The effect of tyrosine hydroxylase on α-synuclein aggregation

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INTRODUCTION: Parkinson’s disease (PD) is a common neurodegenerative disorder. It is the loss of the dopaminergic neurons in the substantia nigra that leads to the motor dysfunction associated with PD. One of the major pathological features of PD is the development of intracytoplasmic inclusions called Lewy bodies. α-synuclein (α-Syn) is a major component of Lewy bodies. It is believed that aggregation of α-Syn has a significant role in the death of the dopaminergic neurons. The selective death of the dopaminergic neurons in PD suggests that the catecholamine system may play a role in the disease pathogenesis. Tyrosine hydroxylase (TH) is the rate limiting enzyme that controls catecholamine synthesis. It has been shown that TH can directly bind to α-Syn. This raised the possibility that TH may influence the aggregation of α-Syn. MATERIAL AND METHODS: Recombinant human TH isoforms and α-Syn were expressed in E-coli and the proteins were purified. Their interaction was examined by co-incubation at 37°C for up to 18 hours. TH induced the formation of an SDS resistant α-Syn multimer of 90-100 kDa. This complex was only found in the pellet after centrifugation at 18,000 x g for 20min at 4°C. Incubation of α-Syn with a series of control proteins did not generate the 90-100 kDa α-Syn complex, indicating that it was a specific effect of TH. RESULTS AND DISCUSSION: The formation of this α-Syn complex was found to be TH concentration and time dependent (up to 18 hours). When α-Syn was incubated with the four human TH isoforms, the SDS resistant α-Syn multimers were generated with all isoforms but size of the multimers reflected sizes of each of the human TH isoforms. Analysis of α-Syn deletion mutants indicated a critical role of the NAC region of α-Syn in the aggregation process. It was further shown that mutant α-Syn molecules can alter the aggregation process. In particular the A30P and A53T mutants show increased formation of the TH/alpha-synuclein SDS resistant complex and generate larger aggregates. CONCLUSION: This data suggests that the aggregation of α-Syn is influenced by the presence of TH and therefore the aggregation process in TH containing neurons may be different from that in other neurons.