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Na^+-Dependent Inhibition of Microglial Activity and Its Contribution to Brain Disorders

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Summary

Microglial cells play a fundamental role in the central nervous system. Their activation can often cause neurodegeneration and the inflammatory responses, resulting in brain diseases such as schizophrenia and Alzheimer's disease. Recent studies have revealed that activation of microglia influences blood pressure through brain inflammation. Considering that an increase in Na^+ in cerebrospinal fluid (CSF) precedes hypertension through hypothalamic dysfunction, these suggest the possibility that salt load affects microglial activity and the subsequent systemic abnormalities.

Serum- and glucocorticoid-inducible kinases (SGKs) are associated with important physiological and pathophysiological events. Recent studies suggest SGK1 to participate in inflammatory responses in various types of immune cells. We reported that SGKs are expressed and that they may contribute to inflammatory responses in microglial cells. Here, we investigated the relationship between microglial activation and salt load, which can be caused by contemporary diets, through SGK1, in a microglial cell line, BV-2.

We first employed CRISPR/Cas9 system and created *SGK1*-deleted microglial cells ($SGK1^{-/-}$cells). iNOS protein and TNFα release induced by lipopolysaccharide (LPS) were diminished in $SGK1^{-/-}$ cells. These results indicate that SGK1 regulates activity of inflammatory responses positively. Then, application of additional NaCl (salt load) augmented SGK1 at the protein level. Activation of stress-induced MAPK signals was assessed, and phosphorylation of p38 MAPK and JNK was elevated by salt load. Inhibitors of p38 MAPK and JNK were administrated, and salt load-induced SGK1 protein was attenuated, suggesting that upregulation of SGK1 is, at least in part, regulated by those signaling pathways. Next, we examined whether salt load influences microglial inflammatory responses. When cells were incubated with salt load in advance, LPS-induced expression of iNOS and nitric oxide (NO) production were enhanced. In contrast, LPS-induced TNFα release was attenuated. Levels of both mediators were reduced in $SGK1^{-/-}$ cells. Taken together, these findings suggested that salt load modulates microglial activity and that SGK1 accelerates microglial inflammatory responses.