Transmission of pain signals to the brain

In this article...

- How pain signals travel up the nerves to the brain
- How the brain processes pain signals
- Pain management strategies that interrupt the pain pathway

PART 2 OF 3: PAIN MANAGEMENT

The first part of this series described how pain is detected in the body. This article describes the process of pain transmission and how this relates to pain management.

As discussed in the first article in this series (Swift, 2015), pain is a complex process that involves emotional and sensory components. To be able to manage pain, it is necessary to understand the pain pathway so that, by interrupting the pain signal or harnessing the body’s own pain-relieving mechanisms, pain can be adequately managed.

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). A signal is then transmitted to the brain so it becomes aware of the threat and can decide how to respond (fight or flight).

The first article in this series described how the body first senses pain; this article describes how that pain signal is carried to the brain and sets in motion the pain response. A glossary of terms is provided in Box 1.

Transmission of the pain signal

Axons travel throughout the body back to the spinal cord. Their pathways look like a tree, where the spinal cord is the main trunk with branches extending out into the body, and twigs and side shoots spreading again so all tissues are reached. A pictorial representation of this is called a dermatome map (Fig 1). This shows where the various nerves enter the spinal column. For example, the sensory nerves that supply the outer edge of the foot and the back of the leg enter the spinal cord in the sacral region. Damage to the sciatic nerve – which is the S1 nerve – results in sciatic pain, which is typified by extending down the back of the leg and into the outer foot.

The pain signal is rapidly conducted along the axon by the movement of sodium and potassium ions – like a series of action potentials being generated one after another in a wave of depolarisation. The signal travels more quickly in larger axons, and quickest of all when a nerve has a myelin sheath. The A-delta fibre is large and myelinated, and pain signals travel very quickly along this – providing us with “first pain” – an immediate, sharp painful sensation at the time of injury. The C fibre is small and unmyelinated, and pain signals travel more slowly, providing the “second pain” – a duller, more persistent pain which is felt after the first pain has subsided.

1 Pain travels at different speeds along different nerve fibres
2 The closer local anaesthetic application is to the spinal cord the more widespread the pain relief
3 When intense/prolonged pain is experienced the central nervous system becomes sensitised – making it easier to excite (feel pain)
4 Some painkillers make it harder for a pain signal to be transmitted across the dorsal horn
5 The body’s own pain-relieving chemicals can be stimulated by exercise, laughter, sex and meditative relaxation techniques
and carries pain signals slowly, giving us the dull aching sensation of "second pain" that follows.

**Implications for practice**

Local anaesthetic (for example lidocaine) injected around the nerve blocks sodium channels and so prevents transmission of the pain signal. This is used to prevent pain associated with procedures such as cannulation or surgical incision. The closer the local anaesthetic application is to the spinal cord, the more branches of the nerve will be blocked and therefore pain relief will be more widespread.

An epidural is an example of blocking the sensory nerves as they enter the spinal cord, and this blocks sensation from the skin. These can be used to reduce pain caused by sensory nerves that are spontaneously firing or overactive – for example, to treat post-herpetic neuralgia, the pain that can follow an episode of shingles (Malec-Milewska et al, 2015).

**Transmission from primary afferent fibre to secondary neuron**

Sensory neurons enter the spinal cord via the dorsal route (at the back) and then make electrical and chemical connections with other cells. The key connections happen in the superficial (outermost) and deep (innermost) layers of the grey matter of the spinal cord (Fig 2).

The sensory neurons entering the spinal cord are called primary afferent fibres. Primary afferent fibres need to pass the pain signal on; this is usually achieved by transmitting the signal across a synapse (Fig 3), a fluid-filled space between one neuron and another. Transfer of the signal also occurs electrically to any other cell to which it comes close via what is called a gap junction. Synaptic signalling is performed by neurotransmitters – chemicals produced inside the nerve cell that interact with receptors on nearby cells once they have been released. The nearby cells with which these neurotransmitters can interact include glial cells, interneurons and secondary neurons.

The key signalling is between the primary afferent fibre and the secondary neuron across the synapse. The secondary neuron will conduct the signal to the brainstem and from there it will be relayed to the cortex. The other cells with which the primary afferent fibre communicates are involved in modulating the pain signal - which means they can amplify it or inhibit it.

An electrical signal arrives at the central terminal of the primary afferent fibre in the dorsal horn of the spinal cord. Its arrival at the central terminal changes the electrical charge in the cell membrane and leads to the release of neurotransmitters, which are stored in the nerve terminal. The neurotransmitters that are released are agonists for receptors on the secondary neuron; they include amino acids such as glutamate and neuropeptides such as substance P.

Once bound to the receptors on the secondary neuron, the agonists cause reactions inside that cell, and ion channels open so that positively charged ions (calcium) can move into the secondary neuron. As with the creation of an action potential in the periphery, this increase in positive charge reaches a threshold that is high enough to trigger an action potential to be initiated, thus moving the pain signal onwards to the brainstem and the brain.

The likelihood of the threshold being reached depends on the quantity of neurotransmitters released by the primary afferent fibre and the number of receptors available on the secondary neuron. High-frequency firing in the sensory nerve causes the release of neurotransmitters, and conditions in which pain is intense or long lasting cause an increase in the number of receptors on the secondary neuron. This means that, when the body experiences intense or prolonged pain, the central nervous system becomes sensitised and is therefore easier to excite. This is called central sensitisation and represents a lower threshold for activation. When pain signals stop coming into the dorsal horn, the system usually resets. However, in cases where this does not happen, patients can be left with chronic pain that is extremely difficult to manage.

**Implications for practice**

Some of the pain medications in common use are designed to reduce the release of neurotransmitters from the primary afferent fibre, and some increase the activation threshold of the secondary neuron. Both actions make it more difficult for a pain signal to be transmitted across the dorsal horn successfully, and so reduce the level of pain experienced. Drugs such as anticonvulsants (for example, gabapentin and pregabalin) reduce pain partly by reducing the release of neurotransmitters from the primary afferent fibre (O’Connor and Dworkin, 2009) as well as by having an

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**BOX 1. GLOSSARY**

- **Allodynia**: pain produced by an innocuous stimulus, for example normal temperature or light pressure
- **Axon**: a long, slender projection of a nerve that transmits pain signals away from the neuron’s cell body
- **Cerebral cortex**: the outer layer of the brain, composed of folded grey matter
- **Dermatome**: the area of skin supplied by a nerve from a single spinal root
- **Endorphins**: endogenous opioid neuropeptides produced by the central nervous system and pituitary gland as a response to stimuli such as pain, stress or fear
- **Gap junction**: a direct connection between two cells in which the cytoplasm in each is shared and so allows electrical and chemical signals to pass
- **Glial cells (sometimes called neuroglia or glia)**: non-neuronal cells with a number of functions, including forming myelin, and protecting and supporting neurons in the central and peripheral nervous systems
- **Glutamate**: the most common excitatory pain neurotransmitter
- **Interneurons**: neurons that create circuits to enable communication between sensory or motor neurons and the central nervous system
- **Locus coeruleus**: a nucleus in the brainstem involved with responses to stress or panic, the principal site for brain synthesis of noradrenaline
- **Myelin**: a fatty substance that forms a sheath around axons to allow electrical impulses quickly and efficiently
- **Rostral ventrolateral medulla**: part of the brain that controls autonomic activities
- **Serotonin**: a neurotransmitter thought to be responsible for maintaining mood balance
- **Substance P**: a protein neurotransmitter, fits into the NK1 receptor
- **Suprathreshold**: stimulus that exceeds the pain threshold
- **Ventral horn**: route from which (most) motor nerves take, the front portion of the cord
Morphine works by reducing the release of neurotransmitters from the primary afferent fibre and also by making it more difficult for the secondary neuron to reach its activation potential (Trafton et al, 2000). Wide dynamic range cells can:
- Differentiate between incoming pain and touch signals;
- Code their own outgoing signal to communicate to the brain the intensity of the pain signal.

Although this system is clever, it is also complex and when it goes “wrong” it can cause problems that are extremely difficult to cope with or manage. Some forms of chronic pain involve a sensation called allodynia, in which light touch is perceived as very painful. This is as a result of the input from A-beta fibres being misinterpreted.

When the body is experiencing pain as a result of a tissue injury, the pain can be cancelled out to some degree by rubbing the skin vigorously somewhere along the pathway of the sensory nerve involved. This is because it forces the wide dynamic range cell to process the mechanical sensation instead of the pain. Some settings on a transcutaneous electrical nerve stimulator (TENS) also work in this way.

### The role of the brain

When the secondary neuron is activated by neurotransmitters released from the primary afferent fibre, it generates an electrical signal, which it transmits along its axon to a number of areas in the brain.

- The brain undertakes several different functions with respect to pain:
  - It locates the pain and determines its intensity (through the somatosensory cortex);
  - The signals allow us to decide what the pain means and what to do about it (undertaken by the prefrontal cortex); they also allow us to remember other experiences of pain to help with this (performed by the somatosensory cortex);
  - The body responds by increasing the heart rate and blood pressure (through the amygdala) and preparing for fight or flight (using the hypothalamus);
  - There is also an emotional response, perhaps fear (controlled by the anterior cingulate cortex) and attention is drawn to the pain – it is difficult to ignore (determined by the posterior cingulate cortex);
  - The brain integrates and coordinates responses to all these experiences (using the thalamus and insula).
pain, also triggers an inhibitory response from the brain, in which dopamine, noradrenaline, endorphins and serotonin are released. The structures involved in this are the prefrontal cortex, the nucleus accumbens, the periaqueductal grey, the locus coeruleus and the rostral ventromedial medulla. Once released, the chemicals move to the spinal cord where they inhibit incoming pain signals from releasing neurotransmitters from the primary afferent fibre and prevent the secondary neuron from reaching its threshold to produce an action potential.

**Implications for practice**

There are many techniques that can reduce the pain we experience by boosting our innate pain-relieving systems. Endorphins, serotonin, noradrenaline and dopamine are very powerful pain suppressants and can be stimulated by exercise, sex, orgasm, laughter, chocolate, TENS, acupuncture and meditative relaxation techniques (Wood, 2008; Castel et al, 2007; Wang et al, 1992). The substances stimulated by these techniques travel down to the spinal cord and inhibit the transmission of pain signals.

**Summary**

Pain physiology is far more complicated than the summary of a relatively straightforward pathway presented in this article and Part 1 of this series. It is far easier to appreciate which therapies are likely to work for a particular type of pain if you can work out what the cause of the pain is and how it is being transmitted (Fig 4).

Acute pain is often (but not always) initiated by a threatening or harmful stimulus. The stimulus directly or indirectly acts on sensory nerve fibres, generating an action potential that is used to transmit the pain signal to the dorsal horn of the spinal cord. The signal crosses the spinal cord and eventually reaches the brain, which is when we become aware or conscious of the pain. Various properties of the signal – including the frequency of action potentials evoked by the stimulus – code the pain for intensity.

The structure of the brain and the nervous system enable us to determine the location of the painful stimulus, to interpret it and to respond to it. When the pain system works in this predictable and logical way, we are able to interrupt the signal or dampen it using both pharmacological and non-pharmacological techniques.

Part 3 of this series, to be published next week, discusses pain assessment.

**References**


