Progetto

Effects of social isolation during adolescence on neuroinflammatory-related processes in male and female adolescent rats.

Early social and emotional experiences differently shape individual's neurodevelopment inducing substantial changes in neurobiological substrates and behavior (Rullo et al., 2023). Exposure to early life adversity (ELA) affects brain development differentially, depending on the type of adversity and the timing of exposure. ELA may trigger chronic neuroinflammation, which in turn affects key brain structures and functions, particularly in regions like hippocampus, amygdala, prefrontal cortex, and ventral tegmental area (Andersen, 2022). Early life stress (ELS) may induce long-lasting epigenetic modifications (e.g., DNA methylation) that increase vulnerability to neuroinflammation later in life, perpetuating a cycle of stress and immune dysregulation. For instance, it has been shown that overactivation of the amygdala due to neuroinflammation can lead to heightened emotional reactivity and increased susceptibility to anxiety disorders. Similarly, prolonged isolation during adolescence, which represent another critical developmental window, led to increased anxiety-like behaviors. These behavioral changes were accompanied by heightened excitability of pyramidal neurons in the basolateral amygdala, a brain region central to emotional processing (Lin et al., 2017).
Chronic stress and neuroinflammation may also impair the development of the prefrontal cortex, which is associated with decision-making, impulse control, and attention. In this frame, epigenetic mechanisms, including the activity of Jmjd3 (or KDM6A, histone demethylase), play a pivotal role in how early-life experiences like maternal separation have long-lasting effects on brain development. Maternal separation (an early-life stressor) likely triggers the activation of Jmjd3 in brain regions like the prefrontal cortex and hippocampus.

Once activated, Jmjd3 demethylates repressive histone marks (H3K27me3), leading to the expression of genes involved in inflammatory pathways. This includes cytokines and other inflammatory mediators. Therefore, early-life stress can "program" certain genes to become more or less active later in life through epigenetic modifications. For example, Jmjd3's activation may be an adaptive response to stress in early life, but over time, its role in promoting neuroinflammation may

become maladaptive, contributing to vulnerability to psychiatric disorders (Wang et al., 2020). Interestingly, social isolation during adolescence increased levels of H3K27me3 in the prefrontal cortex of female mice, specifically at promoters of genes related to synaptic function and plasticity (Li and Yan, 2023).

Neuroinflammation also influences opioid and cannabinoid receptor signaling, as chronic inflammation can desensitize or downregulate these receptors, contributing to the dysregulation of pain and reward circuits. The endocannabinoid and opioid systems play protective roles in regulating stress and neuroinflammation, and their dysregulation due to epigenetic changes from stress during critical windows of development can have long-term consequences. The combined effects of epigenetic changes, neuroinflammation, and dysregulation of the endocannabinoid and opioid systems create a feedback loop that increases vulnerability to various psychiatric and neurological disorders (Catale et al., 2022).

It has previously been demonstrated that KDM6A increases in response to proinflammatory signaling, influencing the transcription of genes that PPARs regulate. PPARα and PPARγ, important in reducing inflammation and metabolic stress, are modulated by the activity of KDM6A. When KDM6A is inhibited, there is an increase in the expression of PPARs, indicating a balancing act between these molecules to control neuroinflammatory processes (Rullo et al., 2021).

Based on this evidence, the aim of this research project will be the evaluation of potential molecular alteration induced by social isolation during adolescence on KDMs, PPARs, and neuroinflammation mediators such as ILs, TNF-α, as well as endogenous opioids and their receptors. To assess this aim, molecular analysis will be performed in stress- and emotional-related brain area (hippocampus, amygdala, prefrontal cortex, and ventral tegmental area) of adolescent male and female rats housed in either standard condition or subjected to a protocol of social isolation (during post-natal day 20-45).

In addition, since several evidence suggested also a critical role of the dynorphin/kappa opioid receptor (KOR) system in mediating the behavioral and neurobiological consequences of social isolation stress, particularly through its interaction with neuroinflammatory pathways (Haj-Mirzaian et al., 2019; Karkhanis et al., 2016; Zan et al., 2022), the expression and regulation of dynorphin and KOR will be examined.

This approach will allow for the identification of sex-specific and region-specific molecular signatures associated with adolescent social isolation, providing insights into the mechanistic underpinnings of stress-related vulnerability to psychiatric disorders.

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