Modulation of alpha-synuclein aggreagation by dopamine analogs

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Parkinson's disease is a fatal neurodegenerative movement disorder, which affects an estimated four million people worldwide [1]. However, no known cure exists. The action of dopamine on the aggregation of α-synuclein (α-syn) is associated with the onset of the pathogenesis of the disease and recent studies have revealed that dopamine and its analogs can inhibit aggregation of α-syn [2-6]. Here, we have used a combined computational and experimental/microscopical approach to investigate the effect of dopamine mimickers on the aggregation of α-syn.

Using computational methods, small molecules were found in the ligand.info database [7], which are structurally and electrostatically similar to dopamine. Molecular dynamics simulations showed that binding to α-syn is much weaker than that of dopamine, which inhibits fibrillation [8]. Five of the identified molecules were tested in an *in vitro* fibrillization assay and analyzed by high-resolution atomic force microscopy (AFM) (Figure 1) and transmission electron microscopy (TEM) (Figure 2).

Whilst complete inhibition of the assembly of α-syn fibrils was not observed, both AFM and TEM did hint that all of the predicted molecules had some effect on the aggregation process, but to a varying extent. These results are consistent with the prediction from the MD calculations.

Our results suggest that a detailed *in silico* and *in vitro* microscopy approach may provide a more rational strategy, than currently employed, to developing potential therapies that are needed to combat this fatal disease.

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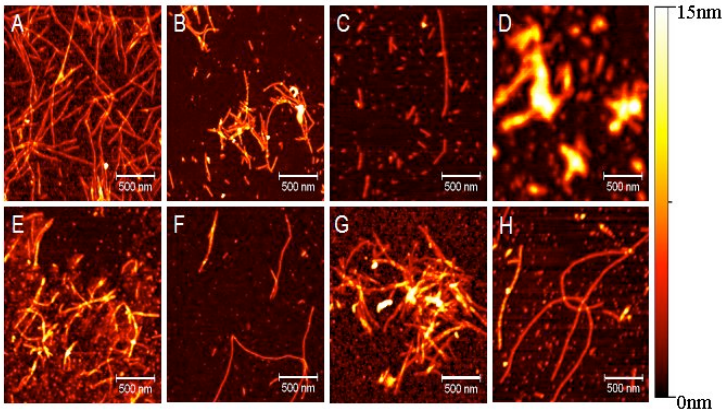

Figure 1. AFM images of the aggregation of α-syn in the presence of the predicted compounds. Images were acquired after 100 hrs of incubation and deposited on a freshly cleaved mica surface. All images are plotted using the same color scale as shown on the right hand side. (A-B) 5-hydroxyindole; (C) 4-(2-aminoethyl) aniline; (D-E) 6-aminoindole; (F) 2-amino-4-tert-butylphenol; (G-H) tyramine.

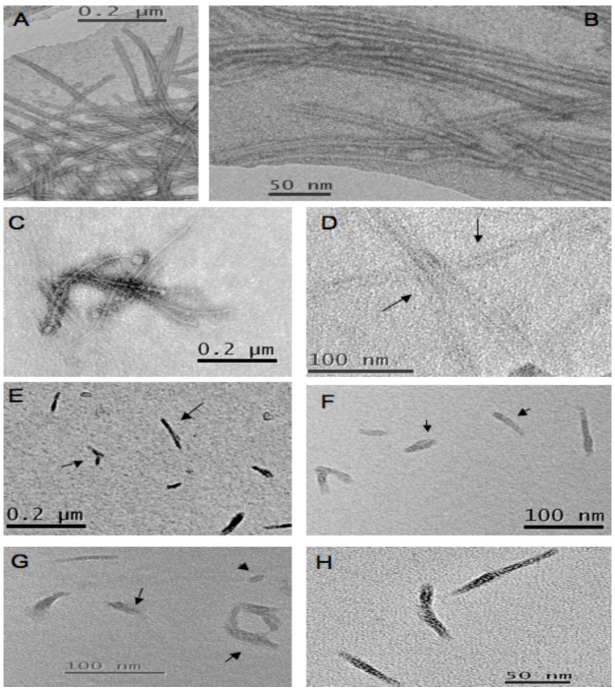

Figure 2. High power TEM micrographs showing the effect on the aggregation of α-syn in the presence of two of the predicted compounds, 6-aminoindole and 5-hydroxindole, after 100 hrs of incubation. Whilst both samples revealed similar kinetic data, typical of a nucleation /polymerization process, TEM revealed contrasting data. (A and B) α-syn only; (C and D) 5-hydroxyindole; and, (E-H) 6-aminoindole.

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