Tibetan Medicine Suppresses the Hypoxia-Related Inflammatory Responses by Inhibiting Oxidative Stress and NF-κB Activation in Microglia

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論　文　名	Tibetan Medicine Suppresses the Hypoxia-Related Inflammatory Responses by　Inhibiting Oxidative Stress and NF-κB Activation in Microglia （チベット薬は低酸素によるミクログリアにおける酸化ストレスならびに NF-κB 活性化に依存した炎症反応を抑制する）
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論　文　審　査　の　結　果　の　要　旨

Ratanasampil (RNSP) and Rheum tanguticum Maxim. ex Balf. (Rt), are the traditional Tibetan medicines, which have been clinically used in the hypoxia-related disease treatment. However, mechanism underlying the effects of RNSP and Rt on regulating microglia-mediated neruoinflammation is still unknown. In this study, firstly the effects of RNSP on hypoxia-reoxygenation-induced microglia-mediated neuroinflammtion were clarified using MG6 microglia. MG6 cells exposed to hypoxia (1% O2) for 6h, then returning to normoxia (20% O2) for various time points. The pretreatment with 10 μg/ml RNSP significantly meliorated the cytotoxicity of MG6 cells induced by hypoxia-reoxygenation (H6/R12), significantly suppressed the H6/R24-induced upregulation of pro-inflammatory mediators, IL-1β, TNF-α and iNOS and reversed the H6/R24-induced downregulation of anti-inflammatory mediators, TGF-β1 and Arginase-1. In addition, the H/R-induced ROS generation, DNA damage, and IκBα phosphorylation were significantly suppressed by pretreating with RNSP in MG6 cells. Thus, RNSP regulated the H/R-induced inflammatory responses through inhibition of oxidative stress and activation of NFκB in activated microglia. Secondly, the effects of Rt on activated microglia following treatment with 10 nM chromogranin A (CGA) and 10 nM pancreastatin, the endogenous microglial activators present in senile plaques were examined. 10 μg/ml Rt significantly inhibited the production of IL-1β in the CGA-treated organotypic hippocampal slice cultures. In addition, Rt significantly inhibited the productions of IL-1β, TNF-α and nitric oxide in the CGA treated microglia. Furthermore, neutralizing IL-10 antibody significantly canceled the effects of Rt, indicating the effects of Rt mediated by the anti-inflammatory mediator, IL-10 from microglia. In conclusion, the present findings demonstrate that RNSP and Rt directly suppress the microglia-mediated neuroninflammation. Therefore, Tibetan medicines may be beneficial in the prevention and management of Alzheimer's disease.

The paper has included novel data clarifying the anti-inflammatory effects of RNSP and Rt on the microglia-mediated neuroninflammation. Therefore, it could be recommended for a DOCTOR OF PHILOSOPHY in Kyushu University.