Lecture 4 – Glia in the Normal and Diseased CNS

Types of Glial

- Glial are not just brain-filler but have many important roles in supporting neurons
    - Amongst the 4 types of cells that make up a synapse (pre- and post-synaptic neurons, astrocytes and microglia) the supporting cells can modify the way that communication occurs
- Macroglia (astrocytes, oligodendrocytes, schwann cells, ependymal cells and Muller cells) have passive and active functions → **originate from same embryonic origin as neurons DIFFERENT TO MICROGLIA**
    - Passive functions
        - Deactivation of NTs by reuptake or recycling – e.g. glutamate and GABA transporters expressed where inhibiting these transporters causes them to not work and therefore more depolarisation
        - Siphon potassium (to remove high K^+ outside neuron to stop depolarisation through inwardly rectifying potassium channels) to safer areas (vasculature, surrounding tissue)
        - Provide energy metabolites to neurons (envelope blood vessels and take glucose from blood to neurons) as well as sensing their needs → therefore must rely on non-neuronal methods of controlling blood vessels
        - Maintenance of BBB
    - Active functions
        - Control neural function as glia are excitable (but don't fire APs) where they show modulations in intracellular calcium (calcium waves) that are initiated by NTs (ATP, glutamate from glial cells), trauma, spontaneous and inflammatory mediators
        - Release gliotransmitters as glia contain a small number of synaptic vesicles
        - Modulate the vasculature via calcium waves which cause release of NTs from glial cells – affecting/inhibiting neighbouring neurons. Can also interact with blood vessels (such as astrocytes which completely envelope so form the BBB) and calcium wave can cause vasoconstriction or vasodilation within astrocyte.
- Microglia → completely different cells compared to macroglia → **originate from IMMUNE precursors (bone m.)**
    - Immune cells (resident in the brain because BBB stops immune cells so need existing protection) → CNS is immune privileged → microglia are 5-20% of cells in mouse retina/brain → change rapidly in response to inflammation or injury resembling macrophages (phagocytic action) → also **constantly survey environment important for development and maintenance**
    - Shape synapses → high amount of connections formed at the start of development → pruning dendrites involves microglia (dendritic refinement) seen in visual system and other systems **also** cone photoreceptors modified by microglia (release specific transmitters in maturation process, surveying to protect against infections)
    - Modulate neural function

Glial in Disease

- Disease = loss of any glial function
    - Loss of NT uptake = excessive neuron stimulation = ultimately death
        - Large area affected in stroke which dies (no blood supply) → but also area surrounding affected area (penumbra) where blood vessels cannot support neuron activity properly (this area is where neurons fail to reuptake neurotransmitters leading to chronic overstimulation and further neurone death)
    - Loss of K^+ uptake and/or aquaporin expression = Δwater balance = oedema (water following K^+) and problems in vision (K^+ important in vision)
- Gliosis
    - Hypertrophy + hyperplasia of glial cells + ↑intermediate filaments in most CNS diseases
        - Intermediate filaments support their larger structure so responds to diseased area of brain to try and isolate/enclose it to protect rest of brain
    - Result in functional changes = ΔK^+ channel expression affecting NT uptake, energy metabolism and water balance
- Loss of microglia
    - Exacerbates neurodegeneration + faster acceleration of disease (ALS, Alzheimer's disease, retinal degen.)
    - Synapses are coated with **complement** (which triggers microglia to destroy failing neurons) where **Aβ in Alzheimer's disease stimulates removal of complement via microglia (engulfment of synapses)**

Lecture 8 – Vision 2

Vision pathway:

- Retina → optic nerve → optic chiasm → LGN → optic radiations → visual cortex|

Ganglion cells:

- M (motion) & P (colour, visual acuity) type ganglion cells bring visual information to our attention with 95% of cells targeting the LGN (4 other non-visual targets)
- Melanopsin ganglion cells: subconscious vision (superior colliculus)
    - "Blind sight"
        - Patients with only half a brain (hemisphere) had normal ipsilateral motor function but also pathways from the superior colliculus to area MT is intact → resulting in brain being able to see and react by avoiding obstacles but has no way of knowing consciously anything is there

Non-visual functions of GCs

- Intrinsically photosensitive ganglion cells (iPGCs)
    - Can directly respond to light not reliant on Ph via visual pigment (melanopsin – invertebrates have similar form) causing DEPOLARISATION (not hyperpolarisation as with Ph)
    - Blind people melatonin levels are suppressed by light and if they still have ganglion cells their activity and sleep is not disturbed (maintain circadian rhythm if ganglion cells intact)
- Target:
    - Suprachiasmatic nucleus (circadian rhythm)
        - Biological clock develops naturally from birth to about 15-20 weeks (mess to order)
        - Maintain circadian rhythm if ganglion cells intact → blind people
        - Located in nucleus of hypothalamus
        - Outputs: Pineal gland (driver for circadian rhythm) and brainstem (autonomics)
    - Pretectal nucleus (midbrain) - pupil responses
        - If one pupil constricts, this ensure other pupil follows → delayed and less apparent in blind studies = dependent on being able to detect light and a functioning iris muscles
            - Dilator pupillae → contracts to open pupil
            - Sphincter pupillae → contracts to close radius of ring = aperture smaller
        - Coordinated by the midbrain where light sensation onto retina results in motor innervation
            - GC target pretectal nucleus which projects to R and L Edingerwestgal nucleus in the midbrain where fibres here pass information to the cilary ganglion/iris
            - GC nerves do not synapse to LGN but to pretectal nucleus that has a neuron that innerves motor pathway for both sides
            - Pathway: iPGCs → PN → EWN → CG (ciliary ganglia) = tells pupil how much light there is in the environment so they respond by changing the aperture
    - Ventral posterior thalamic nuclei/VPN (photophobia/pain is worse when the lights are on)
        - Gets input from other sensory systems (pain) where if patients lack an Optic Nerve and with migraines → pain is not worsened in those with no visual aura
        - VPN neurons can be light sensitive and can exacerbate pain fibres in the same region
    - Superior colliculus (eye movements)
        - Integrates visual and motor information
        - Inputs: retina GC, cortex (parietal, frontal eye fields), basal ganglia
        - Outputs: Area MT via pulvinar (thalamus), brainstem
            - "blindsight" above where vision adapts by forming an alternate pathway following destruction of V1

Lecture 15 – Pain 1 – Peripheral Mechanisms for Pain Initiation

PAIN

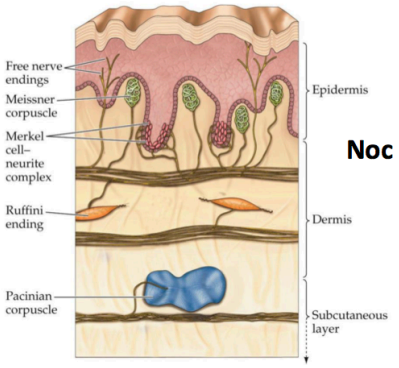
- Unpleasant **sensory or emotional experience** associated with **actual or potential** tissue damage
  - **PERCEPTION resultant FROM NOCICEPTION**
- Protective mechanism and how we learn about the environment
  - Awareness of damage occurring or about to occur
    - For disease, disorders etc. pain we don't want particularly chronic pain = problematic
  - **Multiple dimensions to pain**
    - **SENSORY-DISCRIMINATIVE** → spatial (where), temporal (how long), intensity
    - **MOTIVATIONAL-AFFECTIVE** → unpleasantness, anxiety, distress, fear and depression – how they make you feel
- **Compared to NOCICEPTION**
  - The **sensory system PROCESS** that monitors harmful or potentially harmful stimuli, including chemical, mechanical and thermal stimulation
  - For **somatic tissues** → the nociceptive system leads to sensation of pain
  - For **visceral systems** → other complex sensations may manifest

Perception of PAIN

1. *Initiator is **cellular damage***
2. *Then, sensory receptors are stimulated and connect (input) to CNS*
3. Spinal processing (not this lecture)
4. Ascending and descending neural pathways (not this lecture)
5. Subcortical and cortical sensory processing sites (not this lecture)

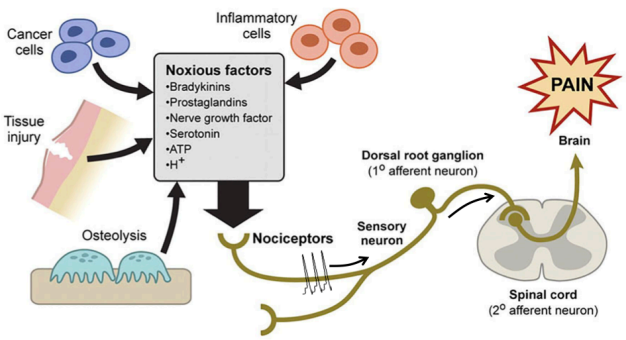
STRUCTURE: Primary Afferents

- Nociceptors are UNSPECIALISED **free nerve endings** that are **sensory nerve terminals** that project out in periphery and another into the spinal cord
- **Important for detection of tissue damage or potential damaging stimuli**
- Coexist with lots of different types of endings - touch etc.
- Free nerve endings are important for pain = noxious stimuli
- Unlike touch receptors that are usually tonically activated - **nociceptors are inactive at rest**, **silent because no noxious stimulation**



FUNCTION: Primary Afferents/Nociceptors

- Nociceptors usually quiescent, but respond to large variety of stimulus modalities (polymodal - chemicals, mechanical, temperature, osmolarity etc.)
  - Release of inflammatory factors - **damage signalling molecules detected → activate nociceptors**
- **Classification by MODALITY**
  - **MECHANICAL** nociceptors → **Aδ-fibres (LIGHTLY MYELINATED)** → stimulated by **CUTTING, CRUSHING**
  - **THERMAL** nociceptors → **Aδ- (MYELINATED) AND C-fibres (UNMYELINATED)** → respond to **noxious CHANGES in temperature**
  - **POLYMODAL** nociceptors → **Aδ- AND C-fibres** → response to *all* kinds of damaging stimuli, chemicals
- **ALL ARE:**
  - **High threshold** receptors
  - **Normally activated** by stimuli that **produce tissue damage** or **have potential to do damage**
- **RESULT IN 2 TYPES OF PAIN PERCEPTION** THAT IS BECAUSE OF THE WHOLE CIRCUIT NOT JUST THE NEURONS
  - **FAST PAIN** – localised, sharp/acute/pricking pain felt *immediately* after noxious stimuli applied, typically **disappears when stimulus ceases → THROUGH ACTIVATION of Aδ-fibres (FASTER axons)**
  - **SLOW PAIN** – diffuse, aching, throbbing or burning pain → **THROUGH ACTIVATION of C-fbires (SLOWER axons)**



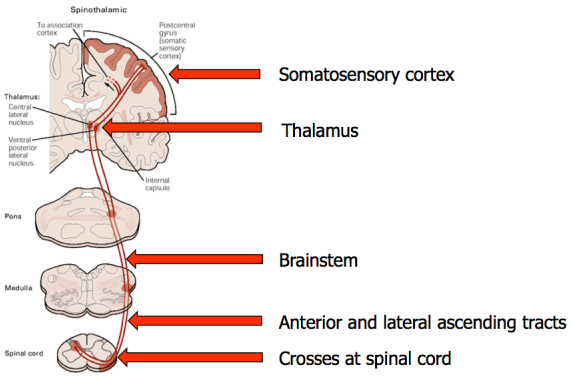
Lecture 17 – Pain 3 – Ascending and Descending Pain Pathways

Perception of PAIN

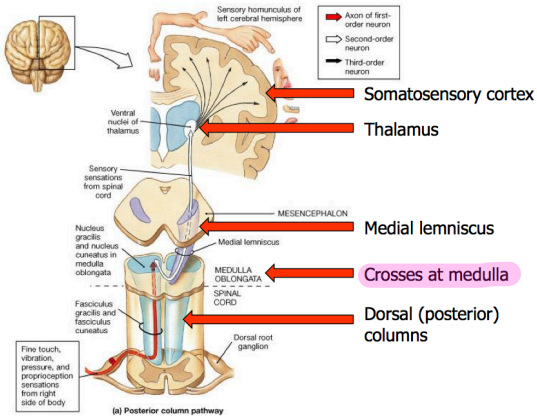
1. Initiator is cellular damage (last lecture)
2. Then, sensory receptors are stimulated and connect (input) to CNS (last lecture)
3. Spinal processing (last lecture)
4. ***Ascending and descending neural pathways***
5. Subcortical and cortical sensory processing sites (not this lecture)

Dorsal Horn of the Spinal Cord

- Recall that peripheral nociceptors terminate in the dorsal horn of the spinal cord connecting at different laminae to 2nd-order neurons that a fed into the brain via white matter tracts that vary in size at different spinal cord levels for processing
- Neurons responsible for **PAIN, TEMPERATURE, CRUDE TOUCH** are **SPINOTHALAMIC/SPINORETICULAR/SPINOMESENCEPHALIC NEURONES in the ANTEROLATERAL SYSTEM**
    - Neurons enter dorsal horn and ascend **contralaterally** crossing at the medulla oblongata travelling up through the medial lemniscus to the thalamus and the somatosensory cortex
    - Not all spinothalamic neurones have projections to thalamus, some terminate only in thalamus or only elsewhere (next slide) → **3 TERMINATIONS**



        - **(1) THALAMUS**
            - Spinothalamic neurons are about knowing about the **sensation/feeling pain** in location and intensity → for all spinal dermatomes (face is via trigeminal nerve)
                - **(A) Lateral NEOSPINOTHALAMIC tract → FAST A-fibre PAIN**
        - **(2) RETICULAR FORMATION IN MEDULLA** then another neuron connects to the thalamus and sensory cortex
            - Coordination with **autonomic function** that accompanies pain (affective/emotional possibly as well)
                - **(B) Anterior PALEOSPINOTHALAMIC tract → Spinoreticular tract → SLOW C-fibre PAIN**
        - **(3) MIDBRAIN**
            - Turns our **attention** to noxious stimuli orienting eyes and ears to stimulus, contributes to controlling descending modulation via PAG
                - **(C) Anterior PALEOSPINOTHALAMIC tract → Spinomesencephalic tract → SLOW C-fibre PAIN**
- Neurons responsible for **TOUCH, VIBRATION and PROPRIOCEPTION** generally are **part of the dorsal column lemniscus system**
    - Neurons enter dorsal horn and ascend **ipsilaterally** crossing at the medulla oblongata travelling up through the medial lemniscus to the thalamus and the somatosensory cortex



Nociceptive processing and the thalamus

- Neurons that synapse at the thalamus → specifically the **VPL** (ventral posterolateral nucleus) **gets information and passes it to primary sensory cortex**
    - There is topographical organisation within thalamic processing nuclei **AND** primary sensory cortex
        - PSC: Medial = foot, leg whereas tongue etc. is more lateral