PHOSPHODIESTERASE 7 INHIBITOR S14 REGULATES BRAIN AMYLOID-B LEVELS IN APP/PS1 MICE

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Introduction: Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by elevated levels of amyloid beta-peptide (Ab), in the brain which promotes local neuroinflammatory responses.

Aims: Phosphodiesterase 7 (PDE7) inhibitors are able to regulate the inflammatory response through cAMP signaling cascade and thus could play a central role in neurodegenerative disease, including AD. The aim of this work is to test the efficacy of this new class of therapeutic agents in an animal model of AD.

Methods: As pharmacological tool, we used our own PDE7 inhibitors. Among these, the quinazoline derivative called S14 has sown ability to increase cAMP levels, and an interesting anti-inflammatory property within a therapeutic window. Using parallel artificial membranes methodology, we can predict that this compound is capable of crossing the blood-brain barrier. We use this compound to evaluate their efficacy in the double mutant amyloid precursor protein/presenilin 1 (APP/PS1) mice.

Results: In this study we show that daily intraperitoneal administration of this PDE7 inhibitor during 1 month reduces Ab burden in the hippocampus and cerebral cortex from APP/PS1 mice. This decrease in Ab levels observed was accompanied by a reduction in reactive astrocytes expressing GFAP in these cerebral areas. Moreover, the amount of reactive astroglia associated with Ab plaques appeared significantly increased suggesting modulation of local inflammatory processes and phagocyte attack to participate in the processing of Ab.

Conclusions: Our preliminary findings led us to propose the potential therapeutic value of PDE7 inhibitors, specifically of S14, in neurodegenerative diseases, mainly in AD-related amyloidosis.