ASTROCYTE AND GLUTAMATERGIC DYNAMICS IN PREFRONTAL CORTEX AND NUCLEUS ACCUMBENS IN A RAT MODEL OF PAIN

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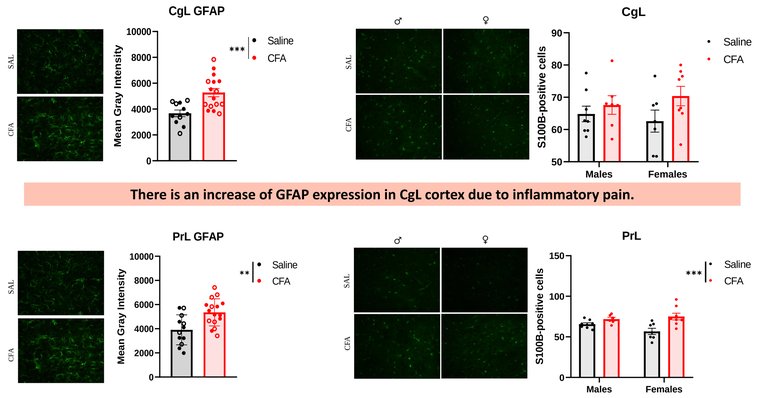
Chronic pain is a complex health burden which is usually associated to other pathologies such as anxiety, depression, drug abuse disorders and cognitive impairments. Interestingly, prefrontal cortex (PFC) and nucleus accumbens (NAc) play a role in both pain processing and its comorbidities. Clinic evidence suggest that neuroplastic events related to astrocytes and glutamate homeostasis are associated with pain chronification and the development of its comorbidities, even though the role of this in the PFC to NAc projection is not very clear yet.

Effects of neuroinflammatory pain on astrocytes in the MCLS

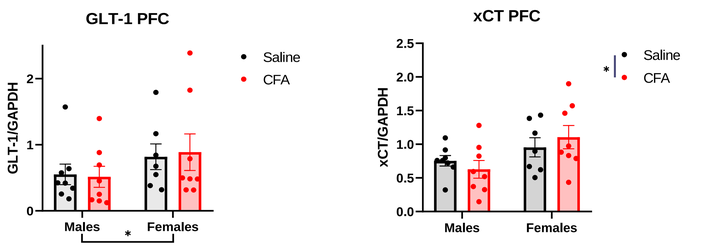
Prefrontal cortex



There is an increase of GFAP expression in CgL cortex due to inflammatory pain.

Inflammatory pain significantly elevates astrocyte proliferation and activation in PrL cortex.

Inflammatory pain significantly augment astrocyte activation in IL cortex in a sex-dependent way.



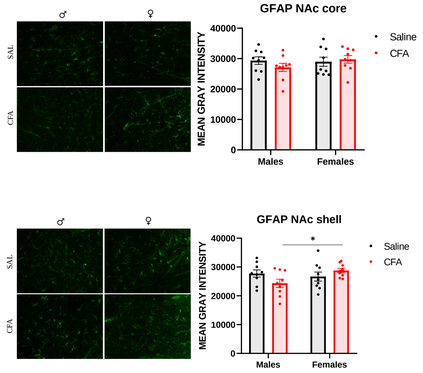
GlT-1 expression is higher in males in PFC. Inflammatory pain enhances xCT expression in PFC.

Astrocytes have as their main function the maintenance of glutamate, potassium and water homeostasis; although their activation can lead to neurotoxicity and neuroinflammation.

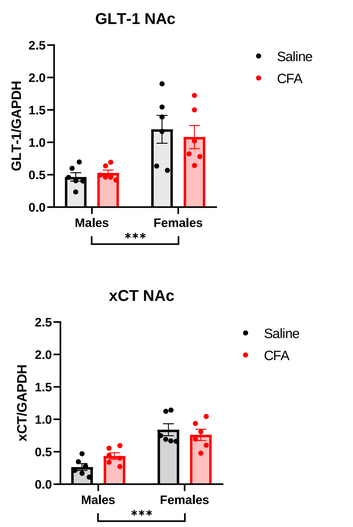
GFAP (Glial Fibrillary Acidic Protein) and **S100B** (calcium-binding protein) predominantly expressed in astrocytes, useful markers for identifying astrocyte proliferation and activation, respectively.

GLT-1 (Glutamate Transporter 1) and **xCT** (Cystine/Glutamate Antiporter) in astrocytes regulate extracellular glutamate levels.

Nucleus Accumbens



Inflammatory pain increases GFAP expression in NAc shell.



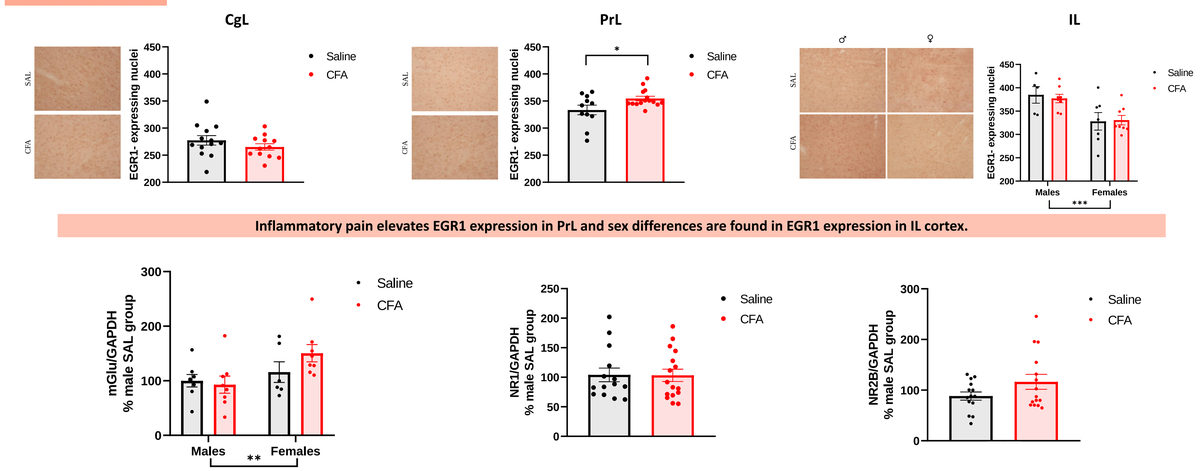
GLT-1 and xCT expression is higher in female rats in NAc.

Influence of neuroinflammatory pain on glutamate receptors in the MCLS

Glutamate receptors, including **mGlu and NMDA receptors**, are essential in **neuronal plasticity**. Neuroplastic events are believed to have a crucial role in producing adaptations in synaptic excitability and maintaining a state of hyperalgesia in central sensitization during chronic pain. The NMDA receptor is ionotropic and controls a ligand-gated ion channel. The **NR1 subunit** is an essential part of the NMDA receptor, acting as anchor for the other subunits. **NR2A** and **NR2B subunits** appear to be implicated in controlling synaptic plasticity, memory and learning.

EGR1 is a transcription factor which acts as a marker for neural plasticity in response to different stimuli.

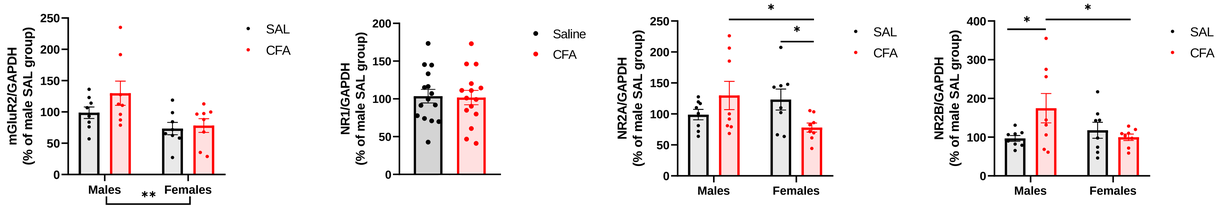
Prefrontal cortex



Inflammatory pain elevates EGR1 expression in PrL and sex differences are found in EGR1 expression in IL cortex.

Inflammatory pain does not alter mGluR2 nor NR1/NR2B subunits of NMDA receptor expression in PFC.

Nucleus Accumbens



mGluR2 expression is sex-dependent in NAc. Regarding NMDA receptors, inflammatory pain decreases the levels of NR2A subunit in females and increase the levels of NR2B in males in NAc, whitout alterations in the expression of NR1 subunit.

CONCLUSIONS

- **Inflammatory pain** is capable of **increasing GFAP expression** in the **PrL** and **IL** regions of the PFC and in the **NAc Shell**. What is more, the levels of **S100B** are **increased** in the presence of **inflammatory pain** in **PrL** and **IL** cortex.
- Physiologically, the expression of the glutamate transporters **GLT-1** in **PFC** and of **GLT-1** and **xCT** in **NAc** are significantly different between **sexes.** Additionally, inflammatory pain promotes xCT expression in PFC.
- The presence of **inflammatory pain** causes a **rise** in **EGR1** levels in **PrL** cortex, indicating neuroplastic events that are not mediated through mGluR2 nor NR1 and NR2A subunits in PFC. Moreover, **sex differences** are found in EGR1 expression in **IL** cortex.
- The **physiological expression of mGluR2** in both PFC and NAc is **sex-dependent**.
- **Inflammatory pain decreases** the expression of **NR2A** subunit in **females** and **increases NR2B** subunit in **males**, without causing alterations in the expression of NR1 in NAc.

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