Are there parallel pathways for pain?

What is pain?

- Pain is both an aspect of interoception and a specific behavioural motivation
- Pain is also part of an interoceptive homeostatic system including itch, temperature and pain (that evolves in man and primates to form the basis of consciousness or the neural basis of the 'sense of self')
- Hypothesis requires labeled lines of sensory information (temperature, itch, pain etc) feeding into the affective (insula) cortex
- Unique relay from motor thalamic nuclei nucleus to the cingulate cortex (motor Limbic cortex)

Nociceptors as homeostatic afferents

A delta units

- Sharp pricking fast pain; precise localisation of insult/stimulus
- Reflex withdrawal

C-fibre units

- C fibres releasing SP / CGRP in periphery
- Vasoactive, promote inflammatory responses and healing

Nociceptors as homeostatic afferents

2 populations of unmyelinated nociceptors

- NF200/N52 (myelinated)
- CGRP (peptide)
- IB4 (non-peptide)

There are 4 major DRG sub-groups based on neurochemistry

- There are 4 major DRG sub-groups based on neurochemistry
- Carbonic anhydrase
- Parvalbumin
- Substance P, galanin, VIP, BDNF
- LA4, FRAP, P2X3
- SOM

3 nociceptive subpopulations have distinct neurochemical and anatomical features
CGRP & IB4 C-FIBRES BOTH PROJECT TO DIFFERENT PARTS OF LAMINA II

CGRP IN LAMINA II, IB4 IN LAMINA II.

CGRP AND IB4 C-FIBRE SUBTYPES TERMINATE IN SLIGHTLY DIFFERENT SUBREGIONS OF THE EPIDERMIS

CGRP - STRATUM SPINOSUM
IB4 - STRATUM GRANULOSUM

WHY ARE THERE 2 GROUPS OF NOCICEPTORS?

Peptidergic

Non-peptidergic

NOCICEPTORS EXPRESS RECEPTORS FOR DIFFERENT FAMILIES OF GROWTH FACTORS

trkC, RET GFRα1,α2 (low threshold mechanoreceptors)

trkB

trkA, RET GFRα3 (peptide-containing nociceptors)

NF200 40% CGRP 40% IB4 40%

ALL DRGS EXPRESS RECEPTORS FOR EITHER NEUROTROPHIN OR GDNF FAMILY MEMBERS,
EACH SUB-POPULATION OF NOCICEPTORS IS SUPPORTED BY DISTINCT GROWTH FACTORS

GFRα1,α2 (non peptide nociceptors)

WHAT ARE THE TARGETS OF NOCICEPTORS IN THE DORSAL HORN?

Peptidergic

Non-peptidergic

HYPOTHESIS 1: INDEPENDENT PROCESSING THEY CARRY SEPARATE INFORMATION TO DIFFERENT NEURONAL POPULATIONS

Peptidergic

Non-peptidergic

R1 HTM e.g. heat

R2 HTM e.g. cold

Peptidergic

Non-peptidergic

Identity?

Stalk
HYPOTHESIS 2: PARALLEL PROCESSING
THEY CARRY THE SAME INFORMATION TO DIFFERENT NEURONAL POPULATIONS

RECENT STUDIES INDICATE THAT IB4 AXONS TERMINATE JUST DORSAL TO THE PKCγ CELLS AND ACT ON A POPULATION OF INTERNEURONS WHICH INNERVATE LAMINA V PROJECTION NEURONS

Summary: 2 types of C fibres
- Peptide positive (SP,CGRP)
- IKB / NGF sensitive
- Terminate in IIo/I
- Terminate on projection neurons
- IB4 positive
- Ret/GDNF sensitive
- Terminate in IIi
- Terminate on interneurons

Ascending Pathways
- Motor Pathways to the cerebellum and midbrain that help regulate movement
- Pathways that inform the brain of ongoing sensory activity inside and impinging on the body.
- These are vital for homeostasis.

Spinoparabrachial - nociceptive
Spinothalamic-mixed (nociceptive & crude touch)
Spinoreticular-mixed
Spinocerebellar-non-nociceptive

Lamina I Projection Neurons
There are two major output pathways from the spinal cord that carry nociceptive information to the brain: in laminae I and V
What is so Special about lamina I neurons?

- Support LTP (as do lamina V neurons). Mediated by Glutamate (NMDA, AMPA mGluR) and Substance P.
- Nearly all projecting lamina I cells express NK1.
- In neuropathic pain, down-regulate KCC2 transporter resulting in increased excitability (Coull et al, 2004).

Summary: Lamina I v Lamina V

- Lateral thalamus innervated primarily by lamina I (STT) and relayed to SI
- Medial thalamus innervated by lamina I and relayed to ACC
- Lamina V projects to medial thalamus but then to motor cortex

What role do affective areas of cortex play in pain behavior?

- Anterior Cingulate Cortex (ACC) thought to be involved in ‘expressing’ motivational states
- ‘Limbic motor cortex’
- Always co-activated with insular cortex
- Only higher primates have a direct pain pathway from the ventral and medial thalamus to the limbic cortex

ACC seems to have at least 2 roles:
1. Analgesia produced by ACC lidocaine injections (whereas stimulation produces facilitation of nociceptive response)
2. Produces an ‘aversive teaching signal’ for associative learning

The functions of the lamina I and V ascending pathways can be revealed by Saporin-Substance P treatment

This effectively destroys the major spinal nociceptive input to insula and anterior cingulate cortex and leaves intact deeper pathways that influence ‘arousal’ and motor pathways.
**Lamina I Neurons can be specifically ablated**

- No effect on acute pain processing
- Later developing pain sensitivity is reduced or lost

- Lamina I controls spinal excitability and the 'plasticity' of the response to injury – especially inflammatory pain

**Results of Lamina I Lesion**

- Electrophysiologically, lamina V neurons have lost much of their 'plasticity'
- Taken together it seems that lamina I neurons have ‘privileged access to descending pathways via the forebrain and hind/midbrain centres

**Insular Cortex**

- Insular is thought to be limbic ‘sensory’ cortex (affect),
- Insula ‘lights up’ following all types of painful & emotionally significant events
- Has separate representations of taste, pain & temperature & Autonomic nervous system

Functions,
1. Important in establishing fear conditioning
2. Descending inhibition to spinal cord raising or lowering pain threshold

**Conclusions**

- Parallel pathways exist for pain
- Peptidergic p’way projects via lamina I to give information about intensity and location
- Non-peptidergic p’way projects via lamina II and V to affective cortex and basal ganglia for emotional processing and response
- Lamina I neurons project to areas of the brain and brain stem which seem to grant privileged access to descending control pathways that set the level of spinal excitability.
- Lamina I informs discriminative, cognitive and affective ‘centres’ of the brain.
- Lamina V neurons seem more concerned with arousal and motor outcomes of nociceptive stimulation