P2-198 CHEMICAL MANIPULATION OF HSP70 ACTIVITY REGULATES TAU PROCESSING

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Background: The microtubule associated protein tau abnormally accumulates in a group of neurodegenerative diseases collectively termed tauopathies. Post-translational modifications of tau subvert its removal by the cellular clearance machinery, allowing it to form filamentous pathogenic tangles. Heat shock protein 90 (Hsp90), a chaperone that shepherds tau as a client protein, possesses ATPase activity, which, when manipulated, can change the fate of tau, either preventing or promoting clearance. **Methods:** Here, we speculated that Hsp70, a chaperone acting proximally to Hsp90 in the protein folding cycle, could also be modified pharmacologically to impact tau processing. We used a newly developed high-throughput chemical screen to accomplish this. **Results:** We identified both inhibitors and activators of Hsp70 ATPase activity. Treatment of cell models with these Hsp70 inhibitors led to a rapid increase in tau ubiquitination and proteasome-dependent degradation, while activators led to tau accumulation. Genetic manipulation of Hsp70 altered drug efficacy. Tau levels were rapidly reduced in mouse brain tissue from both non-transgenic mice and mice over-expressing mutant human tau. **Conclusions:** Our results suggest that manipulation of endogenous basal Hsp70 may be an important therapeutic strategy for tauopathies and perhaps other neurodegenerative disorders involving intrinsically unfolded protein aggregation.

P2-199 INTRANASAL DEFEROXAMINE IMPROVES RADIAL ARM WATER MAZE PERFORMANCE IN P301L TAU TRANSGENIC MICE

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Background: Deferoxamine (DFO), given intramuscularly (IM), has previously been shown in a clinical trial to reduce cognitive decline associated with Alzheimer's disease (AD) by 50% over two years. However, due to side effects and difficulty with administration, IM DFO was not further developed for AD. We have recently shown that intranasal (IN) administration is a non-invasive way to target DFO to the central nervous system. In the APP/PS1 mouse model, intranasally administered DFO slowed the progression of memory loss, as measured by Morris water maze (MWM), with no obvious side-effects. Here, we used a battery of behavioral tests to determine whether intranasal DFO may also have beneficial effects in a transgenic tau mouse model (P301L). **Methods:** Intranasal DFO (10% solution) or vehicle was administered to awake P301L mice and wild-type controls three times per week starting at 2.5 months of age. After 4 months of treatment, mice were subjected to a battery of behavioral tests including radial arm water maze (RAWM), Y-maze, elevated plus maze, open field, MWM, and the optomotor visual test (OPT). **Results:** Wild-type controls had significantly fewer errors and shorter escape latencies than P301L transgenic mice in RAWM, and MWM hidden platform tests. No obvious differences were observed in the elevated plus or open field tests. Transgenic mice performed significantly poorer than wild-type mice in visual tests including MWM visual platform and OPT. Intranasal DFO improved performance over vehicle-treatment in P301L mice as measured by RAWM, where two blocks showed significantly fewer errors in trials 4 and 5. No other significant drug effects were observed. **Conclusions:** RAWM and MWM tests showed that transgenic mice had significantly poorer performance than wild-type controls. However, these results may have been affected by impaired visual ability of P301L mice. Intranasal treatment with DFO improved performance in the RAWM, which is our most sensitive assay. Because intranasal DFO treatment did not affect visual ability, this suggests a reduction in memory loss of these mice. Biochemical studies are ongoing to determine mechanisms underlying this effect.

P2-200 PROTEIN PHOSPHATASE 2A: A NOVEL PHARMACEUTICAL TARGET FOR THE TREATMENT OF ALZHEIMER'S DISEASE

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Background: Signaling imbalances due to aberrant protein phosphorylation play a critical role in the pathogenesis and progress of Alzheimers's disease (AD). The development of therapeutics to correct these imbalances have focused almost entirely on inhibiting kinase activities towards key targets such as the microtubule associated protein, tau. Activation of phosphatases such as protein phosphatase 2A (PP2A) to correct signaling imbalances is a promising alternative approach. The PP2A holoenzyme comprising A, Bα & C subunits accounts for over 50% of total phosphatase activity in the brain. Carboxyl methylation of the catalytic C-subunit of PP2A enhances the formation and stability of ABαC. Methylation is catalyzed by highly specific PP2A methyl transferase (PPMT), and demethylation is catalyzed by a specific methyl esterase (PPME). Considerable evidence suggests that low levels of PP2A activity associated with decreased levels of PP2A methylation, play a key role in tau hyperphosphorylation and neuronal cell death [Vafai, S.B. & Stock, J.B.(2002) FEBS Lett., 518, 1-4]. Building on these observations, we reasoned that an agent that inhibited PP2A demethylation might be useful for the prevention and treatment of AD. **Methods:** To establish proof of principle for this approach, we developed an in vitro biochemical assay for PP2A demethylation, and identified an appropriate pharmaceutical lead, Sig1012. **Results:** Sig1012 is an easily synthesized small molecule (<500 mw) that is orally-bioavailable, readily crosses the blood brain barrier; and, in preliminary studies with mice, shows an excellent safety profile. Mice maintained for 3 or more weeks on a diet supplemented with Sig1012 show dramatically reduced levels of tau hyperphosphorylation. **Conclusions:** These findings strongly support the notion that pharmaceutical agents that enhance PP2A holoenzyme stability by inhibiting C-subunit demethylation provide a promising therapeutic approach.

P2-201 PHARMACOLOGICAL MODULATION OF HUMAN PHOTOSYNTHESIS: A NEW APPROACH TO ALZHEIMER'S DISEASE

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Background: Until today, the only accepted organism that made photosyntesis, are their with chlorophyll. We can define Photosynthesis like the capability of the cell to take energy from water. And this energy are carried by the Hydrogen. All the biochemical process in th eukariotyc cell need energy, but ATP is mainly for reactions that need great quantities, instead, hydrogen from water just cover 34 % of the full daily amount requiered, the other 66 % comes from food. But this 34% (from water) is the basic energy, to impulse the prime reactions of the cell, and this reaction are the support of the reactions that are energyzed by food. When the photosynthesis in eukariotyc cell are diminished, the patient has different manifestations, by example: joint pains, lumbalgia, arthritis, depression, generalizated fibrosis; malfunction of the Central Nervous System manifested by Alzheimer, Parkinson, inflammations and so on. **Methods:** We studied the human retina with angiography, visible and unvisible light; digital imaging registration, and mathematical models to analysis of results. **Results:** We found that melanin has an important role in the physiology of the eye and the body. Has many properties, but no one by themselve explain their beneficial actions on the tissue. **Conclusions:** Melanin are for animal kingdom, like chlorophyll are for vegetable kingdom. Melanin has the extraordinary propertie of unfold or dissociate the water molecule. Transduce photonyc energy into chemical energy. The pharmacological modulation of human photosynthesis increase the redox capability of eukariotyc cell 4 times or more. And the improvement of the Alzheimer disease with th treatment is better explained by the fact that all the cells of the body getting better (CNS, lung, kidney, hepatic function, GI tract; blood, etc.)