Lecture 28 – Introduction to Pain

To **treat** pain, we need to understand how it's **processed** (Descartes)

Described the reflex arc BUT pain is **complex** – different types

An unpleasant **sensory** + **emotional** experience associated with **actual/potential** tissue damage

Pain experience requires **neural processing + conscious perception**

Different types of pain

- Nociceptive (protective)
- Inflammatory (amplification) – pain signal persists (normal physiological response)
- Neuropathic (system damage) – chronic pain
    - **Overstimulation** of pain system and pain signals becomes embedded within the nervous system

Pain depends on the **individual** – different coping mechanisms, thresholds
Not just injury – some are able to modulate pain experience with brain processes

When injury happens…

Control analgesia in early/acute stages of injury → reduce amount of post-traumatic stress

Regional anaesthesia

Pain Transmission

Cascade effect:

Inflammatory activation from injury → Receptor activation (**transduction**) → Neural **conduction** → Spinal cord + brain **modulation** → **Perception** of pain

It's **dynamic**

- Activation + **plasticity**
    - Relay
    - Amplification
    - Attenuation of pain signal
    - Nervous system may be re-shaped
    - Variable responses in individuals (genetic – currently studied)
- Motor/autonomic **reflexes** triggered
    - Reflex withdrawal
    - Hypothalamic/adrenal responses
- Peripheral **sensitisation** ensues
    - Enhanced state of excitability = **hyperalgesia**
    - Contributes to **protection**
    - **Leftward shift** of pain stimulus threshold
    - **Reduced mobility/function** until healing occurs

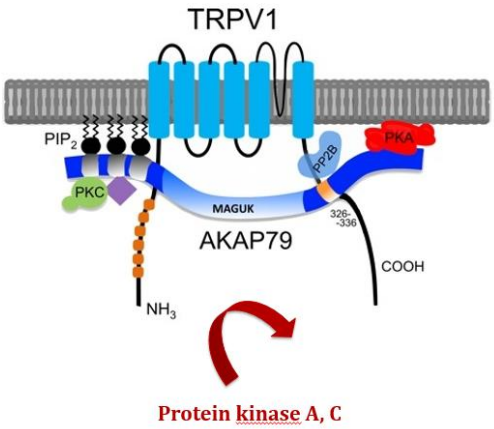
Nociceptors

Sherrington = developed idea of specific nerve endings for pain

Specific nociceptors for noxious stimuli (mechanical, thermal, chemical)

TRPV1 channels

- Transient receptor potential
- Implicated in sensitisation
- Responds to **acid** stimuli, **capsaicin**, **temperature** (heat)
- Look at domains under the receptor like **AKAP79**
    - Develop **drugs** that interact with these + modulate the receptor
- Activates **PKA** and **PKC**



Acute injury – tissue response

- Cell lysis
    - H+ (acid) + ATP released
    - Bind to nociceptors → activation
- Reflex axonal release
    - Substance P
    - CGRP
- Inflammatory response
    - Mast cell
    - Neutrophil
- Multiple mediators in damaged tissues
    - Serotonin
    - Histamine
    - Bradykinin
    - Prostaglandins (COX2 induction)
        - Some drugs target the induction
        - E.g. **aspirin**
    - Cytokines

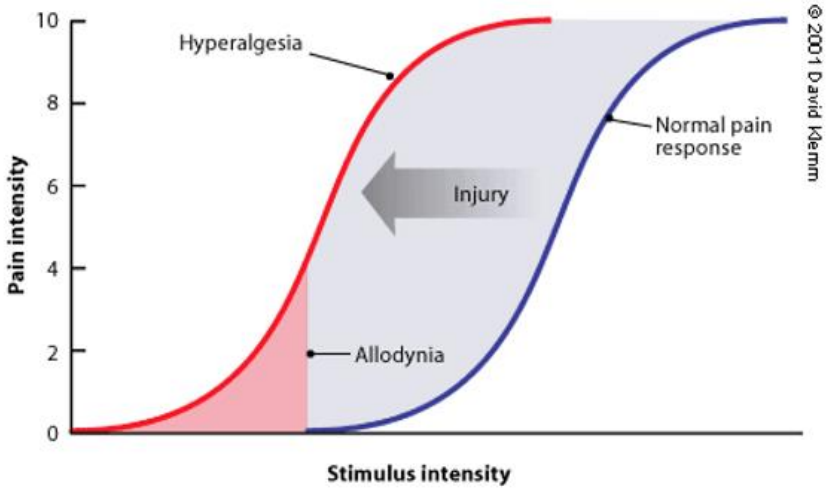
By understanding physiology occurs, can **develop drugs** against this

Peripheral sensitisation

Nervous system activated

- Nociceptors become sensitized
- Induce cellular transcription
- Protein synthesis
- Receptors + ion channels upregulated

Get hypersensitivity – **hyperalgesia** (may be protective) + **allodynia** (pathological)



Visceral pain

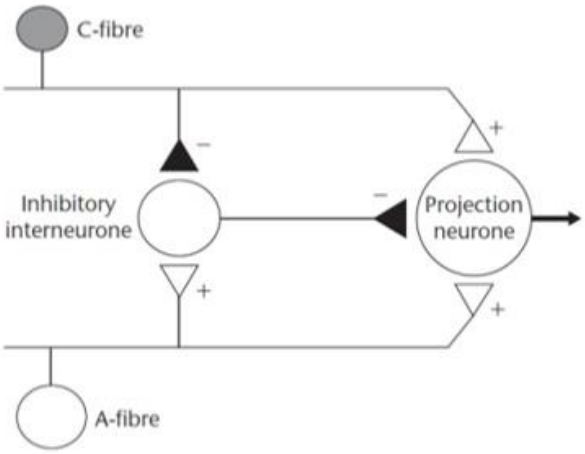
- Nociceptors produce **diffuse**, non-localised area of pain
    - Pain may be referred
- **Convergence hypothesis**
    - Somatic pathway crossover
    - Similar embryological origin
- E.g. **appendiceal** inflammation
    - Initial inflammation
    - Diffuse abdominal pain
    - As it becomes more inflamed it hits peritoneum → localised to right ileum fossa
- E.g. Cardiac ischemia
    - Adjacent referral to arm, neck, jaw

Transmission

- Nociceptors
    - **Aδ fibres** = fast, acute, localised, sharp mechanical/thermal pain
    - **C fibres** = slow aching, throbbing, burning pain
- Filtering mechanisms to attenuate nociceptor signal:

1. **<u>Gate control theory</u>**

There are **interneurons** within nerves going to spinal cord that could attenuate signal



- Interneurons can **inhibit** pain signal (**attenuates** it)
- Neurotransmitter is an endogenous opioid (**β-endorphin**)
  Throughout the NS, opioids play a key role

Opioid receptor – specific structure understood

- Use opioids like morphine to target **spinal cord** (where **most** of them are – in **substantia gelatinosa)**
- Act **pre**-synaptically to **decrease NTS release**
- Act **post**-synaptically to **hyperpolarise** dorsal root neurons
- Receptor **subtypes**: μ, δ, κ, nociceptin, orphanin FQ

Central potentiation

Integration in spinal cord dorsal horn via **relay + inhibitory** neurons

Primary afferents go to different laminae of dorsal horn – interactions between interneurons

Identified neurotransmitters with **immunofluorescence** →

Lots of inhibitory neurons (especially **GABA**ergic + **glycine**rgic neurons) – modulate pain transmission

Not only neurons – also involve **microglia + astrocytes**

Also can modulate