SG-2: A promising lipolytic and pro-autophagic hit-compound to treat Alzheimer's disease

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Abstract

The identification of efficient pharmacological tools for treatment of Alzheimer's disease (AD) represents one of the main challenges of our century. Due to the complex etiopathology and the several biological processes resulting impaired in AD, the drug discovery process should focus on the development of new chemical entities able to target this multi-faceted impairment. We designed and synthetized a new analogue of 3-iodothyronamine, namely SG-2, which shares an interesting pleiotropic activity. Within this study, we explored SG-2 ability to promote beneficial effects in a C. Elegans model of AD, using a novel technique developed at Cambridge University, which exploits an automated system of high-resolution cameras to evaluate in parallel the motility of a huge number of nematodes (up to 5000 at time) in response to drug administration. Our results showed that SG-2 can promote lifespan and restores motility of worms back to the wildtype.

Introduction

Alzheimer's disease (AD) is a progressive pathological condition which affects multiple brain functions and several physiological pathways such as lipid and glucose metabolism, proteins phosphorylation and autophagic flux. This multi-faceted impairment leads to an aberrant protein aggregation and uncontrolled neuronal cell death, resulting in the well-known decline of cognitive functions. Today, there is a worldwide effort to find better ways to treat AD, delay its onset, and/or prevent it from developing. In this context, the improvement in up-to-date approaches and techniques to investigate new agents capable of interfering with AD progression still represents an urgent entail to be solved. Recently, we have designed and characterized a new class of synthetic small molecules bearing a biphenylmethane scaffold, namely SG compounds, to target the multi-faceted impairment which characterizes AD.[1,2] Among them, SG-2 was identified as a promising hit-compound able to promote a rebalancing of autophagic flux, endowed of neuroprotective effects, and able to induce a metabolic reprogramming to favor lipid consumption.[3]

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Materials and Methods

To assess SG-2 potential in contrasting the progression of AD conditions, we tested it using a novel technique developed at Cambridge University which exploits an automated system of high-resolution cameras to evaluate in parallel the motility of a huge number of nematodes (up to 5000 at time) in response to drug administration. [4]

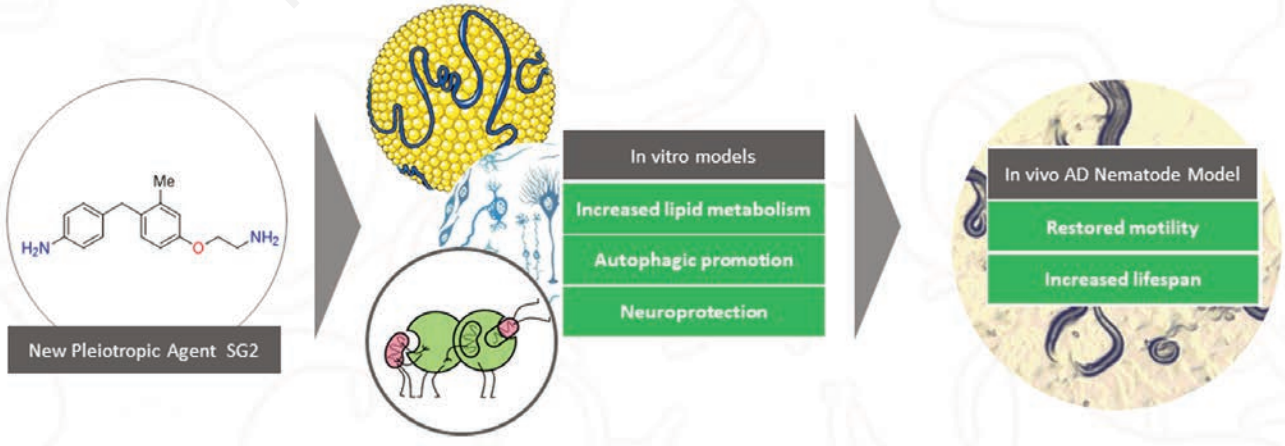

Figure 1. Effect of SG-2 in *in vitro* models and *in vivo* AD Neumatode model.

Results

Our results showed that SG-2 can alter the decline of the morbidity of AD restoring nematode's motility back to the wild type when administrated to C. Elegans at a concentration of 1μM. Moreover, we observed an enhancement of nematodes' lifespan when worms were treated with SG2 at the 4th day of life, *i.e.* when Aβ plaques are already formed. Surprisingly, no direct effect on Aβ formation has been observed *in vitro*. This result let us to speculate that the ability of SG2 to promote autophagy and induce lipid metabolism could represent a new strategy to delay or halt the progression of AD.

Conclusions

We identified a novel lipolytic and pro-autophagic hit-compound able to promote beneficial effects in several AD models. Future studies are planned to outline the specific mechanism of action of this pleiotropic agent in order to validate the potential of SG2 as novel therapeutic tool for treatment of AD.

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