The endocannabinoid system in chronic pain

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Pain: an evolutionary overview

- Why does pain exist?
- What happens when pain pathways fail?

- Why are we able to modulate pain?

Chronic pain

- When normal pain pathways misfire
- Affects half the UK adult population
- Review of current medications – 'none appear capable of eliminating pain or significantly improving functional outcomes for all treated'
- The endocannabinoid (EC) system may be very important in future treatment strategies

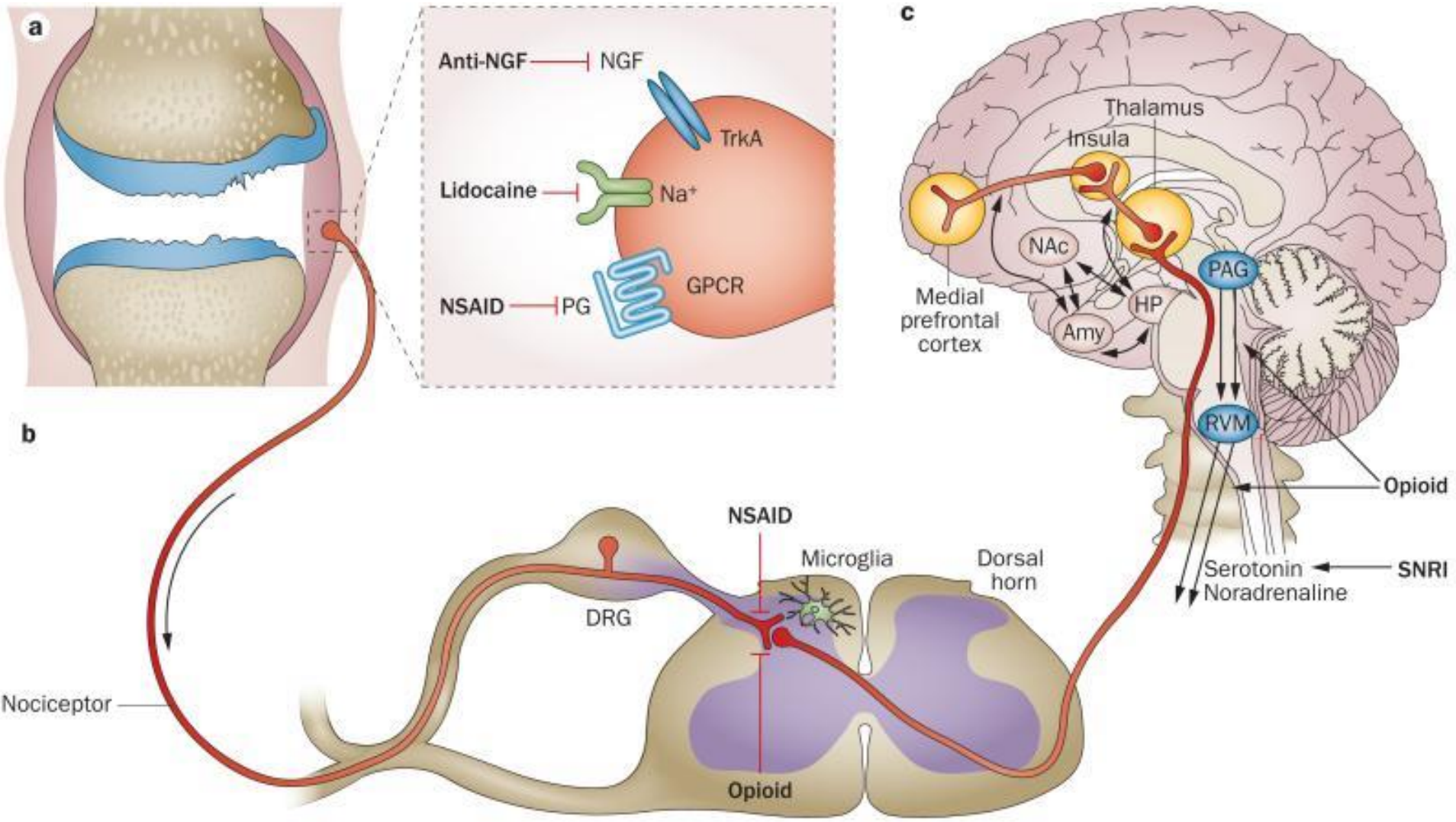
Overview of the EC system

- Group of receptors, neurotransmitters and enzymes involved in a variety of physiological functions
- **Receptors**: CB1 (central) and CB2 (peripheral),
- **Neurotransmitters**: 2-AG and anandamide
- **Enzymes**: fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL)
- **Animal models**
  1. SR141716R (an EC antagonist) > hyperalgesia
  2. FAAH knockout mice > hypoalgesia

History of the EC system

- 2737BC: Use of cannabis as pain relief can be traced back to China
- 1928: Cannabis made illegal in the UK
- 1964: THC isolated
- 1990: CB1 receptor cloned
- 1992: Anandamide identified
- 1993: CB2 receptor cloned
- 1995: 2-AG identified
- 2010: First cannabinoid medication licensed

Pain pathways



CNS: PAG, opioids and CB1

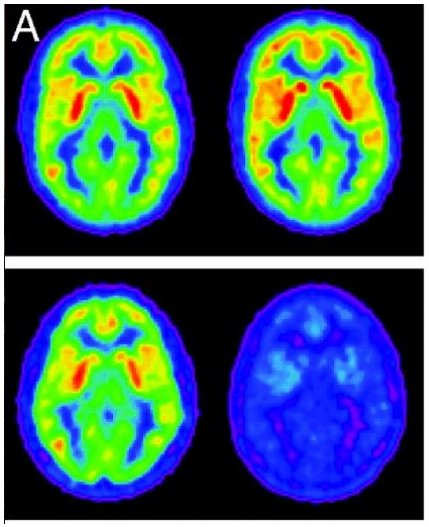
- **1971**: Mayer *et al* electrically stimulated the PAG area in rats resulting in analgesia
- Ventral PAG stimulation – blocked by naloxone (opioid-dependent analgesia)
- Dorsal/lateral PAG stimulation – not blocked by naloxone (opioid-independent analgesia)
- **1999**: Walker *et al* showed that dorsal/lateral analgesia blocked by endocannabinoid antagonist
- Conclusion: CB1involved in descending pain modulation

PNS: Nociception and CB2

- Commonly used animal model for nociception – injection of formalin into hindpaws of rats
- Administration of CB2 agonist increased the threshold for nociceptive fibres to be triggered
- This caused a decreased experience of pain

Affective aspect of pain

- Nociceptive vs affective aspect of pain
- THC has well known psychoactive properties – do endocannabinoids have these as well?
- High density of CB1 receptors in frontal-limbic system of the brain seen in immunohistochemistry and PET scanning
- Oral administration of THC in pain



Cannabinoids in clinical practice?

- Recent meta-analysis concluded 'moderate evidence' to support their use for the treatment of chronic pain
- Psychedelic intoxication of some cannabinoids (THC) restricts their use, but others (e.g. CBD) may be much safer
- Novel approaches – e.g. FAAH inhibitors?
- 2010 – first cannabinoid to be medically licensed in the UK (second line treatment of spasticity in MS)

The future of cannabinoids?

- Aim is to produce orally administered, highly bioavailable and non-psychoactive forms of cannabinoids
- Social disapproval may delay this
- Current research is shaping treatments to potentially provide millions of people worldwide with a new, effective and safe form of pain relief

References

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