Understanding the effect of pain and how the human body responds

Pain, which is caused by an unpleasant (noxious) stimulus, is a stressor that can threaten homeostasis. The body’s adaptive response to pain involves physiological changes, which are useful and potentially life-saving in the initial stages. If the adaptive response persists, harmful and life-threatening effects may ensue.

Pain is noxious, which makes it a powerful protective force: indeed the inability to feel pain is associated with a shortened life expectancy (Shin et al, 2016). After injury, pain encourages us to adopt behaviours that help the healing process; for example, resting the painful part of the body.

This article describes the physiological response to pain, its clinical relevance and its wide-ranging effects on the body. It also explains how nurses can provide effective pain relief to their patients.

Transmission of pain
The initial physiological changes taking place in the body after a pain stimulus are concerned with the transmission of pain, which involves four stages: transduction, transmission, perception and modulation.

Transduction
During transduction, the pain stimulus is transformed into a nerve impulse. Receptors on the surface of the nerve endings, called nociceptors, respond to noxious stimuli, which can be thermal (temperature above 40°C), mechanical (extreme pressure over a small area) or chemical (strong acid or alkali).

The stimulus interacts with receptors, causing chemical changes that lead the nerve to create an electrical signal (action potential). The sensory nerve fibre will only create an action potential if the stimulus is strong enough. A large stimulus creates a higher frequency of action potentials, which is eventually perceived as more severe pain.

Understanding pain physiology allows health professionals to act on pain mechanisms

Key nursing interventions to contain or relieve pain include holistic pain assessments

Transmitters/Adaptive response/Pain signal/Nerve fibres/Mediators

This article has been double-blind peer reviewed

Key points

- Different stages and mechanisms of pain transmission
- Physiological changes induced by pain
- Mediators that inhibit or promote pain

Abstract
Pain sends a signal that the body needs protection and healing. However, if the physiological changes triggered by pain persist, harm will ensue, and acute pain may become chronic, so pain must be contained and/or relieved. The mechanisms through which pain interacts with the body provide health professionals with various routes of entry and modes of intervention. This article discusses the intricacies of the adaptive response to pain and how they can be used to combat pain.

Citation

In this article...
- Different stages and mechanisms of pain transmission
- Physiological changes induced by pain
- Mediators that inhibit or promote pain

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Understanding the effect of pain and how the human body responds
and allowing white cells to move into the extracellular fluid – this is the inflammatory response, an essential part of healing.

Pain can be alleviated by reducing the sensitisation and activation of nerve endings; for example, non-steroidal anti-inflammatory drugs (NSAIDs) can inhibit the production of prostaglandin, one of the main sensitising mediators, while opioids can make it harder for the nerve to create an action potential. Precautions must be taken with both NSAIDs and opioids (Box 1).

**Transmission**

During transmission, the nerve impulse travels from the site of transduction to the brain in three stages: from nociceptors to spinal cord, from spinal cord to brain stem, and from brain stem to other parts of the brain.

The electrical signal is conducted along the nerve by cycling of sodium and potassium ions between the extracellular and intracellular fluid. Transmission is quickest along fibres that are myelinated: A-delta fibres are lightly myelinated, so they transmit pain signals more quickly than C fibres. A-delta fibres transmit ‘first pain’ – the sharp sensation felt immediately after injury. C fibres transmit ‘second pain’ – the duller, burning sensation that follows.

Once the signal reaches the end of the long axon of the primary afferent fibre (PAF), which stretches from the periphery to the spinal cord, it needs to cross a small fluid-filled gap – the synapse. This is achieved by the release of neurotransmitters, which diffuse across the synapse and activate receptors on the next neuron in the chain (secondary neuron), as well as on nearby glial cells and interneurons. A strong pain signal causes the release of enough neurotransmitters to activate the secondary neuron, and the signal then travels onwards to the brain, where it stimulates cells in the brainstem, thalamus and cortex.

The transmission of the pain signal can be stopped by applying a local anaesthetic close to the nerve bundle, and it can be slowed down by administering an anticonvulsant, such as gabapentin or pregabalin. There is some evidence that these drugs help reduce neuropathic pain (Griebeler et al, 2014), but there is a growing concern that some people can become addicted to them, especially if they have a history of opioid addiction (Evoy et al, 2017).

**Perception**

Perception, which is when pain becomes a conscious experience, involves recognising, defining and responding to pain. It takes place in the cortex (location and motor response), the limbic system (emotional response) and the reticular system (arousal response). As part of a wider pain management strategy, distraction can be an effective technique to take the mind off pain; it has proven helpful in reducing the need for opioids in people with severe trauma pain (Jarzyna et al, 2011).

**Box 1. Precautions with NSAIDs and opioids**

Non-steroidal anti-inflammatory drugs (NSAIDs) can lead to slower and poorer bone and tendon healing (Su and O’Connor, 2013) and are linked to gastric irritation and ulceration, renal failure and increased risk of thrombosis (Eccleston et al, 2017), particularly in older people. NSAIDs should only be administered for short periods and after a careful assessment of the risks and benefits (Zingler et al, 2016).

Opioids can cause sedation and respiratory depression, especially in the first 24 hours of use and when the dose is increased. The risk is increased in people with sleep apnoea or who had respiratory difficulties during surgery (Weingarten et al, 2015). Morphine should be given at the lowest effective dose and patients should be monitored for signs of opioid-induced sedation, which usually precedes respiratory depression (Jarzyna et al, 2011).

Opioids are often used to manage chronic pain. They can be used to treat pain caused by injury and disease, such as in patients with needle phobia (Brugnoli, 2016, Uman et al, 2013). The production of endogenous opioids can be stimulated by acupuncture, exercise and transcutaneous electrical nerve stimulation (TENS) (Claydon et al, 2011).

Pain can also be modulated by ascending mechanisms. Activated by touch or pressure, A-beta fibres trigger the same secondary neurons as C fibres. When a C fibre activates the secondary neuron, the signal created represents pain, but when an A beta fibre activates the secondary neuron, the signal created represents touch. A-beta fibres and C fibres compete to activate the secondary neuron, and only one of them can win. If many A-beta fibres are activated, pain signalling is reduced; this is the principle of the gate control theory (Melzack and Wall, 1965).

In TENS, the sensation produced competes with pain signals, which reduces the onward signalling of pain from the dorsal horn of the spinal cord (Suluk and Walsh, 2003). This effect is like that obtained when rubbing the painful area.

When pain signals enter the dorsal horn with high frequency, or with a low frequency over a prolonged period, local changes further increase the pain signal. High-frequency inputs to the dorsal horn stimulate the release of not only the short-acting transmitter glutamate, but also longer-acting transmitters substance P and calcitonin gene-related peptide (CGRP). These longer-acting transmitters stay on the receptors of the secondary neuron for a longer period, allowing summation to take place (Woolf and Salter, 2000). This is where a pain signal is amplified as each change in electrical potential of the secondary neuron is added to others to create a larger stimulation. It leads to an enhanced responsiveness of the secondary dorsal horn neuron, known as central sensitisation.

At the same time nearby cells called glia are stimulated to produce more mediators that can sensitize and activate the secondary neuron. The system usually reverts to normal once the noxious stimulus is removed; inappropriate persistence of this sensitisation is one of the main causes of chronic pain.

Pain can also be amplified by the release of serotonin from the rostroventral...
medulla (RVM). Serotonin increases pain signalling when released in low quantities, but in higher quantities it has an inhibitory effect (Zhuo, 2017). The facilitation of pain caused by serotonin happens when the NMDA receptor is active – during central sensitisation – so when pain signals are high frequency or prolonged, the brainstem can amplify pain even further.

**Responses to pain**
The body responds to pain through numerous and interconnected physiological processes via the sympathetic nervous system (SNS), neuro-endocrine system and immune system, but also via emotions. The effects of these changes on body systems are summarised in Table 1.

### Sympathetic nervous system
The SNS is involved in the body’s immediate response to emergencies, including severe and acute pain; its reaction to pain or fear is known as the ‘fight or flight’ response. When activated, the SNS stimulates brainstem cells that control descending pain mechanisms to release noradrenaline, serotonin and endogenous opioids into the dorsal horn.

The SNS is concerned with the regulation of vascular tone, blood flow and blood pressure, as sympathetic nerves have stimulating effects on the heart (improving circulation) and respiratory system (increasing oxygen intake). Pain therefore increases heart rate, blood pressure and respiratory rate. If these physiological responses are prolonged, especially in a person with poor physiological reserves, it can lead to ischaemic damage (Wei et al, 2014).

The SNS also has an inhibiting effect on digestion, reducing or preventing the secretion of digestive enzymes in the alimentary canal and the peristaltic action in the gut wall. Pain can therefore lead to a reduced ability to digest food, which can in turn cause nausea, vomiting or constipation (Singh et al, 2016).

### Neuro-endocrine system
The endocrine and nervous systems are linked via the pituitary gland at the base of the hypothalamus. Some of the body’s responses to pain are mediated by the nervous and endocrine systems, primarily via the hypothalamic-pituitary-adrenocortical (HPA) axis and the sympathomedullary pathway, and involve the release of mediators such as cortisol, adrenaline and noradrenaline, growth factor and cytokines.

**Adrenaline, noradrenaline and cortisol**
Pain triggers a response in the amygdala, which drives the hypothalamus to produce corticotrophin-releasing hormone (CRH); this is transmitted to the anterior pituitary gland, where it activates the SNS and stimulates the production of adrenocorticotrophin (ACTH). The SNS also stimulates the adrenal medulla to release adrenaline and noradrenaline, which have various effects (Table 2).

ACTH is carried in the blood to the adrenal cortex, where it stimulates the production of cortisol; this mobilises glucose to increase the energy available for the ‘fight or flight’ response, and acts as an anti-inflammatory by inhibiting

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**Table 1. Effects of acute pain and nursing interventions**

<table>
<thead>
<tr>
<th>Body system</th>
<th>Change</th>
<th>Nursing intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Increased heart rate and blood pressure</td>
<td>Monitor and interpret vital signs</td>
</tr>
<tr>
<td></td>
<td>Increased need for oxygen</td>
<td>Administer oxygen as prescribed</td>
</tr>
<tr>
<td></td>
<td>Water retention, potential fluid overload</td>
<td>Monitor fluid balance</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Increased respiratory rate</td>
<td>Encourage DB&amp;C so lungs fully inflate and secretions are evacuated</td>
</tr>
<tr>
<td></td>
<td>Shallow breathing</td>
<td>Provide pad and/or pillow to support abdominal or thoracic wounds</td>
</tr>
<tr>
<td></td>
<td>Increased risk of infection</td>
<td></td>
</tr>
<tr>
<td>Immune</td>
<td>Increased susceptibility to infection</td>
<td>Monitor temperature</td>
</tr>
<tr>
<td></td>
<td>Increased or decreased sensitivity to pain</td>
<td>Use infection prevention and control measures</td>
</tr>
<tr>
<td></td>
<td>Activation of HPA axis</td>
<td></td>
</tr>
<tr>
<td>Endocrine</td>
<td>Increased blood glucose</td>
<td>Monitor blood glucose in patients with diabetes</td>
</tr>
<tr>
<td></td>
<td>Increased cortisol production</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Reduced gastric emptying and intestinal motility</td>
<td>Use anti-emetic medication as prescribed</td>
</tr>
<tr>
<td></td>
<td>Nausea and vomiting</td>
<td>Use laxatives as prescribed</td>
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<tr>
<td></td>
<td>Constipation</td>
<td>Ensure adequate hydration</td>
</tr>
<tr>
<td>Urinary</td>
<td>Urge to urinate/incontinence</td>
<td>Monitor urine output and colour</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Tense muscles local to injury</td>
<td>Encourage relaxation</td>
</tr>
<tr>
<td></td>
<td>Shaking or shivering</td>
<td>Provide more comfortable bedding</td>
</tr>
<tr>
<td></td>
<td>Pilo-erection (goose bumps)</td>
<td>Support movement using analgesia, splinting and/or weight reduction strategies</td>
</tr>
<tr>
<td>Nervous</td>
<td>Changes in pain processing</td>
<td>Provide effective analgesia, closely monitor response and side-effects</td>
</tr>
<tr>
<td></td>
<td>Risk of pain becoming chronic</td>
<td>Raise concerns if pain not well managed</td>
</tr>
<tr>
<td>Brain</td>
<td>Anxiety/fear</td>
<td>Communicate and inform effectively</td>
</tr>
<tr>
<td></td>
<td>Depression</td>
<td>Assess anxiety, depression and catastrophisation</td>
</tr>
<tr>
<td></td>
<td>Poor concentration</td>
<td>Teach effective coping strategies</td>
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<tr>
<td></td>
<td>Inhibition or promotion of pain</td>
<td>Provide reassurance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Be visible and responsive to patient’s needs</td>
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</tbody>
</table>

DB&C = deep breathing and coughing; HPA axis = hypothalamic-pituitary-adrenocortical axis

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Adrenaline, noradrenaline and cortisol Pain triggers a response in the amygdala, which drives the hypothalamus to produce corticotrophin-releasing hormone (CRH); this is transmitted to the anterior pituitary gland, where it activates the SNS and stimulates the production of adrenocorticotrophin (ACTH). The SNS also stimulates the adrenal medulla to release adrenaline and noradrenaline, which have various effects (Table 2).

**ACTH** is carried in the blood to the adrenal cortex, where it stimulates the production of cortisol; this mobilises glucose to increase the energy available for the ‘fight or flight’ response, and acts as an anti-inflammatory by inhibiting
prostaglandin (Hannibal, 2014). The level of cortisol in the blood provides a feedback mechanism to the hypothalamus, thereby preventing over-release.

When functioning well, this mechanism reduces pain and stops the inflammatory response getting out of control. However, long-term pain and stress can reduce the body’s ability to dampen inflammation. In long-term stress and/or pain, the constant production of cortisol leads to resistance in the glucocorticoid receptors. Consequently, feedback to the hypothalamus is impaired and cortisol loses its ability to keep inflammation under control. Some people with long-term pain have higher levels of inflammatory mediators in their blood, and these can contribute to depression, anxiety and sleep problems (Gerdle et al, 2017).

**Growth hormone**

Secreted by the anterior pituitary gland, growth hormone (GH) has a direct effect on cellular activity and the metabolism of protein, carbohydrate and fat. Pain increases the secretion of GH, which contributes to the increase in blood glucose levels and insulin resistance (Greisen et al, 2001). A deficiency in GH causes muscle weakness and fatigue, which are also symptoms of a pain syndrome called fibromyalgia. People with fibromyalgia have been found to have lower levels of GH, and GH treatment has improved pain and quality of life (Cuatrecasas et al, 2012).

**Cytokines**

Cytokines are produced in response to injury and pain by a variety of peripheral cells local to the injury (including macrophages, fibroblasts and monocytes) and by cells in the dorsal horn of the spinal cord and brain (glial cells). Pro-inflammatory cytokines include tumour necrosis factor alpha (TNFα), nerve growth factor (NGF), interleukin 6 (IL-6) and interleukin 1 beta (IL-1β). Anti-inflammatory cytokines include interleukin 10 (IL-10) and interferon alpha (IFNα).

Immediately after an injury, TNFα and IL-1β sensitize sensory nerve endings and stimulate the production of noxious mediators (for example, substance P). In the spinal cord, they encourage the production of pain neurotransmitters (for example, substance P, CGRP, glutamate) and increase the number of receptors for these molecules on the secondary neuron.

At the same time, TNFα and IL-1β inhibit the activity of cells that contribute to the suppression of pain (interneurons that produce GABA and glycine). They are therefore important in the amplification of pain. Pro-inflammatory cytokines also stimulate the hypothalamus, triggering the HPA axis and causing fever; their activity is balanced by the activity of anti-inflammatory cytokines such as IL-10 and IFNα. This is a complex relationship partly determined by the circumstances of the pain (Uceyler et al, 2009).

Blocking the activity of pro-inflammatory cytokines can have dramatic effects on pain; the first clinical trials of anti-TNFα drugs were conducted in the 1990s (Elliott et al, 1994). A range of drugs called monoclonal antibodies and biologics have been shown to be effective in a number of painful conditions (Zheng et al, 2016; Chesell et al, 2012) – a major step forward in the management of difficult pain.

**Immune system**

Damage to tissues, whether mechanical or due to infection, triggers an immune response. Macrophages and mast cells produce immune mediators, such as NGF, that stimulate sensory nerve endings and provoke pain. As well as transmitting the pain signal to the dorsal horn, the sensory nerve ending also conducts signals from the cell back along the axon to the periphery, leading to the release of substances such as CGRP and substance P. These increase vasodilation and vascular permeability,

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### Table 2. Physiological effects of adrenaline and noradrenaline

<table>
<thead>
<tr>
<th>Organ</th>
<th>Effect</th>
<th>How this translates clinically</th>
</tr>
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</table>
| Brain          | ● Activation of cells in the amygdala, locus coeruleus and periaqueductal grey  
● Altered balance between limbic and frontal cortex control of micturition | ● Heightened awareness  
● Fear  
● Analgesia  
● Urge to pass urine or incontinence |
| Heart          | ● Increased heart rate  
● Increased contractility  
● Increased speed of conduction | ● Increased heart rate  
● Increased blood pressure |
| Blood vessels  | ● Constriction of blood flow to skin  
● Dilation of blood vessels to muscles | ● Cold, paler skin  
● Increased exercise capacity |
| Kidneys        | ● Constriction of blood vessels to kidneys  
● Increased production of antidiuretic hormone  
● Increased production of renin  
● Retention of sodium | ● Activation of renin-angiotensin-aldosterone pathway  
● Increased glomerular filtration rate  
● Water retention |
| Gut            | ● Decreased motility to stomach and intestine | ● Inability to digest  
● Nausea, vomiting, constipation |
| Liver/pancreas | ● Breakdown of glycogen into glucose  
● Increased metabolic rate  
● Inhibition of insulin production  
● Increased blood glucose | ● Monitor fluid balance  
● Monitor urine output and colour |
| Skin           | ● Constriction of blood flow to the skin | ● Pilo-erection (goose bumps)  
● Hair standing on end |
| Skeletal muscle| ● Rhythmic contraction | ● Shaking or shivering  
● Teeth chattering |

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stimulating blood flow and helping the translocation of immune cells from the bloodstream to the site of injury.

NGF and other substances important to pain signalling are useful biomarkers to measure pain (Goto et al, 2016). Auto-antibodies (antibodies that act against the self) are involved in a variety of pain states such as rheumatoid arthritis, Guillain-Barré syndrome and complex regional pain syndrome (McMahon et al, 2015). Immuno-therapies that target autoantibodies are emerging (Lahoria et al, 2017) and there is hope that these new therapies will help manage complex, hard-to-treat pain.

Effects on mood

Pain also triggers emotional responses orchestrated by various regions of the cortex, the amygdala, the hypothalamus, various brain stem structures, and nerves in the descending modulatory system. Depending on the circumstances, anxiety and depression can either increase or reduce pain (Wiech and Tracey, 2009). A high threat level induces strong emotions such as fear or intense anxiety, leading to a state of high arousal, awareness and/or vigilance, which in turn reduces sensitivity to pain. A low or moderate threat level causes a less intense response, such as low-level anxiety or depression, which induces a low-to-moderate state of arousal in which pain is more easily felt.

Assessing mood is therefore an important part of holistic pain assessment. Anxiety, and depression make both acute and chronic pain more difficult to manage than others. Acute post-operative pain normally responds well to analgesia, but this should be complemented by strategies such as comfortable positioning, distraction, TENS and reassurance. If poorly managed, post-operative pain is more likely to become chronic (Sansone et al, 2015), so needs to be dealt with effectively.

Good pain management, based on a sound understanding of the physiological effects of pain, is an essential element of nursing care. Understanding the physiology of pain will help you to select and combine the most effective interventions, and appreciate the value of holistic assessment.

Not all pain is the same, not all patients are the same, and not all possess effective coping strategies. You can help by getting to know your patients and tailor your support to their needs.

Implications for practice

Pain induces a cascade of interrelated changes in several body systems. In the acute phase, most are adaptive and helpful, but in the longer term all are potentially harmful, especially in patients whose reserves are already low. Containing and relieving pain is therefore crucial.

Pain often causes recognisable physiological and behavioural changes, but the absence of these changes does not mean the absence of pain. Typically, people experiencing acute pain will have an elevated heart rate, blood pressure and respiratory rate; they may shake or shiver, have goose bumps and pale skin. The more intense the pain, the more visible these signs and symptoms are. Chronic pain is not usually accompanied by physiological or behavioural changes, but these will appear during exacerbations. Such changes can also be related to the person’s condition and treatment, which makes them unreliable indicators, so it is vital to regularly assess patients’ pain using validated tools.

The complexity of pain physiology makes some pains more difficult to manage than others. Acute post-operative pain normally responds well to analgesia, but this should be complemented by strategies such as comfortable positioning, distraction, TENS and reassurance. If poorly managed, post-operative pain is more likely to become chronic (Sansone et al, 2015), so needs to be dealt with effectively.

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