PE10) AMPK/Nrf2 Signaling is Involved in the Anti-Neuroinflammatory Effect of Novel Compound from *Petasites japonicus* in Microglia against LPS

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1. Introduction

Microglia are resident macrophages in the brain that play a prominent role in the first line of immune defense and the neuroinflammatory response. In addition, microglia provide support for the maintenance of brain homeostasis under normal conditions. However, several evidences suggest that activated microglia play a crucial role in the neuropathological course of several neurodegenerative diseases. Mounting evidence indicates that abnormal activation of microglia could increase neurotoxicity through neuroinflammatory and cytotoxic factors stimulated with amyloid beta, glutamate, and lipopolysaccharides. Hence, the identification of natural compounds that inhibit abnormal microglia activation is highly beneficial in the search for therapeutic agents for neuroinflammation-triggered neurodegenerative diseases.

2. Materials and Method

Microglia were investigated by analyzing cell viability, expression of molecules related to neuroinflammatory response, and using biochemical techniques, flow cytometry, and western blot assays.

3. Results and Discussion

The purposes of this study are to consider the effect of Petatewalide B on the LPS-stimulated microglia and to explore the role of AMPK/Nrf2 signaling pathway in the anti-neuroinflammatory effects of Petatewalide B. We found that pretreatment with Petatewalide B strongly alleviated the IL-1b, IL-6 and TNF-α production in LPS-stimulated microglia. Petatewalide B also suppressed overexpression of iNOS, and NO overscreaction in microglia exposed to LPS. AMPK/Nrf2 signaling pathway plays a considerable role in the induction of anti-neuroinflammatory responses. The results of mechanistic studies have shown that Petatewalide B increased the nuclear Nrf2 translocation, expression of HO-1 and NQO1 in dose dependent manner. Furthermore, Petatewalide B also up-regulated phosphorylation of AMPK in dose-dependent manner. We next evaluated whether blocking the AMPK phosphorylation using inhibitor would have a critical effect on anti-neuroinflammatory responses. We found the AMPK phosphorylation was associated with the nuclear Nrf2 translocation and elevated expression of HO-1 and NQO1. Our data also show that AMPK inhibitor pretreatment significantly reversed Petatewalide B-attenuated iNOS promoter activity in LPS-stimulated microglia.

4. References

Wang et al., 2013, A Dietary polyphenol resveratrol acts to provide neuroprotection in recurrent stroke models by regulating AMPK and SIRT1 signaling, thereby reducing energy requirements during ischemia, Eur. J. Neurosci., 37(10), 1669-1681.