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Psychostimulants and neuroinflammation: finding critical players in the crosstalk between glial cells and neurons

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Exposure to psychostimulants has been classically associated with damage to neuronal terminals. However, it is now accepted that interaction between neuronal and glial cells also contributes to the addictive behavior. We have recently shown that acute methamphetamine (Meth), a powerful psychostimulant, causes microgliosis and increases microglia activation through astrocytic-TNF release[1]. We are now interested in clarifying the progression of neuroinflammation under chronic drug exposure and how different brain and immune cells contribute to this inflammatory process.

To explore this, firstly, we performed a proteomic analysis, in different phases of the addictive process, in mice exposed to an escalating dosing of Meth for ten days (Meth10d). To validate the conditioning power of our model, mice were tested in a condition place preference (CPP) at 10d of Meth, and 2 or 10 days of withdrawal (WD). At all these time points, mice were seen to be strongly conditioned by Meth. Next, we conducted a proteomic analysis to compare the different time points (using the hippocampus, where we previously found robust microgliosis under Meth[1]). We found a proteome profile that varied substantially with exposure (Meth10d) and after a short- (WD2d) and long-term withdrawal (WD10d) periods. Interestingly, the most altered pathways were neurotransmitter-related. However, we also identified significant differences in Wnt signaling, which was previously linked to regulation of microglia reactivity. As such, we evaluated the microglia profile after chronic Meth exposure and at withdrawal. In the hippocampus, the number of microglia cells was significantly increased at Meth10d and remained also increased at WD2d. Microglia presented a more ameboid-like shape at Meth10d, but its ramified morphology was recovered at WD2d. Importantly, our proteomic data also revealed that during Meth withdrawal, several microglial receptors were downregulated, suggesting that microglia was in a "primed" state. In addition, as the crosstalk between neurons and microglia seems to be relevant for the behavioral expression of Meth, we are dissecting the modulation of microglia by neurons under Meth exposure, to evaluate neuroimmune regulatory ligand-receptor pairs that seem to impact on the neuron-microglia interaction. Of note, some these ligand-receptor pairs seem to be down regulated by chronic Meth and during abstinence, which may be associated with reduced neuronal ability to downregulate microglia reactivity, and lead to increased neuronal damage.

We foresee that these receptors may prove to be interesting therapeutic targets for the treatment of addiction, and therefore we will manipulate them to confirm their value in reducing relapse rates and improve addiction treatments.

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