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Oral Sessions

Caveolae formation is critical for fatty acid-binding protein 3-dependent uptake of α -synuclein in dopaminergic neurons

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Accumulation of α -synuclein protein into dopaminergic neurons is a pathological hallmark of Parkinson's disease. We previously demonstrated that fatty acid-binding protein 3 (FABP3) is critical for α -synuclein uptake into dopaminergic neurons and its propagation. FABP3 is abundant in dopaminergic neurons and interacts with the dopamine D2 receptor largely distributed in caveolae. In this study, we newly investigated the significance of caveolae formation in the uptake process of α -synuclein, coupled with FABP3. To disclose this issue, we employed mesencephalic neurons derived from dopamine D2-null knockout (D2-null) and FABP3 knockout (FABP3^{-/-}) as well as wild type C57BL6 mice, and treated with dynasore, a dynamin inhibitor, or caveolin-1 siRNA, and analyzed the ability of the uptake of fluorescence-conjugated α -synuclein monomer and fibrils. Our immunocytochemistry revealed that D2 receptors are co-localized with FABP3. Importantly, TH⁺ D2-null neurons did not take up α -synuclein monomers. Moreover, exposure to dynasore, caveolin-1 knockdown, and the deletion of α -synuclein C-terminus abolished the uptake. D2 receptors and FABP3 were also essential for the uptake of α -synuclein fibrils. Intriguingly, D2 receptors and accumulated α -synuclein fibrils were well co-localized. These data indicate that caveolae formation with the D2 receptors coupled with FABP3 is critical for the uptake of α -synuclein via its C-terminus in dopaminergic neurons, suggesting a novel pathogenic mechanism of synucleinopathies including Parkinson's disease.