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.

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.
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:

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- Sensitisation: makes it easier for the
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Nerve signals are conducted along nerve endings leads to excitation of the sensory neuron at the site of an injury, morphine can inhibit excitation of the sensory nerve fibre terminal in the dorsal horn.

**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 μ receptor it acts as an antagonist and makes it more difficult for the cell to achieve its threshold for action potential generation.

**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 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.

**Fig 2. Creation of an Action Potential**

- **1. Tissue damage breaks cells**
- **2. Agonist activates receptor**
- **3. Ion channel opens**
- **4. Action potential achieved**

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.

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 achieved or nothing – either an action potential will be achieved or nothing.

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.

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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.

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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 acids 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) (Hopper 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 chemicals, 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.

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.

References


Evidence on NSAID use in soft tissue injuries

Bit.ly/NTNSAIDSoftTissue