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Sociedad Científica Española de Estudios sobre el Alcohol, el Alcoholismo y las otras Toxicomanías

Mesenchymal stem cell-derived extracellular vesicles attenuate multiple inflammasome pathways activated by chronic ethanol exposure in female mice

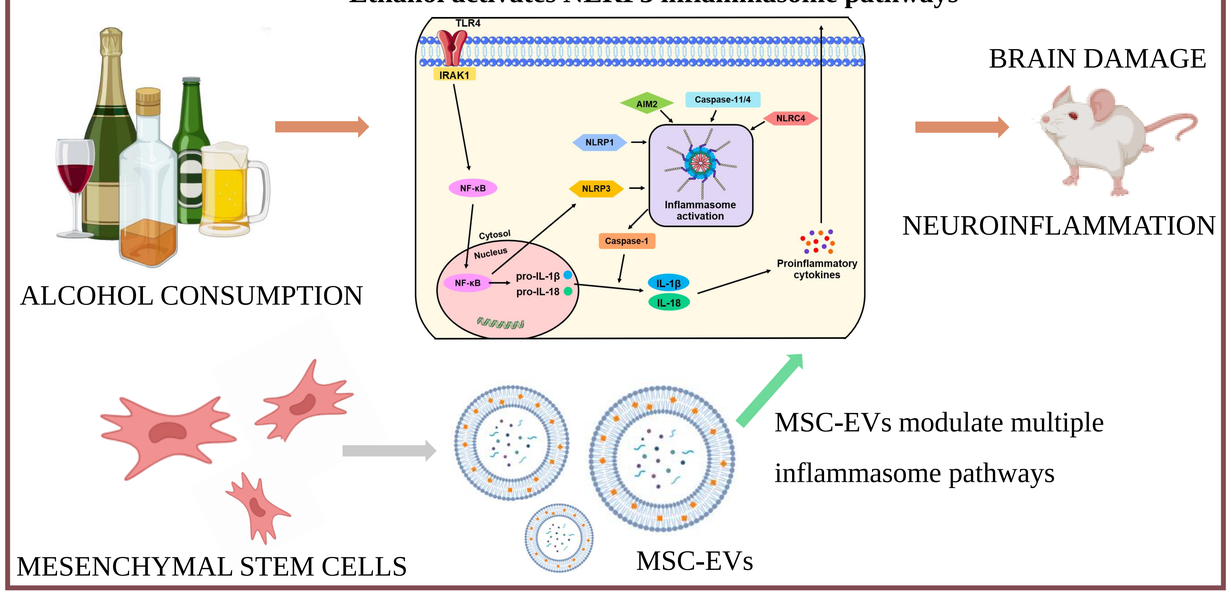
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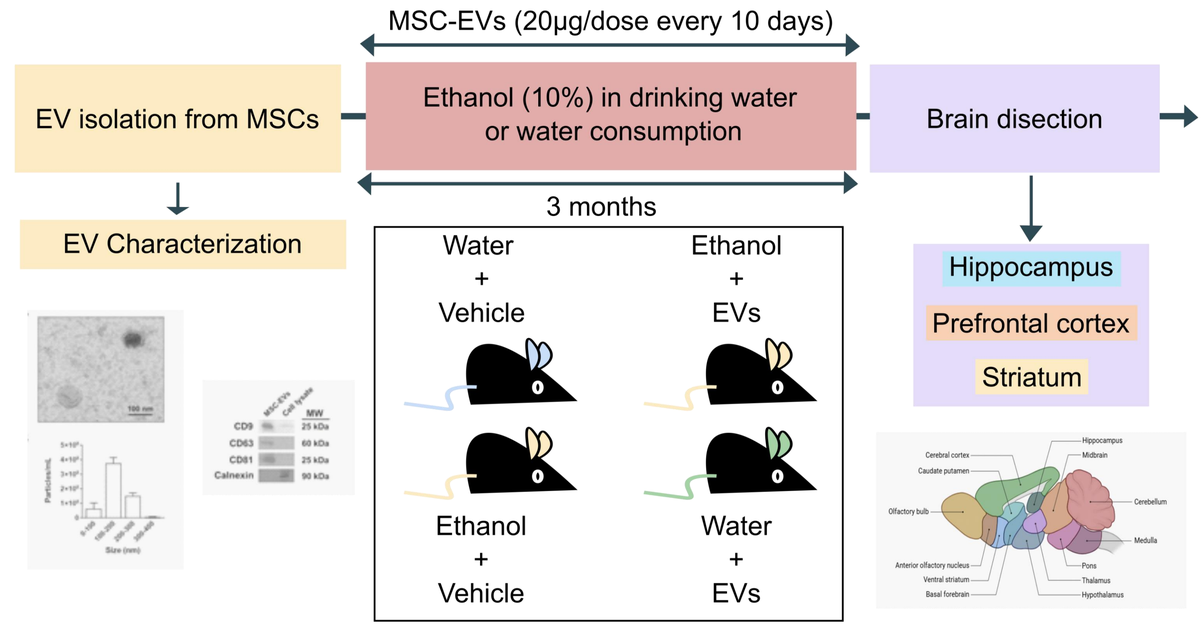
BACKGROUND

Chronic alcohol consumption induces persistent neuroinflammation and inflammasome activation, contributing to alcohol-related brain damage. NLRP3 is one of the cytosolic sensors responsible for this activation through the formation of the NLRP3 inflammasome, which activates caspase-1 and promotes the release of inflammatory cytokines (e.g., IL-1β, IL-18). Mesenchymal stem cell-derived extracellular vesicles (MSC-EVs) attenuate ethanol-induced NLRP3 activation, but their effect on other inflammasome pathways is unknown. We evaluated adipose-derived MSC-EVs on inflammasome-related gene expression in the prefrontal cortex, hippocampus, and striatum of female mice chronically exposed to ethanol.

Ethanol activates NLRP3 inflammasome pathways



METHODS



Analyzed genes

NLRP3 pathway genes:
- Nlrp3
- Casp1
- Il1b
- Il18

Alternative sensor genes:
- Nlrp1
- Aim2
- Nlrc4

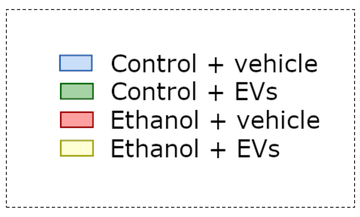
Upstream regulator genes:
- Casp-11/4
- Irak1
- Tlr4

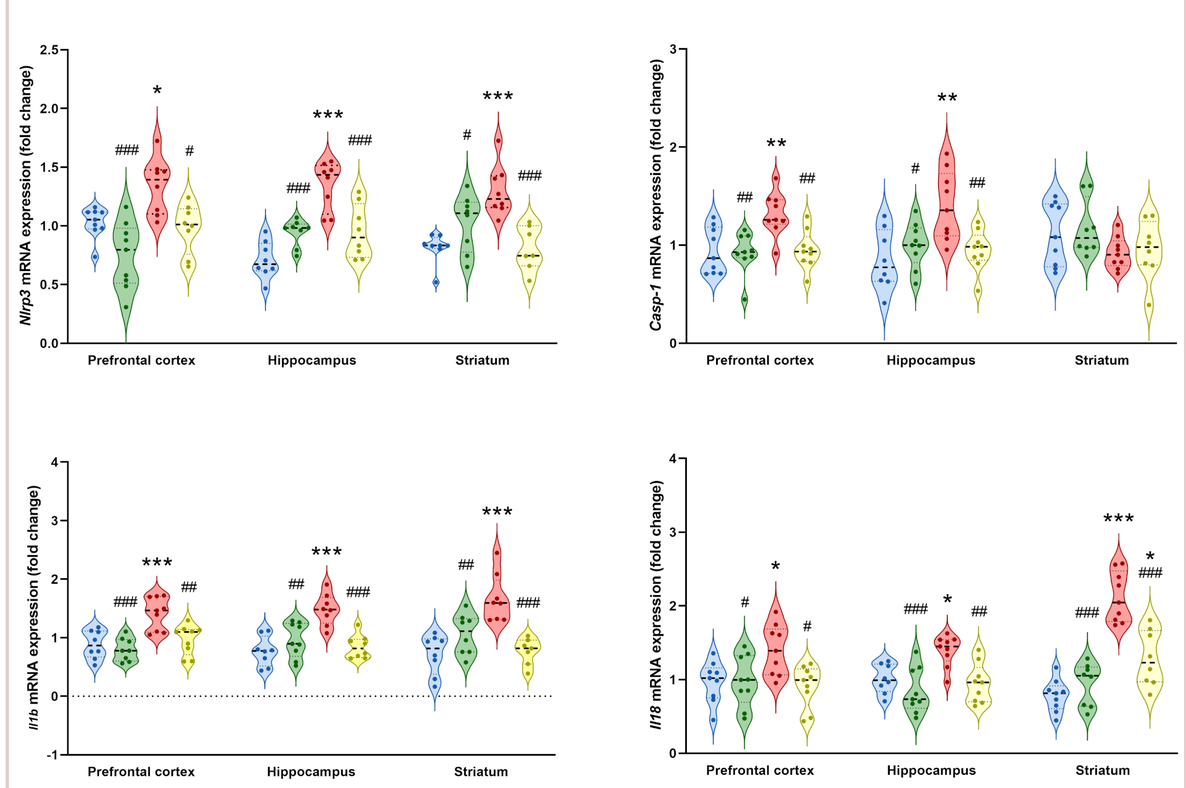
RT-qPCR: RNA extraction – cDNA - amplification

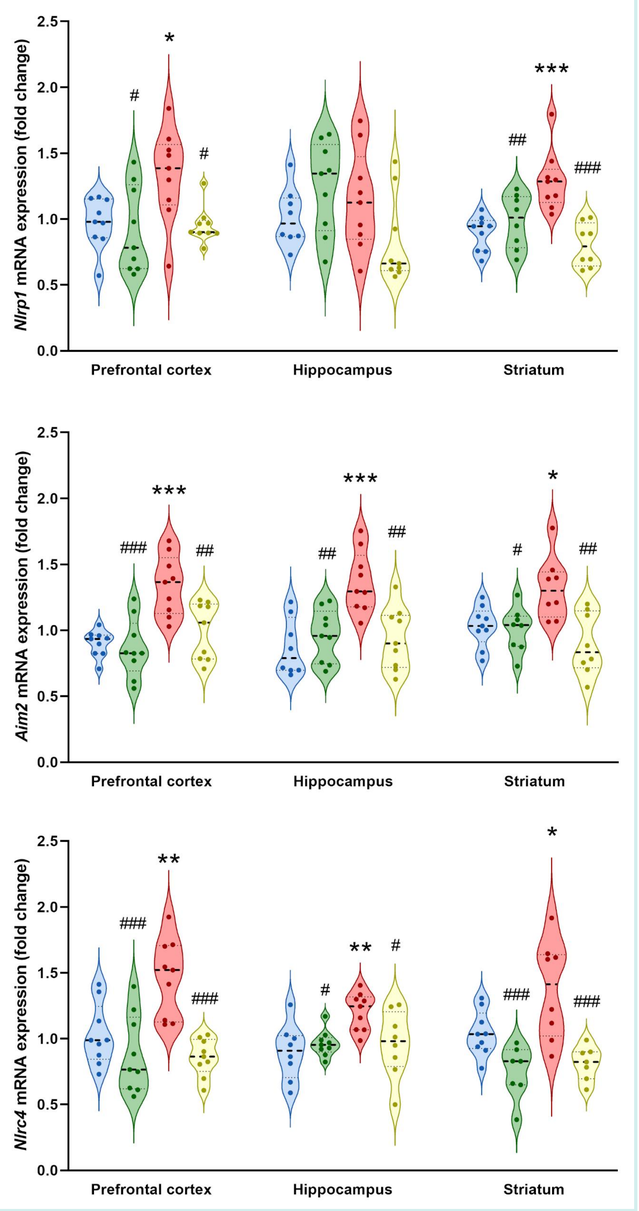
OBJETIVE: To evaluate whether adipose-derived MSC-EVs modulate multiple inflammasome pathways in the prefrontal cortex, hippocampus, and striatum of female mice chronically exposed to ethanol.

RESULTS

Chronic ethanol increased expression of NLRP3 pathway genes (*Nlrp3*, *Casp-1*, *Il1b*, *Il18*), upstream regulators (*Casp-11/4*, *Tlr4*), and alternative sensors (*Nlrp1*, *Aim2*, *Nlrc4*) across all three regions. MSC-EV treatment significantly attenuated these increases, restoring expression toward control levels. *Irak1* was unchanged.







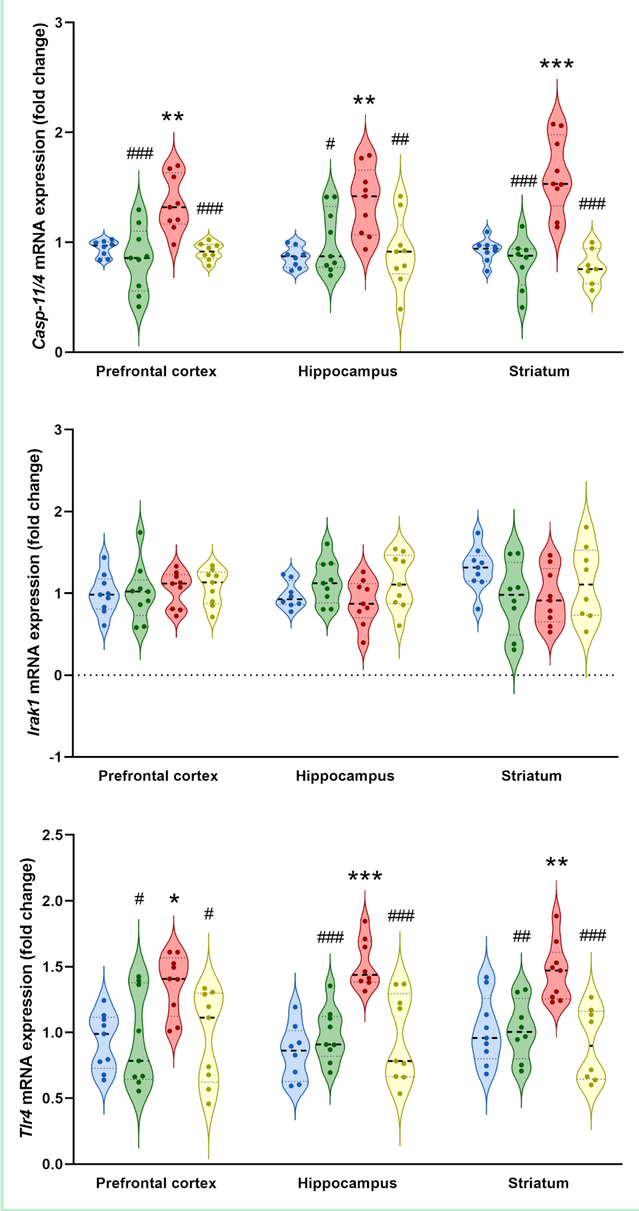


Fig. 1 MSC-EV treatment attenuates chronic ethanol-induced expression of inflammasome-related genes in the prefrontal cortex, hippocampus, and striatum. mRNA levels of inflammasome sensor genes (*Nlrp3*, *Nlrp1*, *Aim2*, *Nlrc4*), upstream regulators (*Casp-11/4*, *Tlr4*, *Irak1*), and downstream effectors (*Casp-1*, *Il1b*, *Il18*) were quantified by RT-qPCR and normalized to Cyclophilin A (ΔΔCq method). Data are mean±SEM, n=8–9 mice/group. *p<0.05, **p<0.01, ***p<0.001 vs. vehicle; #p<0.05, ##p<0.01, ###p<0.001 vs. ethanol.

CONCLUSIONS

Alcohol-induced neuroinflammation involves multiple innate immune pathways beyond NLRP3. MSC-EVs modulated inflammasome sensors, upstream regulators, and effector cytokines in regions key for cognition and reward, suggesting a broad immunomodulatory effect. MSC-EVs are a promising strategy against inflammasome-driven neuroinflammation in chronic alcohol consumption.

TAKE-HOME MESSAGE

MSC-EVs broadly **attenuate chronic ethanol-induced inflammasome activation** across brain regions key for cognition and reward, supporting their potential as a multifaceted therapy against alcohol-related neuroinflammation.

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