References
Ketamine: NMDA receptors and wind-up

Wind-up

Repetitive stimulation of C-fibres by noxious stimuli

NMDA receptors

Ketamine

Neuronal response amplified and prolonged

Ketamine

- Usable for its analgesic and sedative effects during surgery
- Beneficial effect on central sensitization in the spinal cord
- Unwanted side effects → not suitable for every day management of chronic pain

References

NMDA = N-methyl D-aspartate.
Descending control and supraspinal analgesia

- **Supraspinal sites**
  - Area above the spinal cord in the brain
  - Involved in processing of pain

- **Descending controls**
  - Originate in the higher centres
  - Modulate pain
  - Can inhibit or enhance pain sensation

Activation of the opioidergic descending control system by placebo analgesia indicates that opioid receptors at the supraspinal level should be considered in the management of chronic pain patients.

References
Supraspinal opioid analgesia

- Opioids work at the pre- and post-synaptic receptors in the spinal cord
- Opioids at the supraspinal level change descending controls
  - Switch to inhibitory mode to decrease enhancement and excitation
  - Can alter emotional assessment of pain by affecting the thalamus and limbic system

Opioid actions in the mid-brain and the brain stem allow descending controls to further reinforce the spinal inhibition by switching descending pathways into inhibitory mode as well

References
Ananthan S. AAPS J. 2006;8:E118-25.
Descending controls and analgesia

- **Opioids (e.g. morphine)**
  - Switch descending pathways to inhibitory mode

- **Antidepressants (SSRIs, SNRIs)**
  - Block reuptake noradrenaline (NA) and serotonin (5-HT)
  - Modulate descending controls

- **Tramadol**
  - Weak opioid action
  - Blocks reuptake NA and 5-HT

**References**

SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.
Descending controls and analgesia: tapentadol

- MOR-NRI: Tapentadol
  - μ-opioid receptor antagonist (MOR)
  - Noradrenalin reuptake inhibitor (NRI)

Tapentadol is a MOR-NRI, having supraspinal and spinal opioid mode of action, as well as noradrenaline reuptake inhibition.

References
Typical treatment pathway of chronic pain patient

WHO step-up analgesic approach is based on increasing strength of medication, depending on increase in severity of pain

- Underlying mechanisms in patients with chronic pain are not taken into account
- Does not include multidimensional aspects of chronic pain
- Not applicable for patients with chronic pain

The pharmacological treatment of chronic pain should focus mainly on the underlying mechanism and not on the intensity of pain

References
Multiple mechanisms of pain: corresponding medications

Stepped approach:
1. Links drugs to mechanism of pain
2. Has a drug that addresses chemical modulation of one or more pain mechanisms at each step

• If a single drug is insufficient, it is logical to use more than one agent at a time
• Drugs with more than one analgesic mechanism of action, such as tapentadol, target multiple pain pathways and may have a synergy of effect

CNS = central nervous system; NSAID = non-steroidal anti-inflammatory drug; TCAs = tricyclic antidepressants.

References
Treatment pathway in chronic pain patients

- The GP is central in managing a patient with chronic pain as he/she maintains a key relationship with the patient.
- Late referral from GPs to specialists is a key issue in chronic pain patients.

UK survey 2010 with 4438 people:
- 210 suffered chronic pain in previous 5 years
- 63% were aware of option to see pain specialist
- 23% was referred to pain specialist

Information source:
Public attitudes to pain UK pain study available at: 
http://www.patients-association.com/dhims/PUBLIC%20ATTITUDES%20TO%20PAIN.pdf

NSAIDs = non-steroidal anti-inflammatory drugs.
Summary

- Spinal cord is key in the development of chronic pain via central sensitization
  - Repeated stimulation results in prolonged activation of NMDA receptors
  - Enhanced release of neurotransmitters and amplified input to the brain
  - Consequences are allodynia, hyperalgesia and spontaneous pain

- Analgesia may act on supraspinal sites and descending controls
  - Opioids switch descending controls in inhibitory mode
  - Antidepressants modulate descending controls by blocking transmitter reuptake
  - Tramadol has weak opioid action and blocks transmitter reuptake
  - Tapentadol is a µ-opioid receptor antagonist and noradrenalin reuptake inhibitor

- Effective management of chronic pain requires a multidimensional and mechanism-based approach
  - Risk factors for development of chronic pain, such as depression, emotional distress, activity limitation
  - Treatment based on (chemical) modulation of pain mechanism(s)