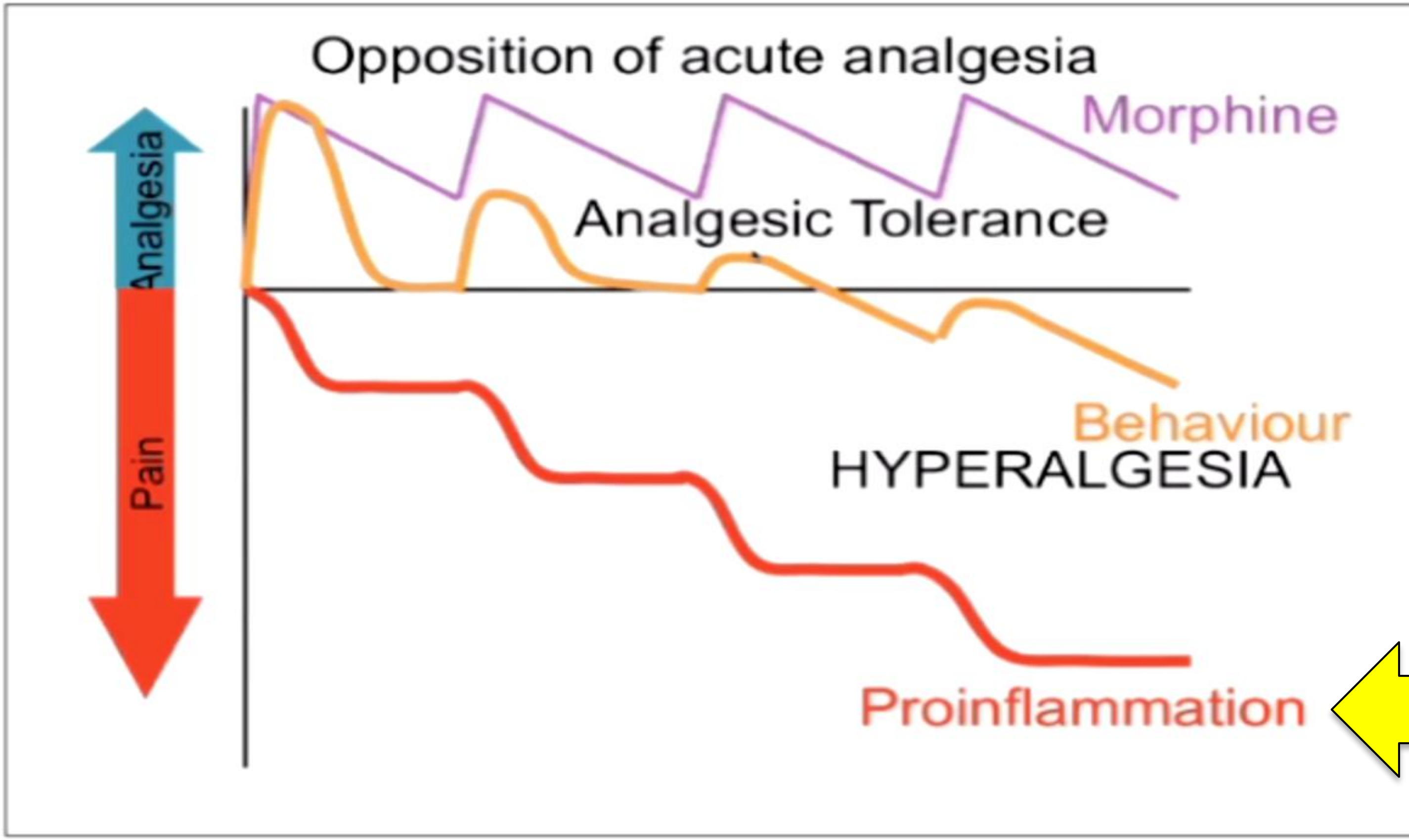
Hyperalgesia, glial cells and naltrexone

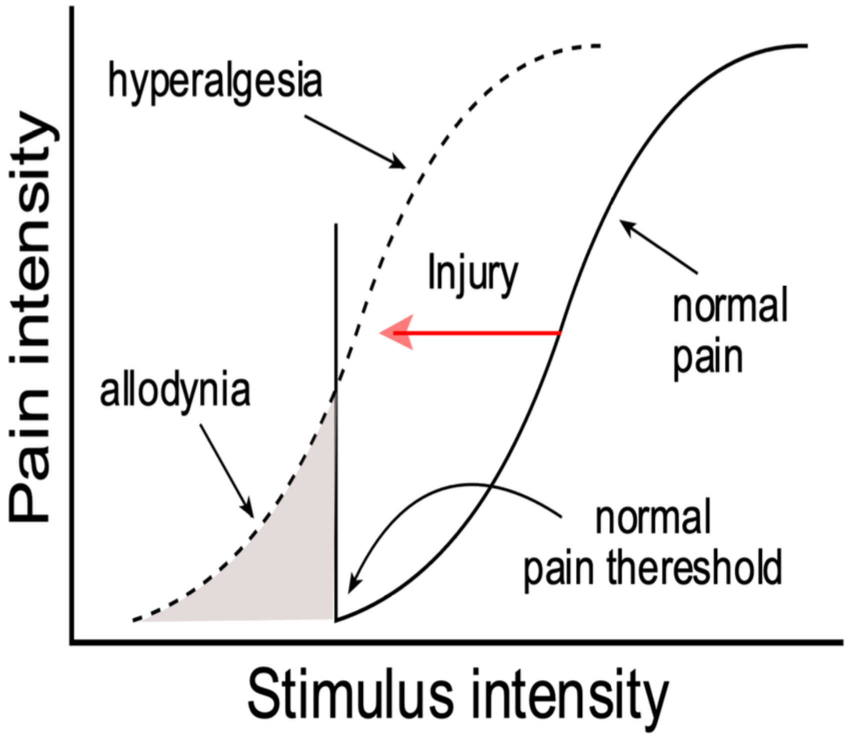
Victorian Opioid Management ECHO
Department of Addiction Medicine
St Vincent's Hospital Melbourne January 2025

UNDER THE STEWARDSHIP OF MARY AIKENHEAD MINISTRIES



Hutchinson et al 2009

Allodynia vs Hyperalgesia



Ref: A/Prof Malcolm Hogg

Role of non-neuronal cells

Non-neuronal cells
- mainly immune and glial cells
- play active roles in the pathogenesis **and** resolution of chronic pain by releasing neuro-active mediators that modulate pain (*Hore and Denk, 2019*)

Among these non-neuronal cells, most studied are:
- **central nervous system**: microglia and 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*
Donnelly ***Neurotherapeutics*** *(2020) 17: 846-860*

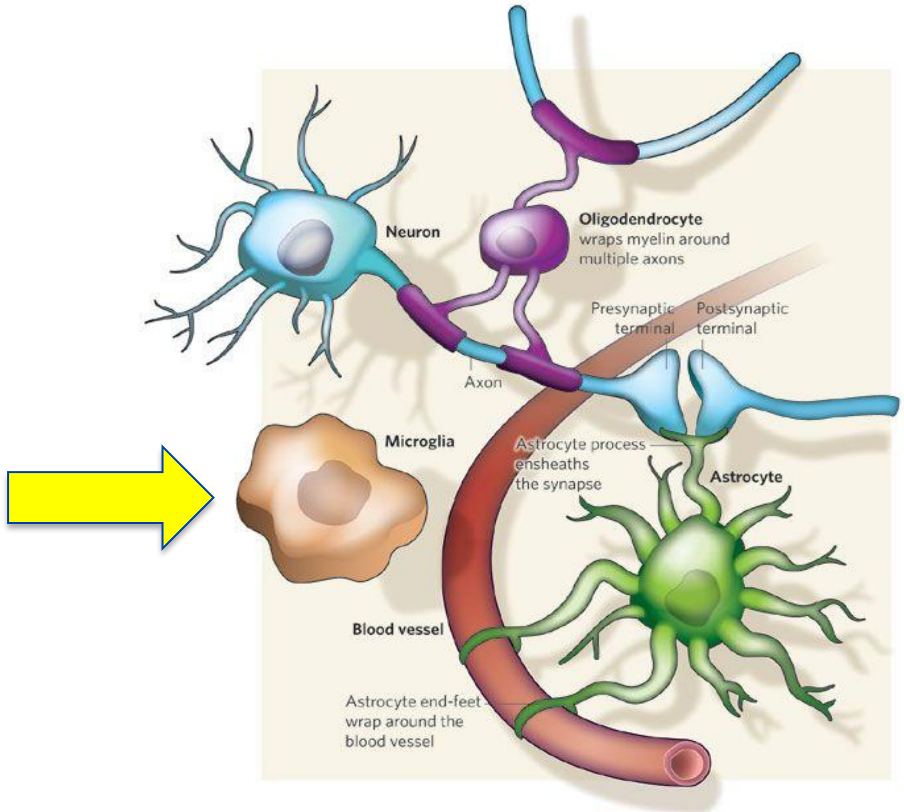
Cross-talk

Cross-talk between neurons and immune and glial cells
> neuro-immune & neuro-glial mechanisms **contribute** to chronic pain states.

Nociceptive neurons can release substances active on glial and immune cells, which can also contribute to the neuro-inflammatory process that is involved in chronic pain.

(Ji et al., 2016)

Glial model



Neuron
Oligodendrocyte
wraps myelin around
multiple axons
Presynaptic
terminal
Postsynaptic
terminal
Axon
Microglia
Astrocyte process
ensheaths
the synapse
Astrocyte
Blood vessel
Astrocyte end-feet
wrap around the
blood vessel

Microglia 1

10% of cells in CNS

Microglia survey local environment with their fine processes on the cell surface

When danger signals are identified, such as bacteria, viruses etc, rapidly undergo

- change in their gene expression and function
- morphological change reverting to an amoeboid appearance
- clear debris, damaged cells, infectious agents
- Synaptic plasticity and pruning, neural circuitry maintenance

Kettenmann et al., 2011
Donnelly ***Neurotherapeutics*** *(2020) 17: 846-860*

Microglia 2

Functional plasticity of microglia:

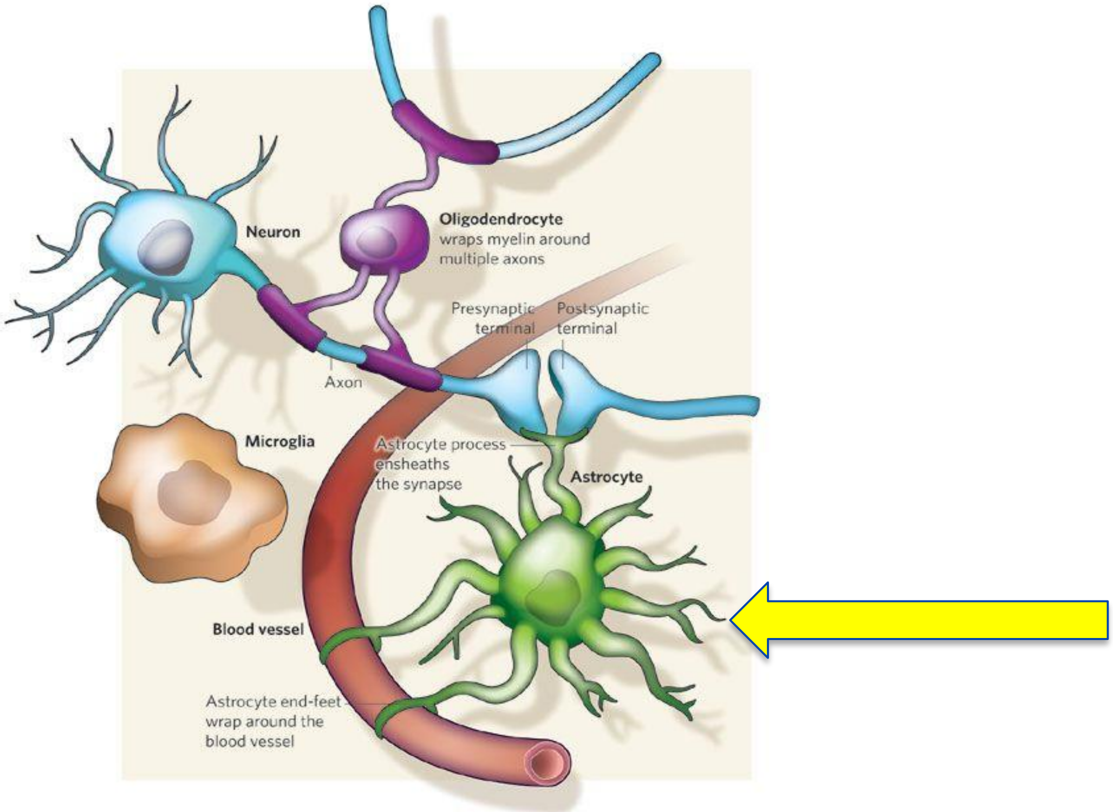
“Microglia activation” is a highly dynamic process with **quite distinct characteristics in different pathological conditions**

Disease control and/or pathogenesis in:

- Alzheimers
- Parkinsons
- Depression
- Anxiety

Donnelly ***Neurotherapeutics*** *(2020) 17: 846-860*
Gomez-Nicola and Perry, 2015; Ransohoff, 2016; Salter and Stevens, 2017

Glial model



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Astrocytes 1

Most abundant glial cells in CNS, ~30 % of glial population

Outnumber neurons over 5-fold (*Ponath et al., 2018; Sofroniew and Vinters, 2010).*

Initially thought to be supportive cells providing ‘scaffold ‘for the distribution and communication of neurons (Sofroniew and Vinters, 2010)

Now know they have important functions in the brain including:

- regulating blood flow
- energy supply and metabolism
- maintaining the homeostasis and pH
- maintenance of blood brain barrier, and
- re- uptake of neurotransmitters

Sofroniew and Vinters, 2010 ; Donnelly ***Neurotherapeutics*** *(2020) 17: 846-860*

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 that may represent damage or danger, astrocytes undergo a series of structural and functional changes known as reactive astrogliosis,

- secretion of cytokines, chemokines & neurotrophic factors

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

Sofroniew and Vinters, 2010 ; Tian et al., 2012
Donnelly ***Neurotherapeutics*** *(2020) 17: 846-860*

Astrocytes 3

Reactive astrocytes have enhanced functions:

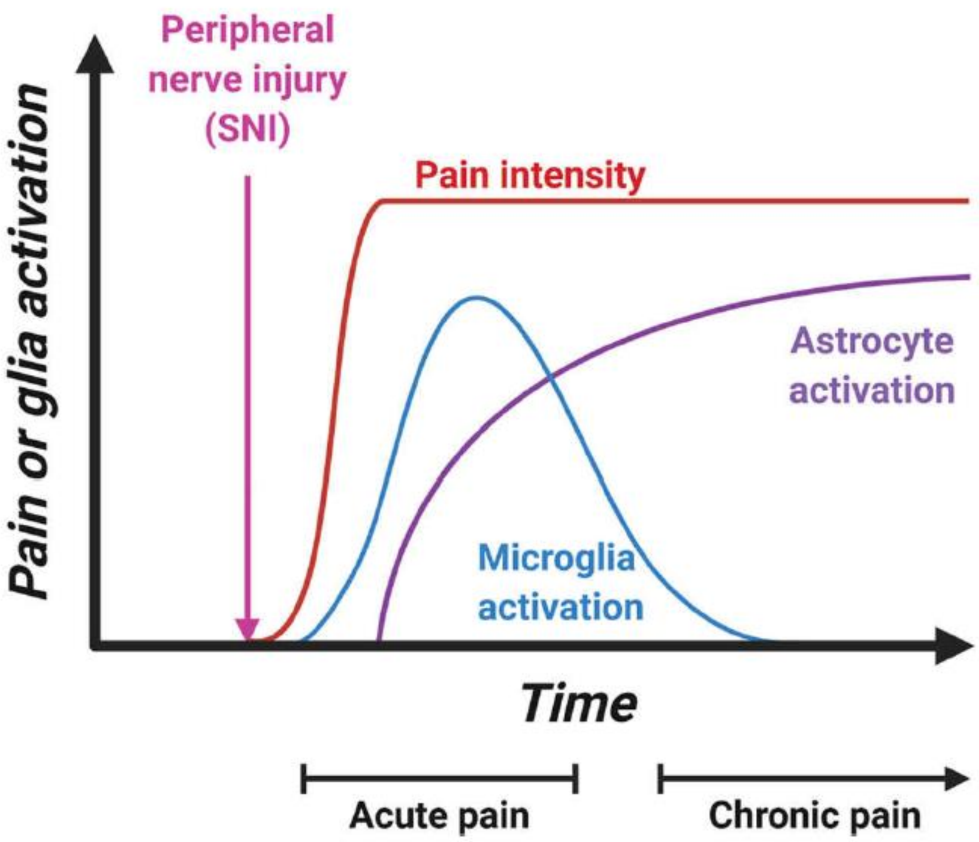
- scavenging excessive glutamate, free radicals and ammonia
- protecting CNS cells and tissues from cytotoxic materials

Sometimes, when the CNS is suffering from 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

Injury and glial cell activation



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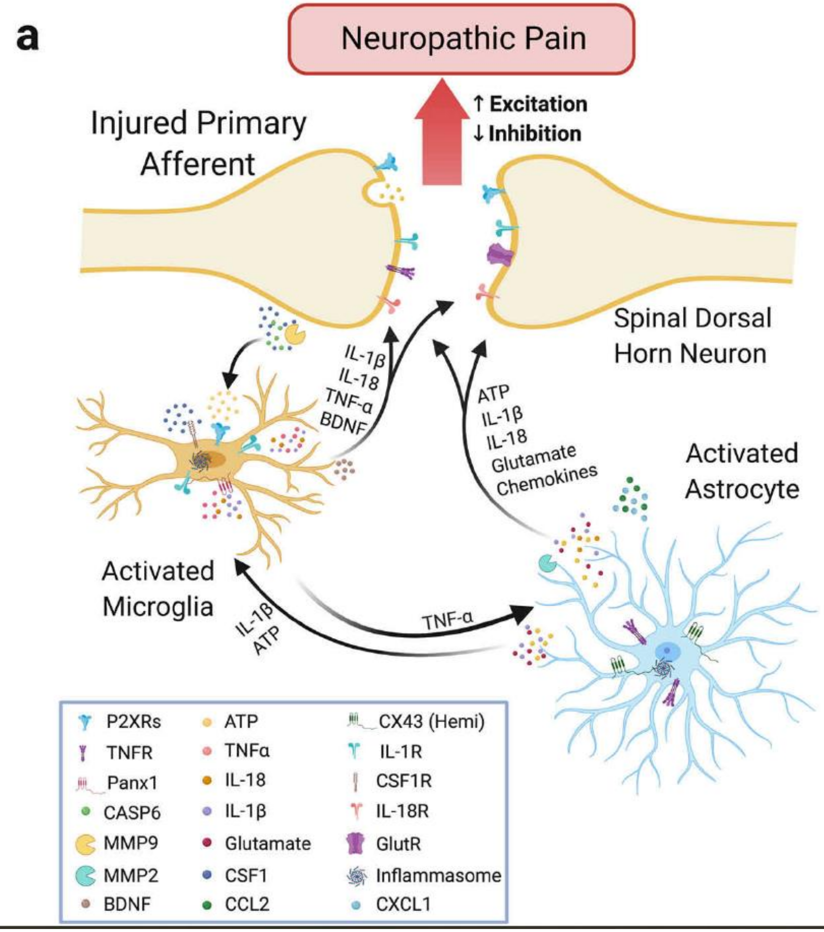
Injury and glial cell activation



Donnelly ***Neurotherapeutics*** *(2020) 17: 846-860*

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

"Sickness syndrome"

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

- TLR4 on glial cells are activated by opioids *Hutchison 2010, 2012*
- Similar to activation by foreign pathogens

Role of low dose naltrexone

Naltrexone

Naltrexone is a pure opioid receptor antagonist (highest affinity for mu receptor)

Dose for alcohol use disorder: 50mg

Low dose 1.5-4.5 mg daily

Ultra low dose / very low dose ~100mcg daily

At these low doses, the threshold for opioid antagonism has not been reached: no precipitated withdrawal

Kim & Fishman. Current Pain and Headache Reports (2020) 24: 64

Low dose naltrexone

Particularly used in:

- Fibromyalgia
- Complex regional pain syndrome
- Inflammatory bowel disease
- Multiple sclerosis

Pain relief
Improved mobility
Reduced analgesic requirements
Improved QOL

Small studies
Variable methodology (eg open label, case series etc)

Kim & Fishman. Current Pain and Headache Reports (2020) 24: 64

Low dose ntx – mech of action?

Action on mu opioid receptor ?

Full dose acts as an antagonist
BUT
Low dose of ‘antagonist’ paradoxically acts as a weak agonist

Kim & Fishman. Current Pain and Headache Reports (2020) 24: 64

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Glial cell modulation?

Low dose has an anti-inflammatory effect through glial cell modulation

Acts as a Toll-like receptor 4 (TLR-4) antagonist

Microglial TLR-4 activation: promote glial release of various cytokines and chemokines including IFN-γ, IL1-β, IL-6, IL-10, CCL4 and CCL17

Kim & Fishman. Current Pain and Headache Reports (2020) 24: 64

In summary, low dose ntx

Mechanism of action not clear yet

Low dose naltrexone (LDN) has good safety profile

May consider trial of LDN for symptoms of central sensitization:
- allodynia
- hyperalgesia

Kim & Fishman. Current Pain and Headache Reports (2020) 24: 64

Questions and discussion