

Nursing Practice Review Pain management

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The first of a three-part series on the management of pain describes how pain is detected in the body and the implications for clinical practice

PART 1 OF 3: PAIN MANAGEMENT

Physiology – how the body detects pain stimuli

In this article...

- › An overview of the pain pathway
- › How pain receptors detect pain
- › How agonists and antagonists are used to manage pain

5 key points

1 Pain (noxious) stimuli may be mechanical, thermal or chemical

2 The threshold of activation of pain receptors varies throughout the body, with the cornea in the eye being more sensitive than the skin, for example

3 The frequency a nociceptor fires relates to the pain intensity; a higher frequency means a greater pain intensity

4 Analgesics such as morphine act as agonists, binding to the pain receptor and so preventing it from firing a pain signal

5 Painkillers such as capsaicin cream work by overstimulating a particular receptor, which is then spent and will not fire for some time afterwards

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Abstract Swift A (2015) Pain management 1: how the body detects pain stimuli. *Nursing Times*; 111: 39, 20-23.

Pain is the body's way of telling us something is wrong. It has a sensory and emotional component. This three-part series focuses on acute pain, describing the physiology of a normal and well-behaved pain pathway and how this relates to commonly used pain-management strategies. This first article introduces the pain system and how the body detects a threatening (noxious) stimulus. Part two describes how that pain message is transmitted to the spinal cord and the brain, and the response of the brain to the stimulus. The third article discusses the assessment of pain.

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage (Merksy and Bogduk, 1994). As a physical sensation pain usually signals a danger to the body from an internal or external stimulus such as an infection or a knife wound. This type of pain is called physiological pain or acute pain and normally resolves once the stimulus has been removed and the damaged tissues have healed. Chronic pain, on the other hand, continues indefinitely and might be related to an ongoing disease process such as osteoarthritis, damage or dysfunction of the nervous system (as is the case in painful diabetic

neuropathy), or to a change in the way the nervous system detects and manages sensory signals (as is the case in chronic low back pain).

Acute pain is best relieved by interrupting pain signals as they travel between their source and the brain, or by boosting the body's own efforts to alleviate pain such as the production of neuroactive chemicals like endorphins. Chronic pain can be more difficult to manage because of differences in the signalling process. Therefore the starting point for being able to provide effective pain management is an understanding of the "normal" pain pathway associated with acute pain. A glossary of terms is provided in Box 1 (page 23).

An overview of the pain system

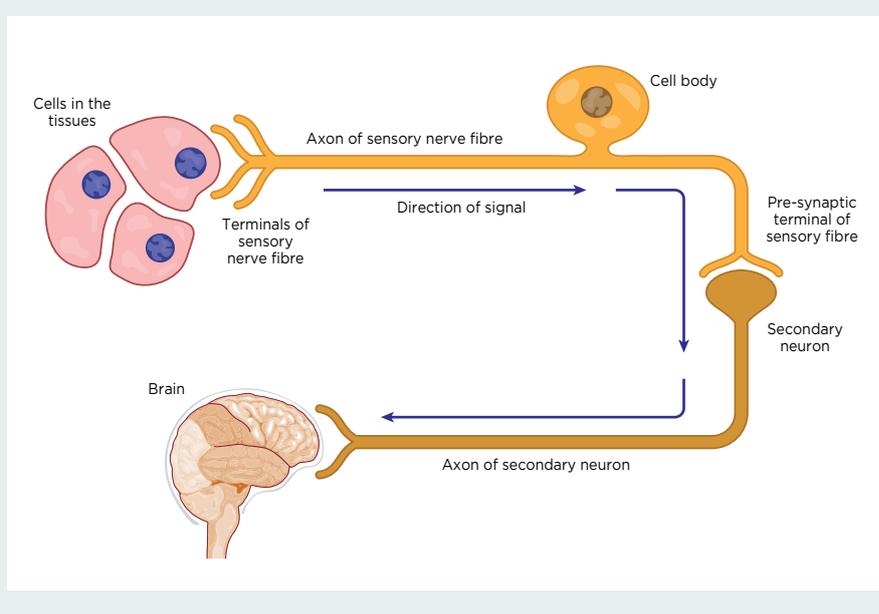
Acute pain is a sensation triggered by a threatening (noxious) stimulus to the skin (cutaneous pain), the musculoskeletal system, or the internal organs (visceral pain), which is then signalled to the brain so it becomes aware of the threat and can decide how to respond (fight or flight). The signal may trigger a reflex response that causes us to move out of range of the threat. The pain "system" comprises a number of elements that detect the noxious stimulus, convert it to an electrical signal and transfer that signal rapidly to the spine and then the brainstem and finally the cortex. These are illustrated in Fig 1.

The basic elements of the pain pathway are different kinds of sensory nerves that connect the tissues to the spinal cord and run together in bundles between the two.



Acute pain is caused by activating pain receptors throughout the body

FIG 1. BASIC ELEMENTS OF THE PAIN PATHWAY



Each sensory nerve terminates in a multitude of specialised receptors that are spread across the skin and organ tissues; these connect by a long axon to their cell body (which lies just outside the spinal cord). The cell body has a second axon that terminates in the dorsal horn of the spinal cord. The sensory nerve responsible for detection of a threat is the first step in the pain pathway and is called the primary afferent fibre (PAF). Afferent means signals travel along it towards the spinal cord.

Once the primary afferent fibre terminates in the spinal cord, it makes chemical and physical connections with other cells including secondary neurons. The signal is passed from the primary afferent fibre to the secondary neuron, which carries the signal to the brain. It is not until the signal reaches the cortex that the brain becomes aware of the pain.

Detection of a noxious stimulus

Pain can be detected (or sensed) in most of the body's tissues except in healthy cartilage and the brain itself. The key elements involved in detection are:

- » A threatening or harmful (noxious) stimulus;
- » Units that can respond to different noxious stimuli (sensory nerve endings with receptors).

Noxious stimuli are traditionally divided into three categories: chemical, thermal or mechanical. To initiate a pain signal, the stimulus has to be above a particular intensity (threshold) that would be enough to cause damage to the tissues. Examples of these include:

- » Chemical: acids, alkalis, irritants, capsaicin (active ingredient of chilli peppers);
- » Thermal: heat (above 42°C), cold (below -15°C);
- » Mechanical: punctate (sharp) pressure, rotation beyond normal functional range (for example joints), distension (for example, bowel).

A noxious stimulus is detected by receptors that are situated on the cell membrane of the sensory nerve ending. The receptors are proteins that are made in the cell body of the nerve and then transferred to the surface of the nerve ending. The types of receptors on the sensory nerve ending determine the type of stimulus that the nerve cell can respond to, and there are many types. The receptors that detect pain

(or noxious stimuli) are found at the nerve endings of primary afferent A-delta and C fibres (Table 1). Primary afferent A-beta fibres respond to non-noxious stimuli, such as touch.

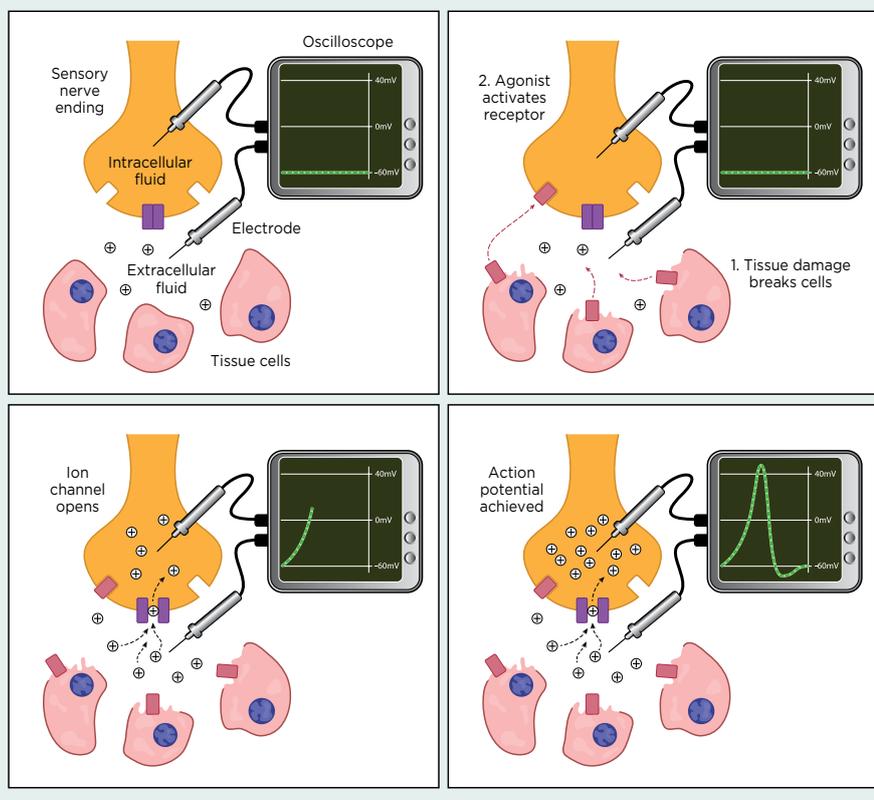
A mechanical stimulus, such as an over-stretch of a muscle fibre or over-rotation of a joint, causes receptors on the surface of the nerve ending to stretch. Noxious heat or cold near the nerve ending and noxious chemicals interact with specific receptors. The receptor responds to the triggering event chemically in one of three ways:

- » Agonism/excitation: the electrical potential of the cell is raised above the activation threshold and an action potential is initiated;
- » Sensitisation: makes it easier for the

TABLE 1. TYPES OF SENSORY AFFERENT FIBRE

Fibre	Size	Relative speed	Myelin	Stimulus type	Alternative name
C	Small	Slowest	None	<ul style="list-style-type: none"> ● Mechanical ● Mechanical and heat ● Mechanical, heat and chemical ● In inflammation only - mechanical, heat and chemical 	CM CMH Polymodal Silent
A-delta	Medium	Medium	Light	<ul style="list-style-type: none"> ● Mechanical and heat ● Mechanical and cold ● High-threshold mechanical 	AMH AMC AHTM
A-beta	Large	Fastest	Yes	<ul style="list-style-type: none"> ● Low-threshold mechanical 	LTM

FIG 2. CREATION OF AN ACTION POTENTIAL



cell to achieve its threshold for action potential generation;

- » Antagonism/hyperpolarisation: makes it more difficult for the cell to achieve its threshold for action potential generation.

Implications for practice

Mu (μ) receptors are found on the sensory nerve endings in the peripheral nervous system as well as in the spinal cord, the brain, the gut and many other places. When an opioid drug, such as morphine, binds to a mu receptor it acts as an antagonist and makes it more difficult for the nerve cell to become excited (Marvizon et al, 2010). Giving morphine by any route allows the spread of the drug through the whole body. However, despite the fact that morphine can inhibit excitation of the sensory neuron at the site of an injury, there is no consensus about whether topical application of morphine to painful wounds is an effective and safe therapy (Farley, 2011).

Converting a stimulus into a pain signal

Agonism of receptors on the sensory nerve endings leads to excitation of the sensory nerve by production of an action potential (Fig 2). Nerve signals are conducted along

axons by the movement of electrically charged ions. To initiate this process the interior of the nerve cell has to change from being negatively charged (about -65mV) to positively charged. This is called depolarisation.

The interaction of agonists with receptors causes changes in the cell membrane – opening up pores called ion channels that allow positive ions (sodium and calcium) to enter the nerve cell. As the positively charged sodium and calcium ions move into the cell it becomes more positively charged. This continues to a peak of around 55mV , which is called the activation threshold.

Once the activation threshold is achieved an action potential is initiated. The threshold of activation of the nociceptors varies throughout the body, with the cornea in the eye being a site where the threshold is relatively low compared with the skin, for example. This means that the degree of stimulus required to trigger pain in the cornea is much lower than the skin.

Reaching an action potential depends on the quantity of stimulus – a large stimulus will cause a reaction in a high number of receptors, and this will help the cell achieve its threshold more rapidly. A low level stimulus might cause an interaction with some receptors and an influx of a

relatively small quantity of positive ions; this will not be enough to trigger an action potential.

Significant tissue damage causes lots of agonists, so the nerve cell will achieve its action potential threshold, and will do so a number of times in quick succession. This means the nerve will fire frequently (for example 50 action potentials per second) – this creates high pain intensity. Less frequent firing (for example one action potential per second) will produce a lower intensity of pain if it leads to pain at all. The maximum number of action potentials that a sensory fibre can achieve is about 100 per second (Bear et al, 2001). The action potential is then rapidly transmitted along the axon until it reaches the sensory nerve fibre terminal in the dorsal horn.

Once an action potential has been created the nerve cell actively pumps positive ions back out into the extracellular fluid in order to return to its resting potential.

These excitable nerve cells can be compared to a bottle of cola: they sit quietly fizzing, and while they have the potential to do something an input of energy is needed. If a soft mint sweet is added to the bottle, action potential is reached and the fizz is no longer quiet but loud and has enough energy to carry cola out of the bottle and into the air.

In the cola scenario you are the stimulus and you interact with the cell by removing the cap (opening an ion channel). The mint sweet represents the positive ions. If you dropped a very small portion of the sweet into the bottle you would still see a reaction but not enough to cause the explosion – you did not reach the activation threshold.

A larger quantity of the mint would cause a larger reaction. There comes a point where there is “enough” of the sweet and the large reaction cannot be prevented. This is the activation threshold and the reason these nerve cells are called all or nothing – either an action potential will be triggered or not. Pain intensity depends on how often the action potentials are triggered.

In situations where there is tissue injury, less stimulus is required to trigger pain and the pain elicited by that stimulus is disproportionately large. This process is called peripheral sensitisation. It is a result of chemicals released in the inflammatory process making the receptors and ion channels more excitable – more ready to react. In the cola bottle analogy this would be like giving the cola bottle a little shake before you put the mint in.

Implications for practice

Understanding of receptors is increasing all the time and this improves the management of pain. The TRPV1 receptor responds to high temperatures (above 42°C), to acid and to the active ingredient of the chilli pepper (capsaicin). The presence of TRPV1 receptors on the mucous membranes is what makes food containing chilli feel hot. These are the receptors that make pepper spray an extremely effective attack-prevention measure, and the reason to avoid rubbing the eyes after preparing chillies.

Repeated activation of TRPV1 receptors can tire them out temporarily so there are many pain-relieving preparations that target these receptors including capsaicin cream, which is applied to the skin. Once the burning sensation has worn off the nociceptor cannot be activated for a few hours. This has been used to alleviate neuropathic pain (caused by damage or dysfunction of sensory nerves) (Hoper et al, 2014), and in arthritis (Laslett and Jones, 2014).

Prostaglandin is a chemical produced in inflammation that sensitises the local sensory nerve endings by interaction with a receptor called PGE2. Anti-inflammatory medication like ibuprofen reduces pain by inhibiting the production of prostaglandin, so the nerve endings have a normal threshold for activation instead of a reduced threshold even when the tissues are damaged.

Unfortunately, although anti-inflammatories are extremely effective in pain reduction, they also have a number of problems associated with their use including gastric irritation and ulceration, renal dysfunction, increased risk of thrombus formation, bronchospasm in some people with asthma, and increased bleeding time (Bruno et al, 2014). The National Institute for Health and Care Excellence has produced guidance on when to use them, and how to use them in a variety of disorders and situations. Generally the advice is to use them in the lowest effective dose for the shortest time (NICE).

Conclusion

Acute pain is a sensation caused by activating pain receptors throughout the body (except the brain and cartilage) with chemical, mechanical or thermal stimuli. It takes a certain amount of stimulus to set off an action potential, but once the activation threshold has been reached the pain signal will be rapidly transmitted to the spinal cord, and from there to the brain. Once the signal reaches the brain we become aware of the pain.

BOX 1. GLOSSARY

- **Afferent:** travelling from the periphery to the spinal cord (dorsal horn)
- **Agonist:** a protein key that fits a specific receptor “lock” and causes a reaction to occur, for example open an ion channel
- **Antagonist:** a protein key that fits a specific receptor “lock” and prevents a reaction from occurring, for example blocking the ion channel
- **Cutaneous:** of the skin
- **Dorsal horn:** the route into the spinal cord that (most) sensory nerves take – towards the back of the cord
- **Nerve:** a bundle of axons (the long conduction cables of neurons), can include a number of different types of neurons
- **Neuron:** a cell that, when excited by a stimulus, produces an electrical or chemical signal (often used interchangeably with nerve)
- **Neurotransmitters:** chemicals that carry signals between one nerve cell and another (amino acids or proteins that provide the key to receptor locks)
- **Nociceptor:** a peripheral sensory neuron that can respond to noxious stimuli
- **Noxious (stimulus):** harmful or potentially harmful stimulus – can be immediately harmful or harmful if left for a relatively long time (for example high temperature or long-lasting medium-high temperature)
- **Mechanical stimulus:** usually a high pressure distributed over a small surface area – often another way of saying punctate pressure when talking about noxious stimuli
- **Punctate pressure:** pressure applied to a very small surface area
- **Primary afferent fibre:** a term used for all sensory neurons arriving in the dorsal horn but usually meaning those carrying pain signals (A-delta and C fibres)
- **Receptor:** a protein molecule found on the cell surface that provides the lock for a specific key
- **Sensitisation:** a process that lowers the activation threshold of the nerve either by causing an increase in the number of surface receptors or by opening ion channels
- **Stimulus:** something that causes a physiological response (single stimulus, plural stimuli)
- **Synapse:** small space between one nerve cell and another across which an electrical or chemical signal is passed
- **Terminal:** an ending, usually the end of the sensory nerve in the spinal cord
- **Threshold:** the lowest stimulus intensity that evokes pain
- **Visceral:** of the (internal) organs

The intensity of pain is usually proportional to the intensity of the stimulus. In an injured part of the body the threshold for activation of the pain receptors is reduced and this increased sensitivity serves to remind us to protect the injured area while healing takes place. Pain receptors can be exhausted by using capsaicin, while the threshold of activation can be raised by using morphine or anti-inflammatory medication.

Part two of this series will look at the movement of the pain signal to the spinal cord and the brain and how knowledge of this pathway can help provide effective pain relief. **NT**

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