plaques. It is also proposed that GSK3ß is associated with neuronal death and a decline in cognitive learning. Hence, an inhibition of GSK3ß could be a powerful strategy to slow down or even prevent the progression of AD. Plants are a rich source of secondary metabolites that can be therapeutically used. In Traditional Chinese Medicine (TCM) *Bupleurum marginatum* (Margined Chinese Thorough wax) is one of the most common plants with a wide therapeutic application. In this study, methanolic, dichloromethane and aqueous crude extracts as well as isolated compounds from *Bupleurum marginatum* were tested for their *in vitro* GSK3ß inhibition. **Methods:** GSK3ß inhibition was measured with an enzymatic radioactivity assay based on the reaction of GSK3ß with phosphatase inhibitor 2. Gas chromatography/mass spectrometry (GC/MS), liquid chromatography/mass spectrometry (LC/MS) and various nuclear magnetic resonance (NMR) analyses were performed to elucidate the phytochemical composition of the crude extracts. **Results:** All three crude extracts showed a strong inhibitory activity of GSK3ß. This can be attributed to the synergistic effects of the chemical compounds contained in these extracts. Especially one novel lignan isolated for the first time from *Bupleurum marginatum* exhibited a very distinctive GSK3ß inhibition. **Conclusions:** These findings suggest that *Bupleurum marginatum* represents a valuable source of natural compounds, which might be used as inhibitors of GSK3ß.

P3-440 NEW METHODS FOR THE ANALYSIS OF COMPLEX DISEASES

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Background: There is a growing awareness that current conceptual models of Alzheimer's disease (AD), dementia and other neurodegenerative disorders may not be sufficient to describe the underlying etiologies or provide therapeutic targets for disease modifying interventions. This presentation will review the proposition of AD as a *complex disease* due to a *systems failure*. The discussion will cover the use of *systems biology* as an approach for discovery-development of novel therapeutic targets focusing on disease modifying interventions. **Methods:** Among the array of impediments confronting drug-discovery/development efforts, one of the critical barriers is the lack of modeling systems that simulate the full spectrum of clinical phenotypes. The nonlinear relationship between biological phenotypes of the disease and clinical symptoms remains a major challenge for therapy development. **Results:** This situation places traditional modeling systems [e.g., transgenic or other animal models] at a particular disadvantage because these models do not exhibit the complete range of clinical features of human disease. A key limitation of these models is the inherent inability to provide insight into the precise functional relationships between the clinical (symptoms manifested) and biological phenotypes (neurobiological markers). As a result, the discovery of a biological marker for a disease or the identification of a molecular target often does not translate into an effective therapy. **Conclusions:** The application of systems biology, in combination with *in silico* and other multi-modeling approaches, may add an important new tool for investigators. These methods offer the unique possibility to understand the relationship between multiple molecular events and the emergent behavior of neural systems—as clinical symptoms of the whole complex system. The discussion will touch upon the concept of a computational modeling system conceived as a shared research resource built on an international network of well-integrated databases.

P3-441 RAPAMYCIN TREATMENT REVERSES MEMANTINE-MEDIATED INCREASE IN SYNAPTIC SIGNALING PROTEINS IN DEGENERATING PRIMARY NEURONS: IMPLICATIONS IN ALZHEIMER'S DISEASE

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Background: Alzheimer's disease (AD) is characterized by excess amyloid plaque formation and loss of acetylcholine and synaptic proteins in the hippocampus. We investigated the effects of the NMDA partial antagonist memantine on the APP pathway and synaptic proteins in complementary neuronal culture models. Several possible downstream signaling pathways may be activated by memantine. The mammalian target of rapamycin (mTOR) pathway was identified as one promising target and investigated here. **Methods:** Primary embryonic rat cortical cultures and human neuroblastoma cells were treated with memantine. Levels of APP and Aß were measured by Western blot and ELISA, respectively. Levels of synaptic markers (SNAP-25 and synapophysin) and of memantine and glutamate were also measured. Treated cultures were subjected to immunocytochemisty to examine glial and neuronal markers. To investigate the mTOR pathway, primary cultures were co-treated with rapamycin and synaptic markers were measured. **Results:** In primary and neuroblastoma cell cultures, memantine altered APP and Aß secretion (Alley et al, 2010; Ray et al, 2010). During chronic treatment, memantine lowered APP and $Aß_{40}$ secretion in neuroblastoma cells. Notably, memantine treatment of degenerating primary neurons promoted survival. Both memantine and MK-801 increased neuronal and synaptic markers (SNAP-25 and SYPH), and immunocytochemistry showed preservation of neuronal morphology with both drugs. Memantine also preserved both PSD-95 and NR1; notably, this effect was reversed by rapamycin. **Conclusions:** Memantine treatment increased neuronal viability, morphology and synaptic protein markers in degenerating primary neurons that are reduced in AD brains. Memantine altered APP processing in cell culture and animal models. APP and Aß are associated with neurite and synapse regulation. These results imply common or synergistic modes of action that could be useful to develop improved therapeutic agents. Inhibition of mTOR signaling blocked memantine's effects on synaptic markers, suggesting that memantine activates the mTOR pathway, leading to increased synaptic signaling proteins and synapse preservation. Moreover, these effects of memantine are opposite to the synaptic deficits that result from exposure to glutamaterigic activation. The relationship of rapamycin and APP pathway, mediated by ADAM10, is being investigated. The response to memantine in these different models has important implications for current and future therapeutic interventions for AD.

P3-442 THE NOVEL TETRAHYDROFURANNE DERIVATIVE ANAVEX2-73 ATTENUATED GSK-3ß ACTIVATION AND TAU HYPERPHOSPHORYLATION IN A NONTRANSGENIC ALZHEIMER'S DISEASE MODEL IN MICE

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Background: Tetrahydro-N,N-dimethyl-2,2-diphenyl-3-furanmethanamine hydrochloride (ANAVEX2-73) is a novel compound binding to muscarinic acetylcholine and sigma-1 receptors with affinities in the low-micromolar range. We previously reported that the drug showed anti-amnesic and neuroprotective potential against amyloid toxicity in mice. In particular, ANAVEX2-73 attenuated the oxidative stress, caspases induction, cellular loss and learning and memory deficits observed in mice several days after the icv injection of an oligomeric preparation of amyloid (25-35) peptide (oAß) (Villard et al., *J Psychopharmacol* 2010). It was recently reported that oAß activates glycogen synthase kinase-3ß (GSK3ß) and provokes the hyper- and abnormal phosphorylation of tau protein, in the hippocampus and cortex of the mice. We therefore analyzed whether the compound is also able to attenuate GSK-3ß and tau phosphorylation in this model. **Methods:** Mice were treated with ANAVEX2-73 (0.1-1 mg/kg ip) 20 min before the icv injection of oAß and animals were sacrificed at different times after injections, their hippocampus dissected out and proceeded for western blot analyses. **Results:** oAß resulted in a rapid decrease in phospho-Akt (P-Akt) levels in the hippocampus at day 1, 3, 5 and 7 after injection. oAß also resulted in the activation of GSK-3ß, evidenced by an increase in Tyr216 phosphorylation of the kinase, at days 3 to 7. Administration of ANAVEX2-73 blocked P-Akt decrease and P-GSK-3ß increase, indicating