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Methamphetamine activates rac1 in striatal microglia

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Methamphetamine (Meth), a powerful psychostimulant, induces profound synaptic and morphological alterations alongside with detrimental neuroinflammatory responses, in the brain reward system. Yet, the mechanisms regulating these processes in microglial cells are not clear. We have previously shown that exposing WT mice to Meth (4x5 mg/kg, 2h intervals) induces microgliosis concomitant with decreased microglia cell volume and ramification[1]. Furthermore, psychostimulants are known to induce structural plasticity mechanisms in neurons, and Rho GTPases, important regulators of the actin cytoskeleton, are involved in these responses. Here, we evaluate if Rho GTPases, specifically rhoA, rac1 and cdc42, are critical in the response to Meth in microglia. Exposing WT mice to the same pattern of Meth administration, we found an increase in the activation of rac1 in the striatum, 15 min following the last administration of Meth. To further explore these results, we then used a conditional mice model for ablation of rac1 in adult microglia ($Rac1^{fl/fl}$:$Cx3cr1^{CreER+}$) and exposed these mutants to the same pattern of Meth administration. We found that rac1 ablation is sufficient to prevent Meth-induced morphological alterations in the striatum. Currently, we are assessing whether ablation of rac1 is also sufficient to prevent the neuroinflammatory response induced by Meth. Overall, we identified rac1 as a novel target of Meth in microglial cells. With these results, we expect to clarify if targeting Rho GTPases may contribute to improving the treatment of addictive disorders.

References

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