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Novel disease-modifying drugs inhibiting alpha-synuclein aggregation in Parkinson's disease model mice

Backgrounds: Accumulation and aggregation of alpha-synuclein in dopaminergic neurons is one of pathogenesis of Parkinson's disease (PD), and its formation is partly regulated by long-chain polyunsaturated fatty acids (LCPUFAs) such as arachidonic acid (AA). Fatty acid binding protein 3 (FABP3, H-FABP) is critical for AA transport and metabolism in the brain. We recently demonstrated that FABP3 is highly expressed in dopaminergic neurons, especially in the substantia nigra pars compacta (SNpc). However, the pathophysiological relevance of FABP3 in PD remains unclear.

Methods: Wild and FABP3 KO mice were treated with 1-methyl-1,2,3,6-tetrahydropyridine (MPTP) and investigated its neurotoxicity in the SNpc.

Results: FABP3 KO mice were resistant to MPTP-induced dopaminergic neurodegeneration and motor deficits. Importantly, MPTP-induced alpha-synuclein accumulation in SNpc was attenuated in FABP3 KO mice compared with that in wild-type mice. In addition, we found that FABP3 overexpression promoted AA-induced alpha-synuclein oligomerization and induced cell death in PC12 cells. Over expression of FABP3 mutant protein lacking fatty-acid binding region did not promote AA-induced alpha-synuclein oligomerization and cell death. Finally, novel FABP3 ligands ameliorated MPTP-induced alpha-synuclein accumulation/aggregation and rescued dopamine neurons from degeneration in MPTP-treated mice.

Conclusion: Taken together, the formation of oligomers of alpha-synuclein is partly regulated by FABP3 through AA binding and metabolism in dopaminergic neurons, contributing to dopaminergic neuronal death seen in PD. We developed FABP ligands to develop as disease-modifying drugs for synucleinopathies in PD.

Biography

Kohji Fukunaga first discovered calcium/calmodulin-dependent protein kinase II (CaMKII) from brain in 1982. He received his PhD degrees from Kumamoto University School of Medicine in 1985. During 1988 to 1990, he worked as Research Fellow in Vanderbilt University (HHMI) under Professor TR Soderling. In 2002, he was appointed a Professor and Chairman in the faculty of graduate school of pharmaceutical sciences. He was Editor-in-Chief of Journal of Pharmacological Sciences (Elsevier) since 2012. He is interested in disease-modifying drug development for neurodegenerative disorders and psychiatry diseases such as autism and mental retardation.

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