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Identifying and Testing Novel Sigma-1 Receptor Ligands for Neurodegenerative Diseases.

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Neurodegenerative diseases (NDs) are becoming more common due to increased life expectancy. There is currently no drug that can slow or halt the progression of Alzheimer's disease (AD). The sigma-1 receptor (σ1R) is a chaperone protein located at the junction of the endoplasmic reticulum (ER) and the mitochondria in a region called the mitochondrial-associated membrane (MAM). Activating the σ1R leads to the chaperoning of ion channels and other proteins involved in cell survival. One of its primary functions in neuron cells is the chaperoning of the IP_3 receptor at the MAM during cellular stress, leading to Ca^{2+} shuttling into the mitochondria, stimulating ATP production, and leading to cell survival, growth, division, or differentiation. The σ1R is an interesting target for treating NDs such as AD since its activation provides various cell survival benefits, including reducing ER stress and regulating autophagy. There are several σ1R drugs currently undergoing clinical trials for NDs.

This study aimed to evaluate the σ1R activity of dipentylammonium (DPA), which has previously been shown to bind to the receptor with nanomolar affinity and have antidepressant-like effects. Furthermore, we hoped to find other novel σ1R ligands.

We have used *in vitro* (PC-12 and HT-22 cells) and *in vivo* (*C.elegans*, wild type, and mutated strains) techniques to evaluate various σ1R ligands, particularly DPA. PC-12 cells were cultured in 6-well plates coated with poly-d-lysine and treated with NGF (10 ng/ml) with or without DPA. The resulting neurites were photographed and measured using Image J. The prevention of damage to 7-day NGF (10 ng/ml) differentiated PC-12 neurites caused by 10 μM $A\beta_{(25-35)}$ by DPA was measured by the MTT assay, and the measurement of neurite length 24 hours after 10 μM $A\beta_{(25-35)}$ treatment. Immunoprecipitation using an antibody specific to the σ1R was used to measure colocalization with Binding Immunoglobulin Protein (BiP) visualized using western blotting with a BiP-antibody.

We have shown that the novel σ1R ligand DPA activates the σ1R, causing the dissociation of BiP from the σ1R in HT-22 cells and potentiated NGF-induced neurite outgrowth in PC-12 cells at concentrations between 1 and 100 μM.

Furthermore, we used the σ1R-ve mutant strain of *C.elegans* to study the effect of DPA and other potential σ1R ligands and compared them to other known σ-ligands such as PRE084 and fluoxetine.

Fluoxetine (5 mM) significantly extends the median lifespan of wild-type *C.elegans* (from 14 to 16 days $p < 0.05$), whereas DPA does not. Fluoxetine (from 9 to 10 days, $p < 0.05$) and DPA (5mM) (from 9 to 10 days, $p < 0.001$) could extend the median lifespan, and DPA could prevent paralysis of mutant human Aβ over-expressing *C.elegans* strains. Neither drug increased the lifespan of the σ1R KO worm.

Modeling of the *C.*elegans receptor compared to the human shows a similar structure despite the differences in sequence. Docking analysis of the σ1R with DPA and other σ1R ligands suggests that DPA may act as an agonist via both the traditional ligand binding site and as an allosteric activator of the σ1R.

In conclusion, we have demonstrated that DPA acts via σ1R activation, which may be a potential starting point for therapeutic development in targeting NDs. Furthermore, we have identified that the σ1R is required for the lifespan-extending properties of fluoxetine in *C.elegans*.

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