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IL-10 AND Cdc42 AS CRITICAL MODULATORS IN METHAMPHETAMINE-INDUCED NEUROINFLAMMATION

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Abstract:
Psychoactive substances, such as Methamphetamine (Meth), can induce complex neuroinflammatory responses that modulate the neuron-glia cross talk and strongly affect behavioral responses. Recently we have reported that Meth stimulates astrocytes to release tumor necrosis factor (TNF) and glutamate, leading to microglial activation, microgliosis and loss of risk-assessment. Here, we started by investigating the anti-inflammatory power the cytokine interleukin-10 (IL-10), resorting to astrocyte and microglia primary transfected with different FRET probes and exposed to Meth (100μM), to elucidate the mechanisms involved. Then after, we confirmed these results in vivo, by employing a transgenic mouse model that overexpresses IL-10 (pMT-10), in time-controlled manner, and administering a binge Meth dosing (4 x 5mg/kg, with 2h intervals). In vitro, our findings reveal that the presence of recombinant IL-10 (rIL-10) counteracts Meth-induced excessive glutamate release in astrocytes, which significantly reduced microglial activation. This reduction was associated with the modulation of astrocytic intracellular calcium (Ca2+) dynamics, particularly by restricting the release of Ca2+ from the endoplasmic reticulum to the cytoplasm. Furthermore, we identify the small Rho GTPase Cdc42 as a crucial intermediary in the astrocyte-to-microglia communication pathway under Meth. In vivo, we observed that IL-10 overexpressing prevented Meth-induced neuroinflammation, microgliosis and Meth-induced behavioral changes. These findings enhance our understanding of Meth-related neuroinflammatory mechanisms, suggesting IL-10 and Cdc42 as putative therapeutic targets, and strengthen the view of a neuroimmune nature for addiction.

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