pathogenesis. They also support the use of drugs restoring DNA methylation levels as a treatment for AD.

P4-036 THE NOVEL AMPA RECEPTOR POSITIVE ALLOSTERIC MODULATOR S 47445 RESCUES IN VIVO CA3-CA1 LONG-TERM POTENTIATION AND STRUCTURAL SYNAPTIC CHANGES IN MIDDLE-AGED MICE

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Background: Positive allosteric modulators of AMPA receptors (AMPA-PAMs) are small molecules that keep the AMPA receptor in an active state by decreasing deactivation or desensitization. They have been proposed to treat cognitive decline in dementias and Alzheimer disease (AD). S 47445 is a novel AMPA-PAM. Here, the mechanisms by which S 47445 could improve synaptic strengthen and connectivity were studied and compared between young (3-months old) and middle-aged freely moving mice (14-months old). **Methods:** LTP was evoked at the CA3-CA1 synapse using high-frequency stimulation (HFS) protocol at two occasions on day 1 and on day 13 after the first administration of S 47445 (3mg/kg or 10mg/kg). Assessment of drug effect on LTP was performed after either acute or chronic treatment. The drug effect on micro-cytoarchitecture in hippocampal (CA1 and CA3) and cortical tissue (L2-3 and L5-6) was also evaluated by confocal microscopy by assessing number and size of positive particles for the presynaptic vesicular glutamate transporter VGlut1 and the postsynaptic protein spinophilin. **Results:** Middle-aged control mice displayed a marked significant deficit of LTP as compared to young control mice following the first presentation of the HFS protocol. After acute administration of S 47445 at 10mg/kg in middle-aged mice, a complete reversion of the LTP deficit was observed on day 1. Then, chronic treatment with S 47445 at 10mg/kg in middle-aged animals significantly counteracted the aged deficit of LTP. During the second HFS presentation, LTP was much smaller than during the previous acute experiment in each mice group, suggesting a loss of LTP-evoked phenomenon. Interestingly, the chronic administration of S 47445 at 10mg/kg in middle-aged mice induced significantly larger LTP values as compared to young control and middle-aged control mice. Moreover, chronic treatment with S 47445 at 10mg/kg significantly prevented the decrease in number and size of VGlut1 and spinophilin in CA1-CA3 and in the cortex of middle-aged mice. **Conclusions:** Collectively, by its different effects observed, S 47445 is able to modulate both the structure and function of hippocampal excitatory synapses known to be involved in learning and memory processes and could provide beneficial effects in dementias such as AD.

P4-037 IDENTIFICATION OF NOVEL TARGETS FOR INHIBITING PRION-LIKE SEEDING AND PROPAGATION OF TAU PATHOLOGY IN VITRO AND IN VIVO

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Background: In AD, Tau pathology progresses in a stereotypic spatiotemporal pattern, strongly correlating with progression of disease symptoms. Prion-like propagation of Tau-pathology, or propagation of Tau-misfolding between cells and functionally connected brain regions, provides a compelling mechanism for this stereotypic progression of Tau-pathology, and hence an attractive therapeutic target. **Methods:** To test and validate novel therapeutic targets capable of inhibiting prion-like progression of Tau-pathology, we have generated combined in vitro and in vivo models recapitulating prion-like seeding and propagation of Tau-pathology. Seeding of pre-aggregated Tau in Tau expressing primary neurons and Tau transgenic mice recapitultes strong induction of Tau-pathology and propagation to the contralateral side. **Results:** Using these models we have analysed and evaluated the modifying potential of different targets on Tau pathology and propagation of Tau pathology. Targets under evaluation encompass Tau-interactome based Tau interacting proteins, including OTUB1 and other identified Tau-interacting proteins, as well as hypothesis based analysis. Within this analysis we identified OTUB1 as Tau deubiquitinase, involved in the accumulation of pathological forms of Tau. We furthermore identified novel targets with modifying effect on prion-like seeding and propagation of Tau-pathology. **Conclusions:** We here present the identification of different targets with a modulatory effect in vitro and in vivo on Tau-pathology and prion-like propagation of Tau-pathology.

P4-038 URSODEOXYCHOLIC ACID FOR THE TREATMENT OF TAUOPATHIES

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Background: Ursodeoxycholic acid (UDCA) is a bile salt which is currently FDA-approved for the treatment of gallstones, and has also been shown to have neuroprotectant properties in a number of model systems. One of its metabolites, tauroursodeoxycholic acid (TUDCA) has shown neuroprotectant properties in cell culture models of tau neurotoxicity. We evaluated the neuroprotective effects of UDCA in animal models of tau-opathy. **Methods:** In experiment 1, h-tau mice (n=31 males and females) and wild-type C57Bl mice (wt, n= 27 males and 26 females) were fed chow containing 0.4% UDCA or vehicle for 6 weeks, starting at age 16 months. At the end of 6 weeks, spatial memory was tested in Morris Water Maze and then mice were euthanized with terminal harvest of plasma and brain tissue for determination of plasma and brain UDCA and TUDCA levels, as well as brain levels of