Neuroinflammation aggravates spreading alpha-synuclein oligomerization in Lewy body dementia mice

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[Background and Objectives] Accumulation and aggregation of alpha-synuclein in mid brain and cortex are causative for neuronal death in Lewy body with dementia (LBD). We found that the pathology is partly regulated by long-chain polyunsaturated fatty acids (LCPUFAs) such as arachidonic acid (AA) (1, 2) and brain inflammation. For example, fatty acid binding protein 3 (FABP3, H-FABP) is critical for AA-induced alpha-synuclein oligomerization (1, 2). However, the pathophysiological relevance of FABP3 and neuroinflammation remains unclear in alpha-synuclein spreading mechanism. We here documented the effect of neuroinflammation in the alpha-synuclein fibril-injected LBD mice. **[Methods]** To address the effects of neuroinflammation in alpha-synuclein spreading, we developed alpha-synuclein spreading model mice with or without LPS administration. The alpha-synuclein fibrils are injected into the dorsolateral striatum and its spreading was assessed by immunohistochemistry. **[Results]** At two months after alpha-synuclein fibril injection, mice exhibited cognitive impairment in novel object recognition task. The phosphorylated alpha-synuclein was detected in the cerebral cortex within two months. The single administration of lipopolysaccharide (LPS) before alpha-synuclein injection aggravated the phosphorylated alpha-synuclein accumulation. The neuroinflammation-induced morphological change in astrocytes was also evident in LPS-treated group. **[Conclusions]** The alpha-synuclein injection into striatum in mice is useful for screening LBD therapeutics which inhibit spreading and aggregation of alpha-synuclein. The LBD pathology is aggravated by neuroinflammation induced by LPS. This research is partially supported by AMED (19dm0107071)(http://lewybody2016.jp/). The authors declare no conflict of interests. (1) Shioda N et al., *J Bilo Chem* 2014;289:18957-18965. (2) Cheng A et al., *Brain Res*. 2019;1807:1980-197.