Fatty acid-binding protein ligands inhibit α -synuclein pathology in Parkinsonian mice

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[Background] Aggregation of α -synuclein (α S) is promoted by polyunsaturated fatty acids such as arachidonic acid (AA). Fatty acid-binding protein 3 (FABP3) is crucial for AA transport in the brain. We previously reported that FABP3 aggravates AA-induced α S oligomerization and cell death (Shioda et al, J Biol Chem, 2014). We here developed novel FABP3 ligands, MF series, and addressed whether these ligands could suppress α S pathology and Parkinsonism in mice.

[Methods] Mice treated with 1-methyl-1,2,3,6-tetrahydropyridine (MPTP) were chronically administrated with MF1 (high affinity for FABP3), MF4 (low affinity for FABP3), or L-DOPA.

[Results] MPTP-induced motor deficits were ameliorated by MF1 like L-DOPA. On the other hand, α S accumulation in dopaminergic (DA) cell bodies and neuronal loss in the substantia nigra (SN) of MPTP-treated mice were ameliorated by MF1, but not by L-DOPA nor MF4. Finally, MF1 also inhibited α S oligomerization and hyperphosphorylation in the SN/VTA of MPTP-treated mice.

[Conclusion] MF1 but not L-DOPA suppressed α S pathology, thereby rescuing MPTP-induced DA neuronal loss and Parkinsonism. We propose novel FABP3 ligands as a candidate for synucleinopathies.