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

孟, 婕

氏　　名　：　孟　ジェイ

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

区　　分　：甲

（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）

論　文　内　容　の　要　旨

Hypoxia-induced oxidative stress plays the critical role in the pathogenesis of the neurodegenerative disorders, including Alzheimer's disease (AD). Because oxidative stress causes the damages of lipids, proteins and DNA through the toxic reactive oxygen species (ROS) generation. Thus, oxidative stress has been well accepted to induce the hallmarks of AD, including neuron death as well as microglia-mediated neruoinflammation. 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, such as stroke. However, mechanism underlying the effects of RNSP and Rt on regulating microglia-mediated neruoinflammation is still unknown. In the present study, firstly I clarified the effects of RNSP on hypoxia-reoxygenation-induced microglia-mediated neuroinflammtion using MG6 microglia. MG6 cells exposed to hypoxia (1% O_2) for 6h, then returning to nomoxia (20% O_2) for various time points. The pretreatment with RNSP significantly meliorated the cytotoxicity of MG6 cells induced by hypoxia-reoxygenation (H6/R12) at 10μg/mL, 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, I clarified the effects of Rt on activated microglia following treatment with

chromogranin A (CGA, 10 nM) and pancreastatin (10 nM), the endogenous microglial activators present in senile plaques. Rt (10 μg/ml) significantly inhibited the production of IL-1β in the CGA treated organotypic hippocampal slice cultures. Furthermore, neutralizing IL-10 antibodies significantly canceled the effects of Rt, indicating the effects of Rt was mediated by 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.