Chronic Pain Physiology

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Modern pain scientists understand pain to be a perceptual experience that is generated in response to perceived threat (for review, see Moseley and Butler 2017). In other words, the brain generates this experience that is pain when its 'best guess' is that bodily tissue is at risk of damage. This inference (that bodily tissue is under threat) relies on a plethora of information from both internal and external sources. These sources could include interoceptive information, knowledge of the context (based on prior first-hand experience or vicarious learning), visual information, somatosensory signalling, body position, information provided by a healthcare clinician, and many other sources.

In the optimal system, pain occurs *before* tissue damage and motivates a change in behaviour that *prevents* tissue damage. A typical example of this is the pain one might feel when climbing into a bath that is too hot – usually one feels pain and gets out again without sustaining tissue damage. That is helpful or *adaptive* pain, because it prevents tissue damage, thus promoting survival.

A functional definition of chronic pain is *pain that has outlived its usefulness*. Formal definitions used for research usually run along the lines of pain on most days (or every day) for three months or longer. The principle is that there is no longer tissue damage, but pain persists. In some cases, there is tissue damage but it is not sufficient to explain the pain. The pain is unhelpful because it does not protect tissue that needs protection. In many people, this chronic pain interferes with their engagement in life, which makes it *maladaptive*.

The brain as an integrator of information

It is helpful to think of the brain as responsible for integrating all the information available to it and generating our perceptual experiences to optimise our survival and engagement with life (Tabor, Thacker et al. 2017). The brain only has access to a certain amount of information, and much of this processing is not done at a conscious level. The prerogative to protect seems strong enough that we get 'stuck' with a bias towards perceiving threat more commonly than we get stuck with a bias towards perceiving safety (think of, e.g., generalised anxiety disorder, chronic pain, social phobias). This is what seems to happen in chronic pain – the brain gets 'stuck' perceiving threat, and so generates pain in response to information that otherwise wouldn't be sufficient to elicit pain.

In clinical reasoning, it can be helpful to think of all the pieces of information that the brain is receiving that could skew its conclusion towards an inference that bodily tissue is under threat or towards the inference that bodily tissue is safe.

Information sources

Historically, research and clinical treatment of pain have focused on trying to modify nociceptive signalling. But nociceptive signalling is only one source of information – and, critically, nociception is neither sufficient nor necessary for pain. There is also a wealth of other information that we have an opportunity to influence. So, while it is important to be aware of the changes along the neuraxis that alter afferent nociceptive signalling, it is equally important to be aware of the influences of other information sources.

Importantly, the terms 'pain receptors' and 'pain pathways' are inaccurate and interfere with the effort to understand and treat pain. Although some are struggling to change their use of this inaccurate language, it is important to use accurate terms and, when reading older papers, to rephrase the terms to one's self – by 'pain receptors' people usually mean nociceptors, and by 'path pathways' people usually mean nociceptive pathways. Similarly, using inaccurate language with patients is also unhelpful and interferes with the priority of helping people to understand and manage their own pain. 'Danger' or 'warning' receptors/messages are more helpful terms and more closely represent the current understanding of nociception and pain.

Changes along the neuraxis associated with persistent pain

Peripheral sensitisation

- Note that a neural fibre may be considered 'nociceptive' if it has a high response threshold – i.e. it only responds to fairly intense stimulation. Therefore, when we speak about nociception, we are speaking of signalling about *intense* stimulation that could be mechanical, thermal or chemical in nature.
- When tissue is damaged, various components of the inflammatory soup can influence afferent signalling:
    - From damaged cells: potassium, histamine, serotonin, bradykinin, ATP.
    - Synthesised at the site of tissue damage: prostaglandin, leukotriene
    - Released by nociceptors: Substance P
- Processes:
    - Reduced firing threshold of nociceptors
    - Increased responsiveness of nociceptors
    - Activation of 'silent' nociceptors
- Note the role of antidromic activity in C-fibres, driving neurogenic inflammation
- Responsible for primary hyperalgesia (increased pain to a stimulus that is normally painful; restricted to the site of tissue damage)
- Net result is that afferent signalling along nociceptive pathways is increased.
- Peripheral sensitisation is *normal and adaptive* when it is an acute-phase response to tissue damage.

Central sensitisation in the dorsal horn

- Nociceptive and non-nociceptive information arrives at the dorsal horn and most of the fibres carrying this information meet synapses at the same level or nearby levels.
- Synaptic transmission is influenced by:
    - Top-down control: facilitation and inhibition of synaptic transmission is regulated by descending modulatory influences from the brain (RVM and PAG are prime players here). In persistent pain, the 'balance' of downward modulation of dorsal horn synapses shifts, resulting in increased facilitation and/or decreased inhibition.
    - The amount of afferent signalling arriving at the synapses. Repeated stimulation has the effect of temporal summation (increased activity in second order neurons); stimulation across a wide area results in spatial summation. Repeated activation of C-fibres leads to the central release of excitatory amino acids, glutamate (excitatory; NMDA/AMPA) and peptides such as CGRP and substance P (NK-1). In addition, prolonged activation of NMDA receptors results in changes in gene expression that lead to reduces firing thresholds of second order neurons.
- Heterotopic facilitation is a kind of cross-modal facilitation effect via which increased activity in some classes of primary afferent neurons results in sensitisation of other classes of neurons and/or sensitisation of neurons that carry information from other (nearby) areas. This manifests as allodynia (pain to a stimulus that is normally non-painful) and/or secondary hyperalgesia (increased pain to a stimulus that is normally painful; in a region adjacent to the site of tissue damage – i.e. in *undamaged* tissue).
- The receptive fields of second order neurons are plastic and their precision is maintained by inhibitory signalling from higher centres. When this inhibitory signalling changes (see above – top-down control), the receptive fields of the second order neurons are no longer maintained as well, and they may widen so that these neurons receive input from primary afferent neurons they didn't previously synapse with. Many second order neurons don't have the capacity to respond to non-nociceptive neurons, so the change in receptive field will only affect their activity if they now synapse with more nociceptive neurons. In contrast, 'wide dynamic-range' secondary neurons are quite versatile and have the capacity to respond to nociceptive or non-nociceptive input. If these neurons' receptive fields shift they may start to respond to innocuous input from non-nociceptive sources. The result is that the brain receives input via a WDR pathway that is usually reserved for nociception, and so it may interpret that signalling as threatening – even if the signal was initially a response to a light touch or another innocuous event.

- Microglia (normally functioning as the macrophages of the CNS, detecting and removing pathogens, etc.) appear to play an important role in limiting inhibition at the dorsal horn – specifically, microglia seem to be activated by peripheral nerve injury and unmask previously inhibited synapses in the dorsal horn.
- Astrocytes form part of the tripartite synapse and influence synaptic function continually in the normal state (respond to neurotransmitters by releasing glial substances into the synapse). Astrocytes respond to synaptic transmission by releasing glutamate (increasing NMDA activation), prostaglandin and pro-inflammatory cytokines, consequently increasing the signalling strength of synapses. They also increase neuronal AMPA expression. They therefore play an important role in upregulation of synaptic signalling in the CNS. Interestingly, astrocytes signal between themselves via 'calcium waves'.

Features in the brain (see Moseley and Flor 2012)

- It is reasonable to consider that the processes underlying changes in neuronal signalling at the dorsal horn probably affect signalling in the brain similarly. In general, there is a loss of inhibition and more widespread activation.
- The loss of cortical inhibition affects brain-held body maps in the homunculus – sometimes called homuncular 'smudging' – resulting in poor localisation or mis-localisation of somatosensory input.
- Studies that image brain activation during experimental stimulation, comparing people with chronic pain and people without pain, have found a generally increased level of activation of areas linked to emotion in those with chronic pain when somatosensory stimulation is provided (e.g. Hashmi, Baliki et al. 2013).
- Beware of the idea of a 'pain matrix': it implies the existence of brain activation patterns that are specific to pain – a specificity that has not been verified. It seems more likely that the patterns of activation in the brain seen on painful stimulation actually reflect salience, or the relevance/importance of the stimulation: the activation diminishes with repetition of the painful stimulation, and similar activations are seen with non-painful but similarly salient stimulation.

Changes in other systems that may affect nociception and/or pain

Immune system:
- Upregulation of glial activity – microglia and astrocytes influence synapses (tripartite synapse)
- The balance in cytokines can influence nociception; a shift in cytokine balance towards a more pro-inflammatory profile is likely to upregulate nociceptive processes.

Endocrine system, stress-related changes:
- Cortisol (regulates healing) may be diminished ('burned out')
- Corticotropin releasing hormone levels may be increased and can promote nociception via several different routes – most notably by upregulating locus caeruleus activity, which results in increased arousal, and by increasing pro-inflammatory cytokine production — or decrease nociception by promoting opioid release.

Autonomic nervous system:
- The vagus nerve has attracted attention as a source of anti-nociceptive activity. There are complex interactions between the autonomic nervous system and the somatosensory system, and the effects of the extremes of arousal (either very high arousal e.g. escape, or very low arousal, e.g. somnolence) seem to be generally to reduce pain. This can be understood at an anti-nociceptive level or at a behavioural prioritisation level (i.e. in high arousal, the priority is to escape a BIG threat rather than to protect tissue from a smaller threat).

Emotions and cognitions:
- These are an important influence on a person's overall sense of threat or safety (Wiech and Tracey 2009). There may be a disconnect between consciously stated beliefs or thoughts and ideas that may not be subject to conscious consideration, and any of these have the potential to shift the inferential balance towards or away from pain. Even in the laboratory, manipulation of the implicit threat value of an experimental somatosensory stimulation can determine whether or not that stimulation elicits pain (e.g. Wiech, Lin et al. 2010).

References

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