The aim of this study is to assess the convenience of exploring long-term synergistic effects when multiple AD therapeutics of different mechanisms, fundamental and symptomatic, are combined. **Methods:** As a symptomatic drug, we selected donepezil, which have significant clinical benefits by activating undamaged cholinergic systems. From our previous study, as a fundamental drug, we prepared a small molecule KMSB600 that disassembles neurotoxic Aβ aggregates back to inert Aβ monomers and reverses the behavioral deficits in 2xTG-AD mice (APP/PS1). During the oral co-administration, we performed Y-maze tasks every week for 4 months and performed fear conditioning tasks after the last trial of Y-maze. Aβ plaques were visualized by thioflavin-S staining. **Results:** Co-administration of donepezil and KMSB600 significantly improved the deficits in the both behavior tests and histology study, compared to individual administration of donepezil or KMSB600 at the same dosages. **Conclusions:** Here, we report that co-administration of donepezil and KMSB600 significantly enhanced cognitive deficits in aged-AD mice in a complementary manner. Our findings imply that the cure of AD may require cocktail therapy of multiple drugs with different modes of action: cholinergic system improvement and amyloidogenic pathology reduction.

P1-424 CHARACTERIZATION OF D-ENANTIOMERIC PEPTIDES BINDING TO MONOMERIC AMYLOID BETA (1-42) IDENTIFIED BY A COMPETITIVE MIRROR IMAGE PHAGE DISPLAY

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Background: Alzheimer's disease (AD) is the most prominent type of dementia in elderly people. Until now there is no curative therapy available.Amyloid beta (Aβ) is assumed to play a major role in the development and progression of the disease. Freely diffusible, toxic Aβ oligomers seem to have a major toxicological impact. **Methods:** We conducted a competitive [1] mirror image phage display selection [2] to identify ligands that specifically bind monomeric Aβ (1-42) while counter selecting for binding to Aβ oligomers and fibrils in order to identify D-enantiomeric peptides that very specifically bind to and stabilize monomers. The most promising peptides were characterized in vitro via different methods like ThT-assay, density gradient centrifugation (DGC), transmission electron microscopy (TEM) and bio layer interferometry (BLI).[1] Hoffmann, S. et al. Competitively selected protein ligands pay their increase in specificity by a decrease in affinity. Mol Biosyst. 2010 Jan;6(1):126-33.[2] Wiesehan, K & Willbold, D. Mirror-image phage display: aiming at the mirror. Chembiochem.2003 Sep 5;4(9):811-5. **Results:** We were able to identify peptides that show increased affinity for monomeric Aβ. The effect of the peptides on Aβ particle size was analyzed by DGC. The peptides eliminated oligomeric Aβ and induced formation of amorphous high molecular weight Aβ aggregates as shown by TEM. **Conclusions:** Taken together we have found new, promising D-enantiomeric peptides that are able to abolish toxic Aβ oligomers. These peptides shift in vitro the equilibria from oligomeric Aβ toward high molecular weight Aβ-peptide co-aggregates. As already shown for D3, a well characterized D-enantiomeric peptide identified in our lab [3], the respective co-aggregates are not amyloidogenic. [3] Funke, AS. et al. Oral Treatment with the d-Enantiomeric Peptide D3 Improves the Pathology and Behavior of Alzheimer's Disease Transgenic Mice. ACS Chem Neurosci. 2010 Sep 15;1(9):639-48.

P1-425 CHARACTERIZATION OF D-ENANTIOMERIC PEPTIDES DERIVED FROM D3 FOR TREATMENT OF ALZHEIMER'S DISEASE

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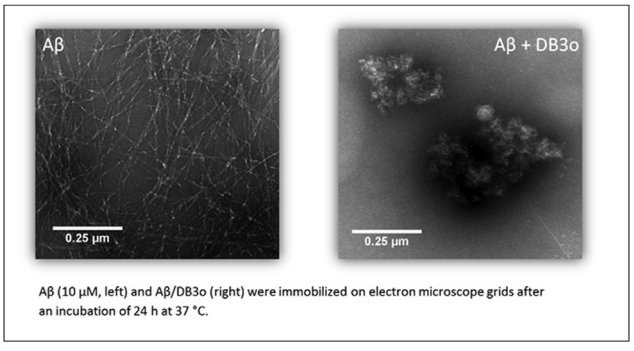
Background: Alzheimer's disease (AD) is the most prominent neurodegenerative disease affecting more than 24 million people worldwide. Currently, it is the sixth-leading cause of death, but until now there is no causal therapy available. The amyloid-beta (Aβ) peptide plays an important role in the pathology of the disease. Especially the soluble, most harmful neurotoxic oligomers of Aβ are discussed to be responsible for the development and progression of the disease. In our group we identified the D-enantiomeric peptide D3 via mirror image phage display, which reduces the formation of Aβ oligomers in vitro [1-3]. In vivo, D3 treatment of tg AD mice yielded improved cognitive abilities and reduced Aβ plaque load compared to untreated mice [4]. **Methods:** Via peptide microarrays we were able to identify derivatives of D3, of which one of them is named DB3. This peptide was characterized via different biophysical and biochemical methods to prove its possible therapeutical abilities. Additionally, we further optimized DB3 and characterized this derivative in vitro, too. **Results:** We could show that DB3 and the optimized version of the peptide (DB3o) inhibit Aβ1-42 aggregation. As already described for D3 [3], DB3 reduced the content of Aβ oligomers and lead to the formation of bigger aggregates. Thereby formed Aβ-DB3-coaggregates feature amorphe structures and do not show any seeding potential. DB3o has the same properties, but is already effective at lower concentrations. Both substances seem to disassemble preformed Aβ protofibrils. **Conclusions:** The D-enantiomeric peptides DB3 and its optimized version modulate the oligomerization of Aβ42 in vitro. Thus, there is a high interest for therapeutically application of DB3 and DB3o in AD. References:[1] Wiesehan, K. et al.(2003); ChemBioChem 4, 748-753.[2] Wiesehan, K. et al. (2008); Protein Engineering Design and Selection 21, 241-246.[3] Funke, AS. et al. (2010); ACS Chemical Neuroscience 1, 639-648.[4] van Groen, T. et al. (2013); Journal of Alzheimer's Disease 34, 609-620.



Aβ (10 µM, left) and Aβ/DB3o (right) were immobilized on electron microscope grids after an incubation of 24 h at 37 °C.

P1-426 BENEFICIAL EFFECTS OF PHOSPHODIESTERASE 4 INHIBITORS ON HYPERTENSION-INDUCED DEFECTS IN MEMORY FUNCTION IN RATS

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Background: Hypertension (HT) is a prevailing risk factor for cognitive impairment, the most common cause of Vascular Dementia, but a pathophysiological mechanistic link is still ambiguous. Cyclic AMP is broken down by cAMP-specific phosphodiesterase (PDE4), that are expressed throughout the brain. Inhibition of PDE4 leads to elevation of cAMP/PKA/pCREB in the hippocampus. This signaling cascade is essential for establishing memory. However, there are no reports whether PDE4 inhibitors may improve the learning and memory dysfunction induced by HT. To evaluate the feasibility of PDE4 inhibitors as a therapeutic agent for cognitive dysfunction induced by HT, we examined the effects of rolipram and roflumilast on the impairment of learning and memory in hypertensive rats.