α-Synuclein-induced production of inflammatory mediators through Toll-like receptors in brain pericytes

Shinya Dohgu[1], Minami Akizuki[1], Atsushi Kobayashi[1], Shunya Morita[1], Fuyuko Takata[1], Junichi Matsumoto[1], Takuro Iwao[1], Atsushi Yamauchi[1], Kazunori Sano[2], Yasufumi Kataoka[1]

[1]Dept. Pharmaceut. Care & Health Sci., Fac. Pharmaceut. Sci., Fukuoka Univ., [2]Dept. Physiol. & Pharmacol., Fac. Pharmaceut. Sci., Fukuoka Univ.

The pathological hallmark of Parkinson disease (PD) is a widespread distribution of the aggregated α-synuclein (α-Syn) proteins in the inclusions known as Lewy bodies. Exogenous α-Syn secreted from neurons could induce inflammatory responses including microglial activation. This activated microglia was observed in the substantia nigra of patients with PD. We previously reported that pericytes, one of the blood-brain barrier (BBB) constituent cells released various inflammatory mediators in response to monomeric α-Syn. Here, we investigated whether Toll-like receptors (TLRs) mediated the α-Syn-induced production of inflammatory mediators in pericytes. In response to monomeric α-Syn, pericytes released the highest levels of IL-1β, IL-6 and MMP-9 than the other cell types of the BBB (brain endothelial cells and astrocytes). TAK242 (a TLR4 inhibitor, 5 μM) but not CU CPT22 (a TLR1/2 inhibitor, 5 μM) attenuated the increased mRNA levels of IL-1β, IL-6, MMP-9 and TNF-α induced by a 24-hr exposure of α-Syn (50 μg/mL). The initial uptake of α-Syn by pericytes was inhibited by CU CPT22 and TAK242. These results suggest that TLR4 may mediate α-Syn uptake and subsequent production of inflammatory mediators in pericytes.

Copyright © The Japanese Pharmacological Society