these patients. In the present study we examine the sleep/wake parameters in a transgenic animal model of familial AD, namely the PD-APP mouse, over a time frame where Aβ42 levels are known to rise. Methods: Experiments were performed in accordance with the Animal (Scientific Procedures) Act 1986. Adult male PD-APP transgenic mice and C57Bl/6N tac aged matched controls (weight range 29-45g, n = 15/group) were implanted with a telemetry i.p. and with a custom cranial implant. At seven months of age animals were evaluated in the SCORE2004™ biosay, which allows continual measurement of electro-encephalogram (EEG) and electromyogram (EMG) (cranial implant), locomotor activity and body temperature (telemetry). Animals were kept under 12/12 light/dark cycle with food and drink ad libitum.

Results: At the first time point, data was compared between 10 PD-APP and 13 control animals. The time spent in REM throughout both the light and dark cycle was significantly reduced (light: PD-APP 27 ± 6 minutes per 12 hour light cycle, control 47 ± 5, P < 0.05; dark: PD-APP 15 ± 3, control 27 ± 4, P < 0.05). Additionally the average REM bout length was reduced during each light phase compared to control (light: PD-APP 0.5 ± 0.1 minutes, control 1.0 ± 0.1, P < 0.01; dark: PD-APP 0.4 ± 0.1, control 0.9 ± 0.1, P < 0.05). No change in the amount of time spent in NREM or wake was observed and no significant changes in latency to NREM or REM were detected after animals were disturbed. Conclusions: In conclusion, preliminary data from this longitudinal study shows that male PD-APP mice aged 7 months have reduced time in REM and reduced average REM bout lengths in both light and dark environments. No changes in REM latency were observed in our male mice however increased latency has been reported in 3-5 month old female PD-APP mice (Huitron-Resendez et al 2002 Brain Res 928: 126-137). Evaluation of these mice, including spectral profiles, is planned to continue until animals reach 22 months of age.

PI-274 AGEING INCREASES VULNERABILITY TO Aβ42 TOXICITY IN DROSOPHILA

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Background: Ageing is the major risk factor for the development of many neurodegenerative diseases, including Alzheimer’s Disease (AD). One of the major unresolved questions in the AD field asks why neurodegeneration occurs late in life. This association could reflect the length or degree of exposure to toxic proteins required for pathology to occur, or could indicate that the ageing process itself increases the susceptibility of neurons to protein toxicity. We aimed to resolve these possibilities by expressing a standard dose of Aβ42 at different ages and measuring the time to develop, and extent of, sub-bout reductions.

Methods: We used the Drosophila GeneSwitch (GS) inducible system to express the Arctic Ab42 peptide in young versus old fly neurons. The degree of Arctic Aβ42 over-expression was modulated by altering the concentration and length of exposure to the inducer mifepristone (RU486). Lifespan was then measured as a surrogate marker of Aβ42 toxicity in ageing flies. Results: Older flies were more vulnerable to Aβ42 toxicity than young flies, as they displayed the largest reduction in lifespan following induction of the peptide under both chronic and standardised conditions. Conclusions: Our results imply that the late age-onset of neuron degeneration is likely to be a consequence of the ageing process increasing neuronal vulnerability to proteotoxicity. Future work will analyse the solubility of Aβ42 peptide in young and old flies, to further our understanding of the relationship between protein aggregation and toxicity with age.

PI-275 EPILEPTIFORM DISCHARGES IN TRANSGENIC ALZHEIMER’S MICE CORRELATE WITH IMPAIRMENTS IN SPATIAL MEMORY AND ARE REDUCED BY ETHOSUXIMIDE

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Background: Hyperexcitability and seizures have emerged as possible mechanisms underlying the neuronal dysfunction in Alzheimer’s Disease (AD). Despite recent advances, it is not known to what extent seizures affect memory function or disease progression in AD, or whether reducing seizures could be an effective therapy in this disease. Here, we address these questions in detail utilizing an Alzheimer mouse model. Methods: APP- PSEN and 3xTg-AD mice were used, both of which harbor APPswe and PSEN1 transgenes, with the latter model also harboring the P301L tau mutation. All underwent continuous EEG monitoring for 72 hours. The APP- PSEN mice were tested in the Morris Water Maze, and their memory function correlated to the presence and severity of seizures. Subgroups with frequent seizures then underwent anticonvulsant therapy with Phenytoin, Ethosuximide, and Levetiracetam to assess effective seizure reduction. In addition, APP-PSEN mice lacking expression of cellular prion protein (PrPC) were also assessed for seizure reduction. The therapeutic effect of anticonvulsant therapy on the memory impairments in AD mice is now being tested. Results: 40% of aged APP-PSEN mice had at least 1 convulsive seizure over a 72 hour recording period, and approximately half had frequent non-convulsive spike-wave discharges (SWDs), lasting 1-2 seconds. Many SWDs were accompanied by a 1-3 second behavioral arrest. The presence of SWDs correlated with both learning and memory, with SWD-positive mice performing significantly worse in both the acquisition phase and the subsequent probe trial of the Morris Water Maze. Ethosuximide was most effective in reducing SWD frequency, with a complete resolution lasting 4 hours after dosing, with return to baseline over 12 hours. Levetiracetam produced an approximate 75% reduction of SWD frequency, while phenytoin caused a slight increase in SWDs. The lack of PrPC expression completely reversed the SWD phenotype in APP-PSEN mice. Conclusions: Our study is the first to detail the correlation between non-convulsive SWDs and the behavioral impairments of AD mice. Our data suggest that the use of anticonvulsants in the treatment of AD has therapeutic potential, either as an alternative or complimentary to current anti-amyloid interventions.

PI-276 AN INTEGRATED MECHANISTIC MODEL TO INTERRELATE CSF Aβ40, Aβ42, SAPPβ AND SAPPα RESPONSE TO β- AND γ-SECRETASE INHIBITORS IN RHESUS MONKEY

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Background: Biomarker response in cerebrospinal fluid (CSF) is commonly used to assess response to inhibitors of brain amyloid protein (Aβ) production acting on either the β-secretase (BACE1) and γ-secretase (GS) cleavage steps. Biomarkers of interest include CSF Aβ40, Aβ42, soluble amyloid protein precursor beta (sAPPβ), and sAPPα. The objective was to develop an integrated, mechanistic, mathematical model of the dynamics of Aβ production in brain and its disposition into CSF, which informs the inter-relationships among these responses and interpretation with respect to inhibition of brain production. Methods: Dose-ranging, biomarker and pharmacokinetic timecourse data from CSF obtained from cisterna-magna-ported rhesus monkeys receiving BACE (1 study) or GS (2 studies - J. Neuroscience 30:6743) inhibitors were used in model development. Nonlinear mixed effect modeling (NONMEM) was used to develop: separate models for each biomarker-inhibitor combination; then an integrated biomarker model with common drug effect term for BACE; and finally comprehensive model with GS incorporated. Models were qualified through cross-validation. Results: For the separate models, a similar model structure was able to account for the timecourse of data across mechanisms of action and biomarker. Similar in vivo potency estimates (EC50) for production inhibition were obtained for both biomarkers, supporting integrated model development. For the BACE study, EC50 (90% CI) estimates of 25 (24.6-26.2), 46 (35-56), 49 (19-79), and 27 (14-40) nM were obtained for Aβ40, Aβ42, sAPPβ, and sAPPα, respectively. In the integrated model, the EC50 estimate