additional tests of episodic verbal memory and visuospatial working memory were developed and incorporated. Collection of census-matched normative data in 750 healthy individuals is currently under way. We describe preliminary findings comparing performance of young (<55) and older (≥55) healthy adults, as well as performance of individuals with subjective cognitive complaints. Methods: Tasks were designed in compliance with guidance for objective psychometric tests (Ferris et al., 1997) and to enable tablet-assisted administration, automatic scoring, and data management in compliance with 21 CRF Part 11 requirements. Data currently includes 143 participants, including 63 healthy young adults (YA, <55 years), 76 healthy older adults (OA, ≥55 years), and 4 individuals with cognitive complaints. Participants with cognitive complaints were classified as such based on total scores of ≥4 on the Mail-In Function Cognitive Screening Instrument (MCSFI). Results: Means and standard deviations are presented for YAs, OAs, and cognitive complainers. OAs underperformed YAs on BAC App endpoints including verbal learning, verbal fluency, symbol coding, and token motor test (p<.01 for all). Although delayed recall did not reliably differ between healthy YAs (mean =9.01, SD =3.02) and OAs (mean =8.38, SD =3.26), cognitive complainers performed well below their normative counterparts (mean =4.25, SD =2.99). Visuospatial working memory performance showed significant decline in OAs as compared to YAs (p<.01), and preliminary data suggest increased decline in cognitive complainers. Conclusions: Preliminary findings suggest the BAC App is sensitive to age-related changes in cognition, and show potential sensitivity to differences between healthy OAs and those with subjective cognitive complaints. Enhancement of the BAC App with additional measures of episodic memory and visuospatial working memory shows potential for increasing the utility of the measure in early MCI-AD.

P4-579

BREAKTHROUGH IN DEMENTIA/ALZHEIMER’S DISEASE THERAPY: THREE DIFFERENT CASES OF ENERGY TREATMENT WITH DELAYED AND SUSTAINED RELEASE OF GLUCOSE

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Background: Lack of energy in human brain causes of Alzheimer’s disease. Supply of glucose in a timely manner is critical to prevent memory decay and management of AD/dementia symptoms. Methods: Taking delayed and sustained release of glucose tablet at bedtime. Results: AD/dementia patients do not have early morning hallucinations, nightmares and night sweats any more. Conclusions: Timed release glucose tablets has proved been very helpful for managing AD/dementia patients. It may also improve patients short term memories.

P4-580

SURPRISINGLY HIGH RESISTANCE OF Aß OLIGOMER ELIMINATING ALL-D-ENANTIOMERIC PEPTIDES AGAINST METABOLIZATION BY ENZYMES CONTAINED IN THE GASTROINTESTINAL TRACT, BLOOD, LIVER AND BRAIN

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Background: Previously, we have developed an Aß oligomer eliminating compound consisting solely of D-enantiomeric amino acid residues. Based on this lead compound we developed the derivative Pri-002 that is currently in clinical phase I. Both D-peptides improved cognition in various transgenic Alzheimer’s disease mouse models even after oral administration and have an oral bioavailability of more than 50%. To further investigate the underlying properties and to predict the safety for administration in humans, we examined in vitro the resistance of the lead compound and Pri-002 against metabolism in media simulating the human gastrointestinal tract, blood and liver in comparison to their corresponding L-enantiomeric mirror images. It was also tested if Pri-002 acts as substrate for the human D-amino acid oxidase (hDAAO) mainly contained in the kidney, liver and brain. We additionally examined, if Pri-002 has any inhibitory effects on the enzymes contained in these experiments. Methods: For the stability and inhibition tests in simulated gastric and intestinal fluid, human plasma and human liver microsomes, the peptides were incubated in these media and potential metabolism was followed by RP-HPLC. Additional inhibition assays regarding the main human CYP isoforms contained in liver microsomes were performed by monitoring isof orm-specific probe substrate metabolites with LC-MS/MS or fluorescence. The hDAAO substrate and inhibition tests with Pri-002 were performed using a coupled enzyme assay. Results: The D-peptides showed high stability in all investigated media in comparison to their L-enantiomeric mirror images. To summarize only the most surprising results, the D-peptides remained stable in simulated intestinal fluid for 24 hours, while the L-peptides were completely metabolized within seconds. Indeed, human plasma and human liver microsomes metabolized the L-peptides several hundred times faster than the D-peptides. Pri-002 did neither act as substrate for hDAAO nor did it have any inhibitory effects on any of the investigated enzymes. Conclusions: This surprisingly high stability allows oral administration of the drug candidate and may also explain the absence of adverse side effects even at high doses due to low levels of potential biologically active metabolites during treatment. In conclusion, all-D-enantiomeric peptides represent a promising new class of drug candidate compounds, especially for oral administration.

P4-581

BROMO-PROTOPINE, A NOVEL DERIVATIVE OF PROTOPINE WITH IMPROVED BIOAVAILABILITY AND BIOACTIVITY, DEGRADAS TAU AGGREGATION THROUGH MODULATION OF HDAC6-HSP90 CHAPERONIC ACTIVITY AND IMPROVES MEMORY VIA STIMULATION OF THE RAS-GRF1/ERK PATHWAY

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Background: Recently, we identified protopine (PRO) as a novel HDAC6 inhibitor with anti-Tau activity from the Chinese medicinal...
herb Corydalis yanhusuo (Durairajan et al., 2015, Neurodegenerative disease, 15 [Suppl. 1]: p1579). In this study, we investigated the mechanism of HDAC6-Hsp90 modulation by PRO and explored whether derivatization of PRO could improve its in vivo efficacy. **Methods:** To optimize the anti-Alzheimer's disease (AD) activity of PRO, we synthesised 8 derivatives of PRO and carried structural activity relationship studies. The docking studies of PRO derivatives with HDAC6 was performed using Autodock program. Using HDAC overexpression, acetyl-lysine immunoprecipitation and co-immunoprecipitation assays, and Western blotting, we determined how PRO modulates the HDAC6-Hsp90 chaperonic activity and stimulated RAS-GRF1/ERK pathway in both neuronal cell lines and primary neuronal cultures. Oral and Intraperitoneal pharmacokinetic studies were conducted to estimate the relative bioavailability of compounds. For the in vivo AD study, P301S Tau and 3XTg-AD mice administered with PRO and its derivative or vehicle until the mice were 4- and 18-month old, respectively. **Results:** Among synthesised PRO derivatives, only bromo-protopine (PRO-Br) showed anti-HDAC6, anti-Tau activity and memory improving activities. The binding affinity of PRO and PRO-Br with HDAC6 is 7.65 and -8.76 kcal/mol, respectively. Treatment with PRO and PRO-Br reduced both phosphorylated PHF-1 Tau and total Tau, and concomitantly increased acetylated α-tubulin and Hsp90, and Hsp70 in SHSY5Y-P301L cells. PRO-Br showed two-fold more activity in reducing HDAC6 activity and tau accumulation than PRO. In pharmacokinetic studies, PRO-Br showed enhanced brain bioavailability than PRO in both oral and intraperitoneal routes of administration. In particular, the Cmax of the PRO was 289.47 ng/gm and 76.5 ng/gm whereas PRO-Br was 425.22 ng/gm and 161.6 ng/gm in oral and intraperitoneal administration, respectively. We further investigated the anti-AD mechanism of PRO and PRO-Br and found that PRO and PRO-Br clear the insoluble Tau aggregates in P301S Tau mice by modulating HDAC6-Hsp90 chaperonic activity and improved memory of 3XTg-AD mice by stimulating RAS-GRF1/ERK/CREB pathway. PRO-Br displayed improved in vivo efficacy in terms of counteracting increased Tau aggregates, motor dysfunction, and memory dysfunction in AD mouse models. **Conclusions:** Our findings suggest that PRO-Br has potential as an anti-AD drug.

**P4-582**

**EFFECTS OF A 6-MONTH AEROBIC EXERCISE PROGRAM ON COGNITIVE BRAIN FUNCTIONS AND ENZYME (APP770) IN THE BLOOD VESSELS IN OLDER ADULTS**

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**Background:** Disproportionate growth of the elderly population has raised the profile of Alzheimer disease (AD) dementia as a major public health concern and motivated intense efforts to identify protective or preventive lifestyle factors. The attention paid to how Aerobic exercise (AE) influences cognitive performance has exploded in the past decade. AE generally refers to exercise that improves the efficiency of aerobic energy producing systems by increasing maximal oxygen uptake and cardiorespiratory endurance. However, in addition to greater preservation of cognitive function in old age and fewer incidences of dementia. This study investigated the effects of AE on cognitive brain functions and enzyme (APP770) in the blood vessel of older adults. **Methods:** All analyses were conducted on the data from 21 participants (12 older adults aged 85 – 90 years and 8 younger adults aged 65 – 75 years). All participants reported being free of neurological disorders, cardiovascular disease, and any medication that influence central nervous system function and had corrected-to-normal or normal vision. This study was reviewed and approved by the Research Ethics Committee, Graduate School of Comprehensive Human Sciences at the Kansai University of Welfare Science, and participants gave their informed consent to participate in the experiment. This experiment consisted of a baseline session and carried out 6-month aerobic exercise program. 6-month aerobic exercise program was dual-task walking (3 minutes) and aerobic walking (3 minutes × 5). We performed the effect measurement in APP770, MPI (memory assessment) and MoCA-J. **Results:** The results indicated that, MPI (memory assessment) following AE programs was a change in three months in younger adults (P<0.05). APP770 and Orientation (MoCA-J) following AE programs was a change was significantly accepted at three months in older adults (P<0.05). However, with both groups, an effect did not continue until six months either. **Conclusions:** The available evidence strongly suggested that AE has a positive influence on cognition in individuals of all age groups, particularly in older adults. We stipulated that AE influences divergent cognitive domains.

**P4-583**

**IDENTIFICATION OF NOVEL APOE4 MODULATORS**

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**Background:** It is not clear to date if Apolipoprotein E4 (ApoE4), the major genetic risk factor in late onset Alzheimer’s disease (AD), influences AD pathophysiology by a gain of toxic function or by a loss of protective function or a combination thereof. Three ApoE isoforms exist – ApoE2, ApoE3 and ApoE4 – that just differ in two amino acid sites. These amino acid substitutions are believed to alter ApoE structure and consequently physiology and be responsible for ApoE2’s protective and ApoE4’s detrimental effects (1, 2).

**Figure 1.** Recombinant expression and purification of ApoE4. We developed a new protocol for the purification of human ApoE4. ApoE4 is expressed as a fusion protein with a thioredoxin (TRX) solubility tag and purified by a combination of immobilized metal affinity chromatography, heparin affinity chromatography and size exclusion. Our purification method exclusively works under native conditions and does not include a denaturation step like other protocols. The TRX tag is removed via on-column digestion with HRV 3C protease and easily enables separation of ApoE4 and TRX. A final polishing step by gel filtration results in highly pure ApoE4 (purity > 95%).