Targeting protein SUMOylation changes in experimental Alzheimer's disease

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Alzheimer's disease (AD) is a neurodegenerative disorder characterized by the progressive loss of neurons, deposition of insoluble aggregates of two proteins in the brain, amyloid-β (Aβ) and the microtubule associated protein tau. Synaptic deterioration occurs early in the disease, well before the formation of Aβ plaques and neuron loss.
SUMO (small ubiquitin-related modifier) is a post-translational modification that is involved in controlling many aspects of cell function also at the neuronal level. Considering the variety of proteins which are SUMOylated in neurons, different studies have indicated that SUMOylation is likely altered in AD, possibly contributing to increase Aβ levels and tau aggregation (Wilkinson et al. 2010; Sarge and Park-Sarge 2011). Indeed, recent data suggest that in AD both the aggregation of Aβ and tau proteins have been linked to SUMO (Lee at al. 2013). Moreover, SUMO immunoreactivity co-localizes with phospho-tau in the Tg2576 model (Takahashi et al. 2008). Ginkgolic acid (GA), a compound known to inhibit in a dose-dependent manner SUMOylation (Fukuda et al. 2009), is a major component of ginkgo leaf extract (EGb 761). Clinical studies show some effect of EGb 761 on memory decline in AD patients or in aged individuals (Gessner et al. 1985, Le Bars et al. 1997).
It is still unclear whether GA, at a concentration able to inhibit SUMOylation, may play a role in synaptic plasticity. In this work, we have investigated the effect of GA, in modulating long-term potentiation (LTP) and excitatory transmission on in vitro hippocampal slices. Also, the effects of GA were evaluated on the same electrophysiological parameters following Aβ exposure.
Our data show that GA increases the magnitude of LTP in a concentration-dependent manner. Notably, GA rescues impairment of LTP and excitatory transmission triggered by Aβ through a presynaptic and postsynaptic mechanism.
Overall our data suggest the ability of GA to improve synaptic plasticity and further validate SUMOylation as a potential therapeutic target in AD and related disorders.

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