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Blockingmethamphetamine-induced microglia reactivity by targeting glutamate receptors

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Methamphetamine (Meth) is an extremely addictive and neurotoxic psychostimulant with high levels of worldwide use. We have recently reported that Meth causes both microglial expansion and activation, showing that activation of microglia under Meth relies on an astrocyte - to - microglia crosstalk mediated *by* glutamate release from Meth-exposed astrocytes[1]. We further demonstrated that this mechanism was driven by Meth-induced TNF production in astrocytes, and that Meth cannot activate microglia in a cell-autonomous way. Of note, glutamatergic regulation of microglia function is complex, including possible negative-feedback loops through group II and III mGluRs, and activation of neurotoxic pathways through group II receptors. Furthermore, because many glutamate receptors are ubiquitously expressed and control relevant pathway, therapeutical approaches targeting glutamate receptors need to be particularly cautious and selective.

To gain novel insight into astrocyte-derived microglia activation, here we used primary cell cultures of astrocytes and microglia to uncover the microglia glutamate receptors responding astrocyte-released glutamate under Meth exposure. To achieve this aim, we used the SCREEN-WELL® Metabotropic Glutamatergic ligand library (Enzo, NY, USA) and an High-Throughput Screening platform. We identified both glutamate receptors from group I - mGluR1 and mGluR5 - as promising candidates. After a careful validation using different microglia activation markers, which was complemented with a systematic review of the existing literature regarding the compounds identified and validated, we selected a modulator of the metabotropic glutamate receptor 1 (mGluR1) for *in vivo* evaluation. Wildtype mice were pre-treated with the selected mGluR1 inhibitor (10mg/kg), administered (or not) 1 hour before Meth binge administration (4x5mg/kg Meth, 2 h apart, intraperitoneally), and sacrificed 24h after the first Meth administration. Brains were collected and Meth-induced microglia evaluated by flow cytometry. The data obtained validated that antagonism of the mGluR1 was sufficient to prevent microglial expansion and activation by Meth. Overall, here, we report having identified mGluR1 as a potential target for future therapeutic action in Meth problematic use.

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References

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