

Introduction

- Chronic pain affects over 30% of people globally
 - \$560-635 billion annual cost to U.S.
- Chronic pain involves neuroinflammatory and synaptic changes in regions such as the spinal cord, thalamus, hippocampus, and periaqueductal gray (PAG)
- The endocannabinoid system (ECS), including endocannabinoids, receptors, and enzymes, modulates pain via neuronal and glial mechanisms
- Microglia and astrocytes exhibit ECS alteration, influencing inflammation and pain relief

Materials and Methods

- Systematic literature review to evaluate endocannabinoid system (ECS) alterations in preclinical models of neuropathic and inflammatory pain
- Brain regions examined included the spinal cord, hippocampus, periaqueductal gray (PAG), motor cortex (M1), thalamus, and anterior cingulate cortex (ACC)
- Experimental techniques encompassed immunohistochemistry for receptor localization, quantitative RT-PCR for gene expression, single-cell RNA sequencing for cell-specific profiling, and pharmacological interventions using CB2R agonists, cannabidiol (CBD), and antagonists

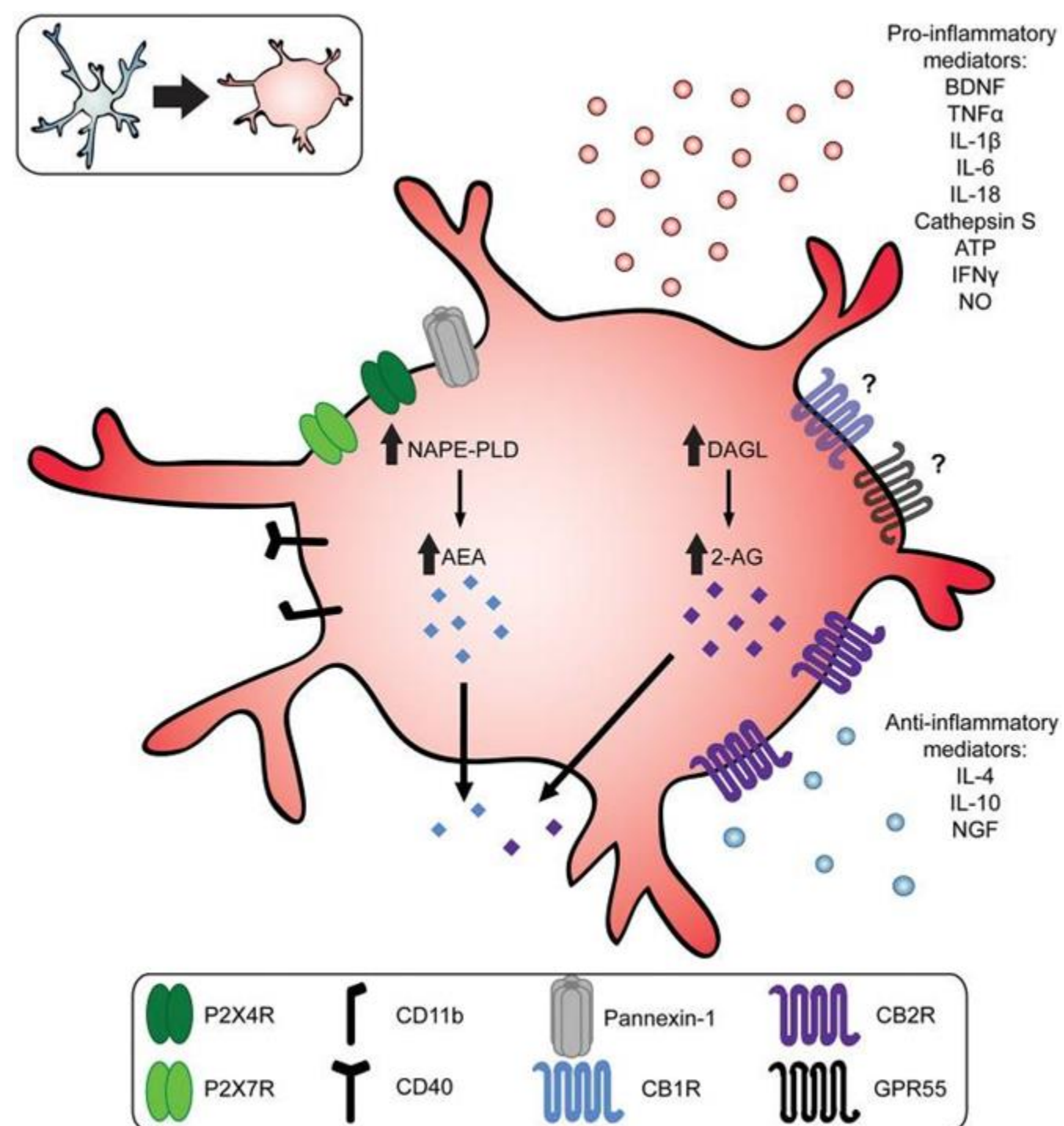
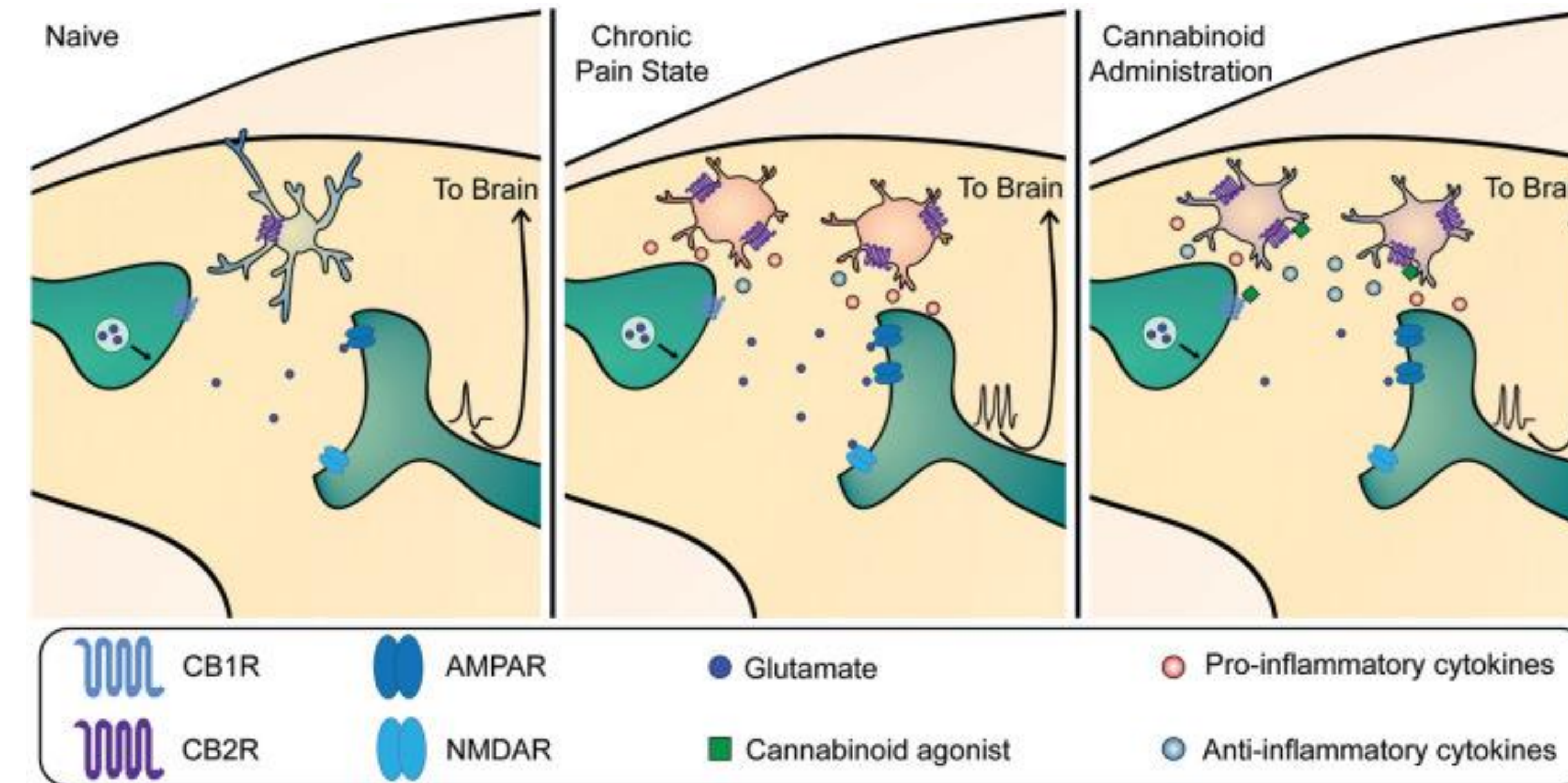


Figure 1. Reactive microglia increase production of endocannabinoids and pro-inflammatory mediators. Endocannabinoids and exogenous cannabinoids act on microglia CB2Rs, which are upregulated in chronic pain states and as a result, upregulate the release of anti-inflammatory cytokines. Microglia transition into reactive microglia during times of infection, injury, or pathology as seen in the upper left panel.



Results

- Emphasis on neuropathic pain models
- Reactive spinal microglia upregulate CB2Rs, promoting a shift from proinflammatory (M1) to anti-inflammatory (M2) phenotypes
 - mitigates allodynia and hyperalgesia
- Microglia increase 2-AG production through calcium-dependent DAGL activation
 - amplifies CB2R-mediated analgesia
- CB2R agonists and CBD further alleviate pain in SNL, CCI, and chemotherapy-induced neuropathic pain
- In the hippocampus and PAG, astrocytic CB1Rs trigger long-term depression (LTD)
 - modulates neuronal excitability
- In the motor cortex (M1) and thalamus, astrocytic and microglial CB2Rs suppress proinflammatory cytokines
 - enhances pain relief

Figure 2. Depicts mechanism of cannabinoid-mediated reduction in dorsal horn hyperexcitability in chronic pain. Left panel shows microglia in surveillant phenotype. Mid panel shows microglia becoming active and contribute to dorsal horn neuron hyperexcitability through release of pro-inflammatory mediators in chronic pain states. Right panel shows binding of endogenous and exogenous cannabinoids binding to CB1Rs on both neurons and microglia within the dorsal horn. Together, neuronal and microglial CBR activation lead to a reduction in pain.

Discussion

- Cannabinoid-mediated glial modulation via microglial CB2Rs and astrocytic CB1Rs
- Offers a promising strategy for chronic pain management
- CB2R activation and CBD reduce neuroinflammation while astrocytic CB1Rs regulate synaptic plasticity
- Variability in ECS expression across pain models necessitates region- and phenotype-specific therapies
- Future research should optimize CB2R agonists and elucidate glial-neuronal interactions to enhance analgesia while minimizing side effects

References

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