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Activation Of Melanocortin Receptor 4 With RO27-3225 Attenuates Neuroinflammation Through AMPK/JNK/P38 MAPK Pathway After Intracerebral Hemorrhage In Mice

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Purpose:
Neuroinflammation plays an important role in the pathogenesis of intracerebral hemorrhage (ICH)-induced secondary brain injury. Activation of melanocortin receptor 4 (MC4R) has been shown to elicit anti-inflammatory effects in many diseases. The objective of this study was to explore the role of MC4R activation on neuroinflammation in a mouse ICH model and to investigate the contribution of AMPK/JNK/p38 MAPK pathway in MC4R mediated protection.

Materials and methods:
Adult male CD1 mice (n=189) were subjected to intrastriatal injection of bacterial collagenase or sham surgery. The selective MC4R agonist RO27-3225 was administered by intraperitoneal injection at 1 hour after collagenase injection. The specific MC4R antagonist HS024 and selective AMPK inhibitor Dorsomorphin were administered prior to RO27-3225 treatment to elucidate potential mechanism. Short- and long-term neurobehavioral assessments, brain water content, immunofluorescence staining, and western blot were performed.

Results:
MC4R was expressed by microglia, neurons and astrocytes. Activation of MC4R with RO27-3225 improved the neurobehavioral functions, decreased brain edema, and suppressed microglia/macrophages activation and neutrophils infiltration after ICH. RO27-3225 administration increased the expression of MC4R and p-AMPK while decreasing p-JNK, p-p38 MAPK, TNF-α and lL-1β expression, which was reversed with inhibition of MC4R and AMPK.

Conclusion:
Our study demonstrated that activation of MC4R with RO27-3225 attenuated neuroinflammation through AMPK dependent inhibition of JNK and p38 MAPK signaling pathway, thereby reducing brain edema and improving neurobehavioral functions after experimental ICH in mice. Therefore, the activation of MC4R with RO27-3225 may be a potential therapeutic approach for ICH management.