THE ANTI-PARKINSONIAN DRUG SELEGILINE (R(-)-DEPRENYL) INHIBITS THE NUCLEATION PHASE OF α−SYNUCLEIN AGGREGATION.

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Parkinson`s disease (PD) is a chronic disorder characterized by the formation of intraneuronal inclusions called Lewy bodies mainly composed of α-synuclein (α-syn), a natively-unfolded protein with unknown function. Its implication in PD is due to the fact that two mutations (A30P and A53T) are linked to early-onset forms of PD. Selegiline (R(-)-deprenyl) is a noncompetitive monoamino oxidase-B inhibitor which has neuroprotective effects. It has been administered to PD patients either as monotherapy or in combination with L-dopa. However, its mechanism is unknown. We evaluated the effect of Sel in the *in vitro* aggregation of A30P either in the presence or absence of amyloid seeds (small fibrils acting as a nucleus). We observed that Sel (1:0.5 or 1:1.5 protein:Sel ratio) delays fibril formation by enhancing the nucleation phase. Sel effects on fibril formation are abolished when previously added seeds are present, suggesting that Sel interferes with nucleus formation, and is dependent of the A30P:Sel ratio. This inhibitory effect of Sel on the nucleation phase was also evaluated by using another amyloidogenic, natively-unfolded protein, Sup35, but in this case, the effect of Sel was not abolished when Sel was added after the end of the lag phase. We also observed that Sel in combination with dopamine (DA) favors fibril formation. Currently, we are mapping A30P-Sel interaction by NMR. We observed that in the presence of Sel (1:2 ptn:Sel ratio), very little changes occur in the HSQC spectra of the isotopically labeled protein. These results suggest that in the presence of DA, Sel favors the conversion of the toxic protofibrils into the non-toxic fibrils, alleviating the dopaminergic neurons from toxic effects. In the non-dopaminergic neurons, Sel would slow down the fibrillation process, probably by forming large spherical aggregates.