16. Peripheral Mechanisms for Pain Initiation (11 Sep PM, SM)

- Pain is an unpleasant sensory or emotional experience associated with actual or potential tissue damage (or described in terms of such damage)
    - Pain is a sensation but also an emotional experience
    - It is a protective mechanism in which we learn about the environment and what we should or shouldn't touch/do because it can cause tissue damage and pain
    - Pain can also become a problem e.g. chronic pain, headaches, sprains and in diseases
        - There are very few medication that are effective at treating pain especially chronic pain
- Nociception is the sensory system process that monitors harmful or potentially harmful stimuli, including chemical, mechanical and thermal stimulation
    - Pain is a perception as a result of nociception detecting the sensation
    - For somatic tissues, nociceptive detection leads to the sensation of pain but for visceral systems, other complex sensations may manifest that are still dependent on nociceptive processing

<u>Pain perception</u>

- There are multiple dimensions to pain mapped by different networks:
    - Sensory discriminative: spatial, temporal and intensity encoding
        - Where is the pain coming from (spatial)
        - How long does it last (temporal)
        - How strong is the pain (intensity)
    - Motivational-affective: unpleasantness, anxiety, distress, fear and depression
        - How does it make you feel/how unpleasant is it?
        - Does it create anxiety, fear, change in mood or distress?
        - More difficult to understand but are still important components of pain
- Perception of pain is dependent upon
    - **Cellular damage or the potential for cellular damage**
        - Mechanical trauma and extreme temperatures can cause cellular damage initiating sensation
    - **Sensory receptor stimulation and input into CNS**
    - Spinal processing
    - Ascending and descending neural pathways
    - Subcortical and cortical sensory processing sites
- There is no designated 'pain nucleus' in the brain but instead the multiple dimensions of pain depend upon complex higher brain processing in networks distributed around the cortex

<u>Peripheral pain processes</u>

- Skins, muscles and joints are innervated by sensory neurons with different modalities with different types of nerve endings that contribute to different sensations e.g. touch, pressure, stretch
- Neurons with free nerve endings are activated by tissue damage or potentially damaging stimuli at high stimulation and are nociceptive
    - They have cell bodies in DRG and synapse into the dorsal horn and their noxious information is sent up to the brain for the conscious perception of pain
    - These neurons are not normally firing AP and are only activated in response to noxious stimuli e.g. noxious mechanical stimuli, water balance, and temperatures in the noxious range
    - Chemicals released by other cells can be noxious e.g. bradykinins, prostaglandins, NGF, 5HT, H+, ATP
        - An injured/dying cell releases a large amount of ATP into the ECF and the nociceptive terminals expressed, particularly p2x, signals the damage
    - Infiltration of inflammatory cells can cause the release of noxious factors
        - Cancers are associated with pain due to release of inflammatory molecules or the driving of inflammation itself
    - Chemical-based processes activate the nociceptors that drive the sensation of pain perceived in the cortex

Nociceptors

- Nociceptor axons are classified by their modality i.e. the sensory stimulus that activates them
    - Mechanical nociceptors: Aδ-fibres
        - Stimulated by cutting, crushing
        - Conducts fairly quickly at 5m/s
        - Lightly myelinated
    - Thermal nociceptors: Aδ- and C-fibres
        - Respond to noxious changes in temperature
        - Less conducting, <5m/s
    - Polymodal nociceptors: Aδ- and C-fibres
        - Responds to all kinds of damaging stimuli and chemicals
- These are high threshold receptors that are normally activated by stimuli that cause tissue damage or have the potential to produce damage
- There are two types of pain perception elicited by activating nociceptors:
    - Fast pain: a localised sensation of sharp, acute, pricking pain felt immediately after a noxious stimulus is delivered and usually disappears when the stimulus ceases
        - Activation of Aδ-mechanical fibres
    - Slow pain: a diffuse aching, throbbing or burning pain
        - Activation of polymodal C-fibres

Sensory Transduction

- Nociceptors transduce noxious stimuli into AP at the nerve terminal
    - Free nerve fibres are lined with VGNaC of different varieties and they need a stimulus to gate them
    - Transduction channels are non-selective cation channels and when activated, it results in a local change in the membrane potential
    - This stimuli causes influx of Na and if the resulting depolarisation is sufficient, the VGNaC gates open and initiates AP firing
- TRP channels (Transient Receptor Potential Channels) are thermo-, chemo- and in some cases mechanosensitive non-selective cation channels that helps conductance at nerve terminals
    - These channels are polymodal themselves as they are thermosensitive but also activated by different types of chemicals and activation allows Na to enter the cell and depolarise it and potentially fires AP
        - TRPV1 is activated by capsaicin and noxious heat >43C
        - TRPV2 is thermosensitive at a higher temperature
        - TRPV3 is activated by camphor and lower temperatures
        - TRPM8 is a cool-sensitive channel and is activated by menthol
    - Some stimuli that cause pain are GPCR ligands e.g. bradykinin and prostaglandin, and the coupling between GPCR on the membrane and TRP channels allow the GPCR ligand to cause pain through intracellular gating of TRPV1 e.g. phosphorylation and opening of channel

Action Potential propagation

- AP goes along the axon into the DRG and eventually the spinal cord, but sensory neurons have a T-junction at the cell body level where the processes splits to go to the periphery and the spinal cord
- This allows opportunity and modulation of AP propagation at the level of DRG and 3 possible outcomes:
    - Inhibition of AP formation as it gets to the DRG such that it doesn't reach spinal cord
    - Filtering of some AP to pass through and reach spinal cord
    - Generation of AP from the DRG itself independent of peripheral terminal activation
- Local environmental conditions contribute to DRG function at the time of stimulation
- In chronic pain, there is constant firing of AP towards the DRG that causes changes in the inflammatory profile of the DRG such that the inflammation in DRG can drive activation of the sensory neurons independent of peripheral stimulation

Peripheral Sensitisation

- A change in neuronal sensitivity that results in heightened pain being generated by normally weak painful (hyperalgesia) or non-painful/innocuous stimuli (allodynia)
    - Change occurs in the 'sensitivity' of nociceptors such that their threshold for activation is reduced so AP generation at the peripheral nerve terminal is easier
        - This change occurs in tissues that are inflamed
    - E.g. tissue inflammation following acute trauma e.g. sprained ankle, topical burn, grazed knee
        - Sunburn: induces pain and heightened sensitivity to thermal/warm stimuli
        - Sore throat: swallowing becomes painful
    - Peripheral sensitisation is important for hyperalgesia and less so for allodynia
- The sensory neurons themselves initiate early inflammatory processes through neurogenic inflammation
    - A sub-population of C-fibre nociceptors have collateral branches that communicates with blood vessels and immune cells (particularly mast cells) and when there is mechanical injury sensed by it, it activates the nerve terminal to activate nearby processes by releasing neuropeptides e.g. substance P and calcitonin gene-related peptide (CGRP)
    - E.g. when you acutely scratch yourself, you see redness and swelling
        - Swelling is due to oedema from vascular dilation as is mediated by CGRP acting on vessels
        - Redness is due to vascular dilation by substance P acting on mast cells and releasing histamine
- This then causes a cascade of inflammatory processes and causes the release of inflammatory soup (protons (H+), prostaglandins, bradykinin, serotonin, histamine, purines (e.g. ATP), nerve growth factor (NGF)
    - NGF is a neurotrophic factor that signals through tyrosine kinases and is very effective at sensitising nerve endings
    - Bradykinin activates TRP channels through indirect gating
- These substances activate receptors on the nerve terminals and depolarises RMP such that there is a reduction in threshold for activation e.g. sensitisation

Nociceptor sensitisation (acute)

- Local inflammation can cause phosphorylation of VGNaC such that they become more voltage sensitive and threshold for AP firing is lowered
    - In some cases, we don't need any generated potential as the neurons become ectopically active and even normally innocuous stimulus can generate AP
- From a wide variety of inflammatory mediators, their mode of action converges on phosphorylating channels that helps to conduct AP
    - Prostaglandins increases sensitivity of TRPV1 channels to capsaicin and heat
    - NGF phosphorylates Na channels to reduce the threshold for activating AP in DRG neurons
- A lot of the drugs that we take to treat pain e.g. aspirin and ibuprofen work by inhibiting COX-2 that metabolises arachidonic acid to form prostaglandin
    - The drugs are not analgesic, but restores normal activity levels of nerve terminals by inhibiting peripheral sensitisation

Maintenance of Peripheral Sensitisation

- Over time, peripheral sensitisation is maintained and becomes less dependent on peripheral inflammatory responses because when NGF binds to its tyrosine kinase receptor on nerve terminals, the complex is internalised and transported back to the cell body of the neuron where it can induce transcriptional changes
    - The neuron undergoes phenotypic changes driven by the retrograde neurotrophic signalling
- NGF changes transcriptional processes to upregulate TRP and Na channels and change the types of NT within the cells to sustain peripheral sensitisation even in the absence of peripheral inflammation
    - These changes contribute to maintaining the reduced threshold of nociceptors