A novel flavonoid-based inhibitor of protein SUMOylation, 2-D08 has a dual anti-aggregatory and protective role against amyloid β fibril formation and neurotoxicity

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Background: Flavonoids form a diverse class of naturally occurring polyphenols ascribed various biological activities, including inhibition of amyloid β ($A\beta$) fibrillisation and neurotoxicity. In this study we evaluated the neuroprotective and anti-aggregative properties of the flavones transilutin, quercetin and the novel semi-synthetic flavone and SUMOylation inhibitor, 2-D08 using neuronal PC-12 cells exposed to $A\beta$ 1-42 and in mouse cortical neural stem cells (mNSC).

Methods: Flavone effects on neuronal viability were assessed morphologically using live cell imaging and morphometric analysis in mNSC, and biochemically in PC-12 cells using the MTT assay following incubation with $A\beta$ (0-2 microM), alone or in the presence of each flavone (10-100 microM) for 48 hr. Effects of each flavone on $A\beta$ fibril formation and aggregation were directly assessed using the Thioflavin T (ThT) fluorometric assay and transmission electron microscopy (TEM) over 48 hr.

Results: 2-D08 and transilutin (10-100 microM) evoked concentration-dependent inhibition of neurotoxicity elicited by $A\beta$ (0-2 microM). Quercetin was neuroprotective at the low concentration (10 microM), but evoked intrinsic neurotoxicity at higher concentrations (50-100 microM). Morphometric imaging analysis demonstrated that 2-D08 and transilutin were both non-toxic to mNSCs and confirmed that quercetin was neurotoxic at the higher concentrations. The neuroprotective effects were associated with a marked inhibition of $A\beta$ fibrillisation, as evidenced by attenuated ThT fluorescence kinetics and microscopic evidence of both altered and diminished $A\beta$ aggregate and fibril morphology.

Conclusions: These findings highlight the neuroprotective role of select flavones on $A\beta$ -mediated toxicity associated with an inhibition of $A\beta$ fibrillisation. In particular, the efficacy of the novel flavone 2-D08 in this regard may direct further lead development with multiple biological actions targeting neurodegeneration in Alzheimer's disease.