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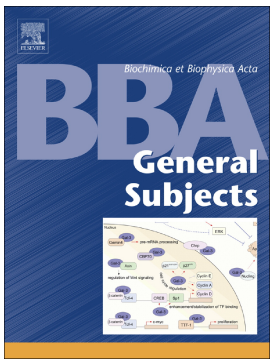

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Integrating *in vitro* and *in silico* approaches to evaluate the "dual functionality" of palmatine chloride in inhibiting and disassembling Tau-derived VQIVYK peptide fibrils

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ABSTRACT

Background: Alzheimer's disease (AD) is the most common neurodegenerative disorder which is characterized by the deposits of intra-cellular tau protein and extra-cellular amyloid-β (Aβ) peptides in the human brain. Understanding the mechanism of protein aggregation and finding compounds that are capable of inhibiting its aggregation is considered to be highly important for disease therapy.
Methods: We used an *in vitro* High-Throughput Screening for the identification of potent inhibitors of tau aggregation using a proxy model; a highly aggregation-prone hexapeptide fragment ^{306}VQIVYK^{311} derived from tau. Using ThS fluorescence assay we screened a library of 2,401 FDA approved, bio-active and natural compounds in attempt to find molecules which can efficiently modulate tau aggregation.
Results: Among the screened compounds, palmatine chloride (PC) alkaloid was able to dramatically reduce the aggregation propensity of PHF6 at sub-molar concentrations. PC was also able to disassemble preformed aggregates of PHF6 and reduce the amyloid content in a dose-dependent manner. Insights obtained from MD simulation showed that PC interacted with the key residues of PHF6 responsible for β-sheet formation, which could likely be the mechanism of inhibition and disassembly. Furthermore, PC could effectively inhibit the aggregation of full-length tau and disassemble preformed aggregates.
Conclusions: We found that PC possesses "dual functionality" towards PHF6 and full-length tau, i.e. inhibit their aggregation and disassemble pre-formed fibrils.
General significance: The "dual functionality" of PC is valuable as a disease modifying strategy for AD, and other tauopathies, by inhibiting their progress and reducing the effect of fibrils already present in the brain.