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Modulation of microglia and presynaptic protein expression after mesenchymal stem cells treatment in a rat model of Alzheimer's disease

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Objectives: Sporadic Alzheimer's disease (sAD) is the most prevalent neurodegenerative pathology with no effective therapy until date. This disease prompts hippocampal degeneration, which in turn affects multiple cognitive domains and daily-life activities. In this study, we hypothesized that long-lasting therapy with human mesenchymal stem cells (MSC) would have a restorative effect on the behavioral alterations and cognitive decline characteristic of sAD, as they have shown neurogenic and immunomodulatory activities.

Methods: We treated intracerebroventricular streptozotocin-injected (icv-STZ) rats, a commonly used animal model of sAD, with 1×10^6 MSC in a tail vein (24 days post-icv-SZT), every 18 days. At the end of the study (3 months post-icv-STZ), we evaluated their cognitive function together with morphological and biochemical changes in the hippocampus.

Results: We observed cognitive deficits, microgliosis, and decreased on presynaptic proteins (SYT1, SYT2, and SYP) and GABAergic neuron marker (GAD65) in the brains of icv-STZ rats. Interestingly, MSC therapy significantly improved its spatial memory and decreased the anxiety, ameliorated microglial activation, and enhanced SYT1, SYP, and GAD65 levels. Additionally, we found significant negative correlation between the hippocampal reactive microglia with the expression of SYT1, SYT2, SYP, and GAD67 proteins, suggesting the modulation of synaptic transmission by glial cells.

Conclusion: These findings, showing that intravenous injection of human MSCs restores behavioral and hippocampal alterations in experimental sAD, support the potential use of MSC therapy for the treatment of neurodegenerative diseases.

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P32.19

Sex-specific alterations in behavior and neuroinflammation in a mouse model of autism

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Autism spectrum disorder (ASD) is a neurodevelopmental disorder with an incidence three times higher in boys than in girls. By analyzing the effect of sex in a mouse model of ASD, we were able to identify immune alterations that could underlie this sex bias.

Pregnant mice were injected subcutaneously with 600 mg/kg of valproic acid (VPA) or saline at gestational day 12.5. Their male and female offspring were evaluated in a social interaction test at adulthood, and only male VPA mice showed reduced sociability levels and a lack of social preference. We then analyzed the hypothalamus–pituitary–adrenal (HPA) response and the neuroinflammatory state in adult and young animals. Adult VPA males exhibited increased basal corticosterone levels, while VPA females showed levels comparable to controls. As male mice showed a blunted HPA activation at PD21 when compared to female mice, we propose that this early dimorphism could explain the different effects of VPA on HPA function. In addition, prenatal VPA exposure resulted in altered astroglial and microglial cell density levels in the dentate gyrus and the cerebellum in adult mice. These neuroinflammatory effects were more pronounced in female than male mice, and appeared at early developmental stages. We propose that these postnatal glial density differences could underlie the behavioral differences observed in adulthood, when only males show a social deficit.

We consider that our work contributes to the understanding of biological mechanisms affected by VPA on male and female rodents, and to shed light on the study of possible resilience mechanisms in the female population and/or susceptibility to ASD in boys.

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P32.20

Psychostimulants are not identical pharmacological agents: Distinct effects of psychostimulant drugs on the regulation of class IIa HDACs in the mouse mesocorticolimbic and striatal systems

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Psychostimulants produce different behavioral and neurobiological profiles. For example, some drugs cause neuroplastic changes leading to addiction and cognitive deficits while others enhance cognition. Epigenetic mechanisms are known contributory factors to drug-induced neuroadaptations. These epigenetic changes include dysregulation of histone deacetylases (HDACs) proposed to participate in maintaining aberrant transcriptional programs associated with altered cognitive functions and behaviors. HDACs are divided into zinc-dependent [class I (HDAC1,2,3,8), class IIa (HDAC4,5,7,9), class IIb (HDAC6,10), and class IV (HDAC11)] and NAD-dependent [class III (sirtuins1–7)] enzymes. Our laboratories have previously reported that psychostimulants differentially influence the acetylation status of histones 3 and 4 at promoters of HDACs in the prefrontal cortex (Addict. Biol., 2019. doi: 10.1111/adb.12737). In the present study, we used acute administration of methamphetamine (1 mg/kg), modafinil (90 mg/kg), caffeine (10 mg/kg) or methylphenidate (10 mg/kg) in C57BL/6 mice to investigate potential changes on the mRNA expression of HDACs 4, 5 and 7 in the medial prefrontal cortex (mPFC) and dorsal striatum (DS). All psychostimulants increased locomotion at these doses. Modafinil decreased HDAC7 and HDAC5 mRNAs in DS but increased their levels in mPFC. Methylphenidate increased HDAC5 mRNA in mPFC but decreased it in DS. Methamphetamine increased HDAC4 and HDAC5 mRNA levels but decreased HDAC7 expression in mPFC. Caffeine did not effect HDAC expression.