Opioids in patients with chronic pain

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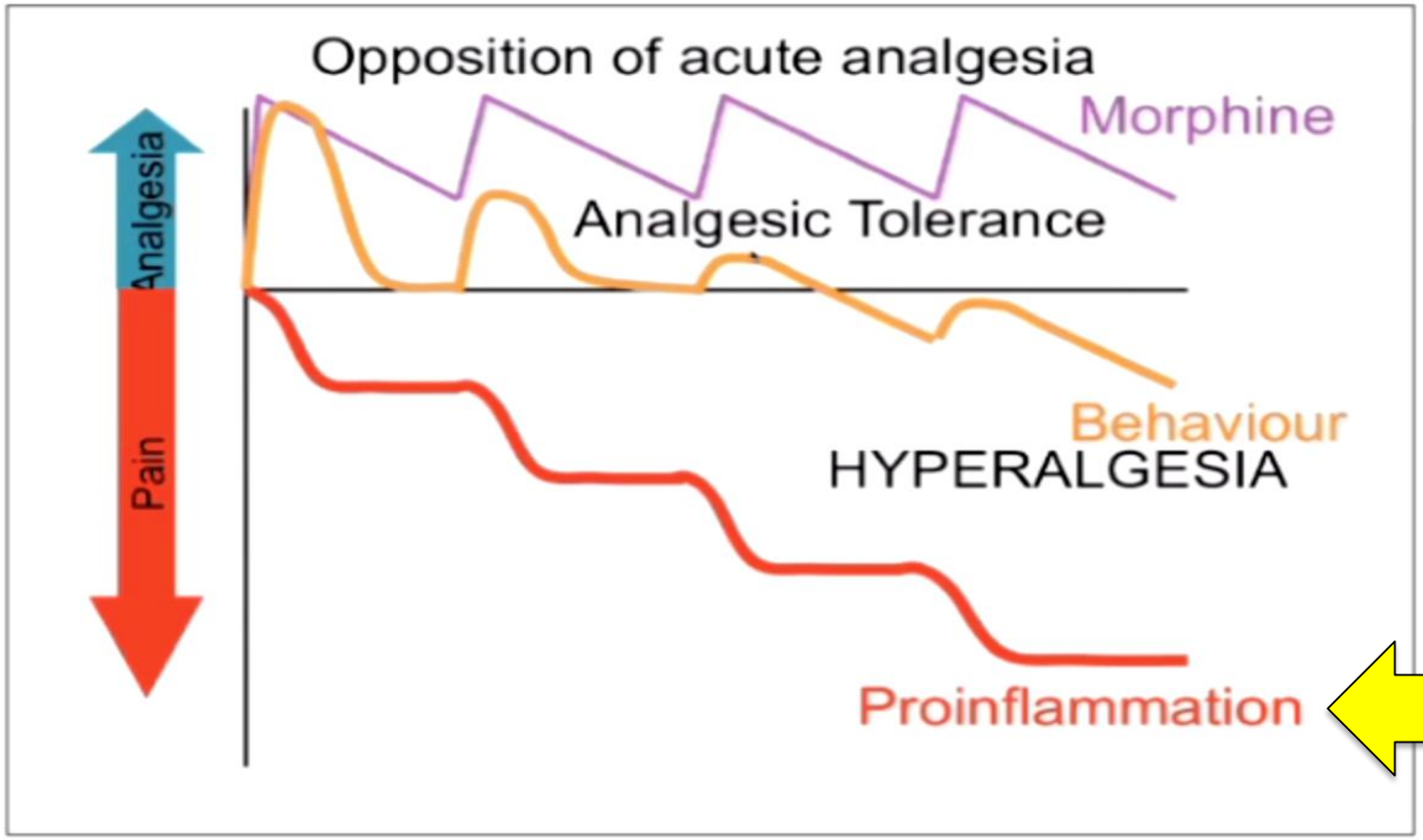
UNDER THE STEWARDSHIP OF MARY AIKENHEAD MINISTRIES

Neuronal cells

Opioid receptors – mu, kappa, delta

Opioids – endogenous, exogenous



Hutchinson et al 2009

Role of non-neuronal cells

Non-neuronal cells

- mainly immune and glial cells
- release neuro-active mediators which are involved in the pathogenesis **and** resolution of chronic pain (*Hore and Denk, 2019*).

Most researched non-neuronal cells are:

- **central nervous system**: microglia, astrocytes
- **peripheral nervous system**: glial cells, macrophages, T cells

Nieto *et al* **Frontiers in Pharmacology** Sept 2020 Editorial: Mechanisms and New Targets for the Treatment of Chronic Pain

Cross-talk

Cross-talk between: neurons, immune and glial cells

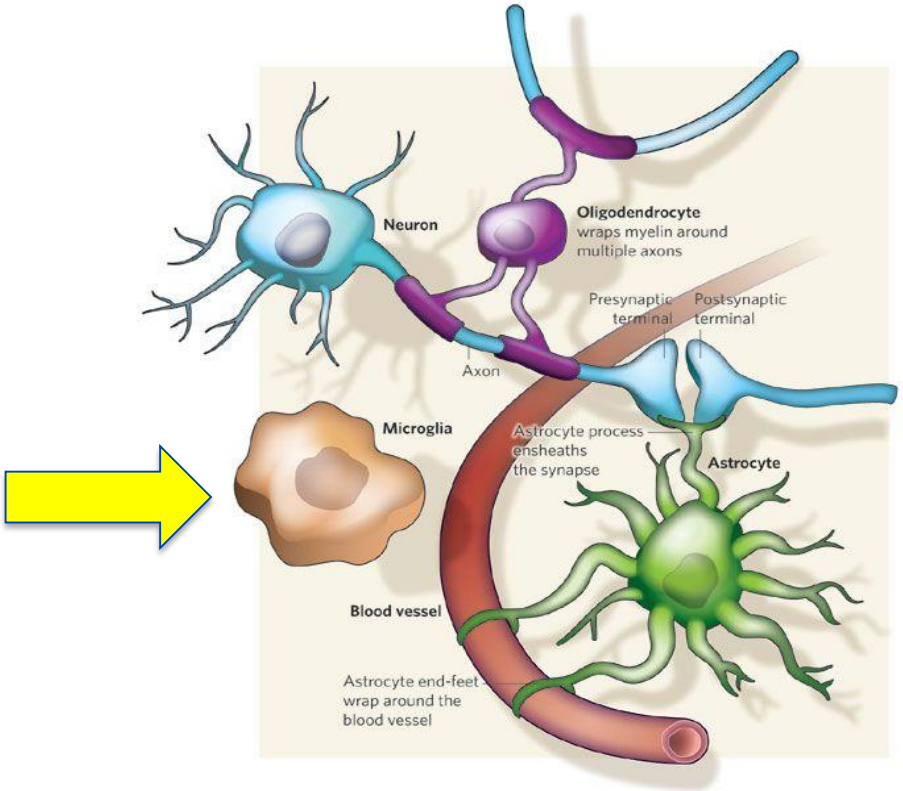
- **contribute** to chronic pain states

Nociceptive **neurons release** substances

- active on glial & immune cells
- contribute to **neuro-inflammatory process** in chronic pain

Ji et al., 2016 https://science.sciencemag.org/content/354/6312/572.full

Glial model



Nature 2009; 457: 675-677

Microglia 1

10% of cells in CNS

Microglia survey local environment *(Kettenmann et al., 2011).*

When danger signals identified, *eg bacteria, viruses etc*, rapidly undergo:

- morphological change reverting to amoeboid appearance *(Kettenmann et al 2011)*
- change their gene expression and function

Kettenmann H, Hanisch UK, Noda M, Verkhratsky A. Physiology of microglia. Physiological reviews. 2011 Apr;91(2):461-553.

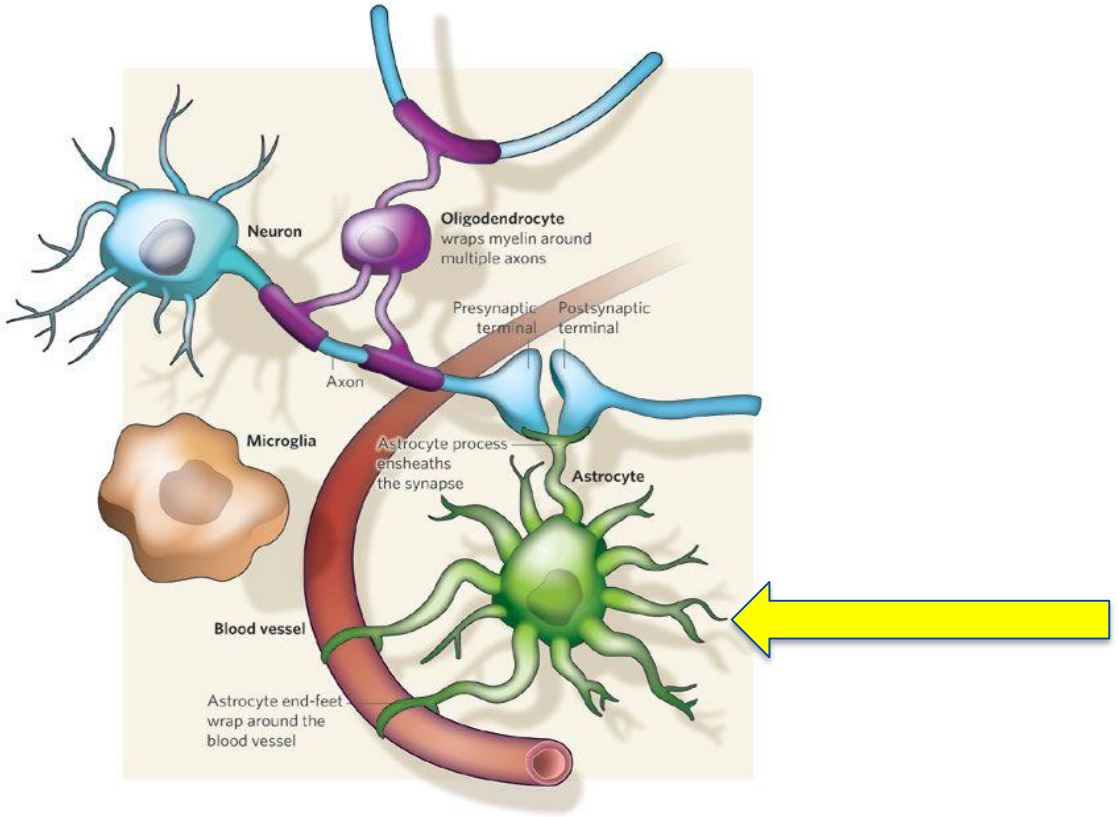
Microglia 2

Functional plasticity of microglia:

"Microglia activation" is a highly dynamic process with **quite distinct characteristics in different pathological conditions**

(Gomez-Nicola and Perry, 2015; Ransohoff, 2016; Salter and Stevens, 2017).

Glial model



Nature 2009; 457: 675-677

Astrocytes 1

Most abundant glial cells in CNS, ~30 % of glial population (*Ponath et al., 2018)*

Outnumber neurons over 5-fold (*Sofroniew and Vinters, 2010).*

Initially thought to just provide ‘scaffold” for neurons (Sofroniew and Vinters, 2010)

Now know they have important functions in brain:

- regulating blood flow
- energy supply & metabolism
- maintaining homeostasis & pH
- maintaining blood brain barrier
- re- uptake of neurotransmitters *(Sofroniew and Vinters, 2010)*

Astrocytes 2

Like microglia, astrocytes are also immune-competent cells capable of **inducing neuroinflammation** in CNS *(Tian et al., 2012).*

When **stimulated** by chemical or electrical signals from **damage or danger:**

- undergo structural & functional change known as **reactive astrogliosis**
- cytokines, chemokines & neurotrophic factors secreted *(Sofroniew and Vinters, 2010; Tian et al., 2012*

These released factors may promote the leakage of blood brain barrier and recruit immune cells to the impaired areas, mediating the elimination of injurious or diseased insults.

Astrocytes 3

Reactive astrocytes have enhanced functions:

- scavenging excessive glutamate, free radicals & ammonia
- protecting CNS cells & tissues from cytotoxic materials
  (Sofroniew and Vinters, 2010)

Sometimes, when CNS suffers severe damage or infection:

- reactive astrocytes induce the formation of **glial scars**
- glial scars limit spread of inflammatory cells or infectious agents into healthy CNS areas *(Sofroniew and Vinters, 2010)*

Opioids and glial activation

Opioids:

- directly stimulate glial cells & lead to their functional conversion
- promote glial release of various cytokines and chemokines including IFN-γ, IL1-β, IL-6, IL-10, CCL4 and CCL17

(García-Pérez et al., 2016, 2014; Hutchinson et al., 2009;; Suder et al., 2009; Zhang et al., 2017; Schwarz et al, 2011)

- TLR4 on glial cells are activated by opioids *Hutchison 2010, 2012*
- similar to activation by foreign pathogens:
  - *Critical to innate immmunity*

Opioids and glial cells

Details that at present remain and require further research:

- ✧ Opioid receptors on glial cells?
- ❖ Opioid activation of glial cells?
- ❖ Opioids immuno-suppressive?
  … or immuno-stimulatory?

Zhang *et al* 2020 Brain Research Bulletin 155 (2020) 102-122

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Questions and discussion