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“Dysregulation of PLA2G6 activity induce degeneration in astrocytes in culture”

Deleterious effects produced by the removal or failure to curb PLA2G6 activity from brain cells include neuroaxonal degeneration with iron accumulation, which is lethal during childhood and may induce Parkinsonian-like disease in adulthood (Guo et al, 2018. *Front Neurol.* 9: 1100). Recently, it was found that fibroblasts of idiopathic or sporadic PD patients showed impaired store-operated calcium entry (SOCE) (Zhou, et al 2016. *Nature Communications* volume 7, Article number: 10332). SOCE controls the activity of Calmodulin, a negative regulator of PLA2G6, so the impairment of intracellular calcium flux suggests a role for PLA2G6 in the PD pathology. We determined that the silencing or overexpression of PLA2G6 induce a decreased content of DHA containing phospholipids concomitantly with a reduced amount of RvD5, a derivative of DHA, by Mass Spec. To determine the damage produced by the dysregulation of PLA2G6 in dopaminergic neurons, a culture of pluripotent cells in vitro differentiated into human dopaminergic neurons was exposed to Bromoenol lactone (BEL), an inhibitor of PLA2G6, and SKF96365, an inhibitor of the store-operated calcium entry (SOCE), in the presence or absence of lipid mediators derived from docosahexaenoic acid (DHA), eicosapentanoic acid (EPA), and arachidonic acid (AA). Immunocytochemistry targeting Tyrosine Hydroxylase (TH) and imaging analysis in IMARIS was used to determine the cell death and integrity of the surviving neurons. Maresin 1, RVD1, and RVD5, bioactive lipids derived from DHA, rescued the deficits in PLA2G6 activity induced by BEL. PLA2G6 is proposed to hydrolyze DHA to be converted into Maresin1, RVD1, and RVD5. LipoxinA4, a derivative of AA, and RVE1, a derivative of EPA, did not rescue PLA2G6 deficiency. Maresin 1 strongly reversed the neurodegeneration induced by SKF96365 and, to a lesser extent, RVD1. Future studies are required; however, these results suggest a role of PLA2G6 dysfunction in dopaminergic neurons and point to bioactive lipid messengers as candidate molecules to be used therapeutically to prevent or halt the neurodegeneration induced by PLA2G6 in PD.