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THE ROLE OF RAC1 IN METHAMPHETAMINE-INDUCED NEUROINFLAMMATION

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Abstract:
Methamphetamine (Meth), a powerful psychostimulant, induces detrimental neuroinflammatory responses, in the brain reward system that seem to contribute to maintenance of addictive behaviour. 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. 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 assessed Rho GTPases, specifically rhoA, rac1 and cdc42, activation in 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 (Rac1fl/fl:Cx3cr1CreER+) and exposed these mice to the same pattern of Meth administration. Rac1 ablation was sufficient to prevent Meth-induced morphological alterations in the striatum. Currently, we are assessing the role of rac1 in the behavioural response to Meth, using a locomotor sensitization test. 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.