The Role Of Transient Receptor Potential Ankyrin 1 (TRPA1) As A Target In Alzheimer's Disease.

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INTRODUCTION: TRPA1 is a member of the transient receptor potential (TRP) superfamily well known to be expressed in the spinal horn and other tissues, and recognized to mediate a diversity of pain and inflammatory states. Alzheimer's disease (AD) is a degenerative disease characterized by accumulation of both tau and Aβ peptides, and for having the disease course affected by progressive oxidative stress and brain inflammation. Products of inflammation, notably reactive oxygen species (ROS) and Ca^{2+} are augmented during AD initiation and progression. Intriguingly, these are endogenous molecules known to be able to activate TRPA1. **OBJECTIVES:** However, the possible role of TRPA1 in AD pathogenesis is still unknown and we aimed to investigate it. **MATERIAL AND METHODS:** We used different approaches (primary cell culture treated with AβOs, AβOs-injected Swiss mice, 5XFAD TG AD mouse model and AD human brains; including respective controls to each) and also two distinct preparations $AβOs_{40}$ and $AβOs_{42}$. Besides behavioral assessments, a variety of molecular and biochemical techniques, namely the evaluation of ROS formation, mitochondrial

membrane potential determination, immunocytochemistry, immunofluorescence in brain slices, western blotting, co-immunoprecipitation, electron microscopy, and others. **RESULTS AND DISCUSSION:** Here we report TRPA1 is largely expressed in neurons and microglia in the brain. TRPA1 is relevant to AβOs binding and AβOs-induced oxidative stress/death in neuronal cells. We demonstrated the correlation between the up-regulation and spreading of both AβOs and TRPA1, in all the approaches used. Herein, we are also reporting TRPA1 augmented expression in the microglia and its possible role in the inflammation process. Of note, TRPA1 selective antagonist (HC030031) oral treatment improved memory deficits in the different mouse models of approach. Besides, reduced Aβ burden in plaques and oligomers with consequent improvement on AβOs-induced synaptic loss. **CONCLUSION:** We propose TRPA1 as novel potential target to AβOs-induced toxicity and further memory impairment, being essential to AD pathogenesis.

Key words: TRPA1 channel, AβOs-toxicity; Alzheimer's disease;

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