Inhibitors of Polyisoprenylated Methylated Protein Methyl Esterase (PMPMEase) cause Neurodegeneration by altering Microtubules and Gβγ in PC12 Cells

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Inhibitors of Polyisoprenylated Methylated Protein Methyl Esterase (PMPMEase) cause Neurodegeneration by altering Microtubules and Gβγ in PC12 Cells

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Neurodegeneration, a progressive loss of nerve cells (neurons), occurs in many neurological disorders including Alzheimer’s disease, Parkinson’s disease, Schizophrenia and drug addiction. Disruption of Microtubules (MTs), a major component of cytoskeleton and aggregation of proteins associated with them is the hallmark of neurodegeneration. Gβγ, an important component of G protein signaling has been shown to induce neurite outgrowth of PC12 cells by interacting with microtubules. The goal of the present study is to understand whether interfering with Gβγ-MT mediated pathway causes neurodegeneration. Because prenylation of γ subunits is important for the interaction of Gβγ with MTs, we used inhibitors (L-23 and L-28) for PMPMEase (polyisoprenylated methylated protein methyl esterase), an enzyme involved in the prenylation pathway to conduct the study. PC12 cells were treated with NGF over the course of three days, followed by overnight treatment with L-28 or L-23. Confocal microscopy was used to analyze the results. We found that more than 70% of PC12 cells exhibit neurite formation in the presence of NGF. Neurite formation was not affected significantly in the presence of PMSF or L-23 (100mM). L-28 (10μM), on the other hand significantly reduced neurite formation as well as MTs and Gβγ labeling. In addition, severe cellular degeneration was observed (more than 60% areas in the slides). The result suggests that inhibitors of PMPMEase could be used as valuable tools to study the mechanism of neurodegeneration and design strategies to develop effective drugs against drug addiction and other neurodegenerative disorders.

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