P2-223 MEMOGAIN; SUPRA-BIOAVAILABLE NICOTINIC ENHANCER FOR THE TREATMENT OF ALZHEIMER'S DISEASE

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Background: Galantamine (Reminyl, Razadyne) is a potent allosterically potentiating ligand (APL) of nicotinic receptors and a moderate inhibitor of cholinesterases. In addition to its cognition-enhancing properties and mediated by its action on α7 nicotinic receptors, galantamine reduces amyloid toxicity and neuronal death. Manifestation of these properties in patients is limited by low dosing necessitated by need to control the usual gastrointestinal side effects (nausea, vomiting, diarrhoea) of cholinesterase inhibitors. We have developed a derivative of galantamine (''Memogain'') for the following purposes: increased bioavailability in the brain and reduced, if not negligible, GI side effects at efficacious doses. **Methods:** Animal model studies to test for enhanced bioavailability in the brain, reduced dosing schemes, absence of gastrointestinal side effects, potency in overcoming drug-induced cognitive impairment, tissue distribution of pro-drug and active moiety, pharmacokinetics and toxicity. **Results:** Memogain is an inactive pro-drug of galantamine having more than 15fold higher bioavailability in the brain than the same doses of galantamine. Memogain is enzymatically cleaved in the brain to release its active moiety galantamine. In animal models of dementia, Memogain produced several fold larger cognitive improvement than galantamine, in the absence of any GI side effects. In the ferret dramatically reduced emetic responses were observed when Memogain was administered instead of galantamine. **Conclusions:** Should the advantageous properties of Memogain seen in animal models hold up to its action in man, we expect a dramatically improved side effects profile, no requirement for up-titration of dose to achieve satisfactory compliance, improved potency because of better delivery to the brain, and neuroprotective activity in addition to symptomatic cognitive enhancement. Memogain may become a second generation antidementive drug of combined symptomatic and disease-modifying properties.

P2-224 ACTIVITY OF PHOSPHOLIPASE A_2 (PLA_2) SUBTYPES IN RAT BRAIN IS ALTERED BY FEEDING CONJUGATED LINOLEIC ACID (CLA) AND LINSEED OIL

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Background: There are growing evidences that pathogenesis of neurological disorders are associated with an altered inflammatory response, where PLA_2 enzyme plays a key critical role. However, different PLA_2 subtypes have been identified in mammals which can differ in several aspects such as substrate specificity. Noteworthy, recent studies found reduced $iPLA_2$ activity in blood samples and postmortem brain tissues of Alzheimer patients. Since certain CLA isomers and n-3 polyunsaturated fatty acids (n-3 PUFA) have been shown to modulate selectively PLA_2 activity, dietary supplementation with these FA could influence Alzheimer's disease progression. **Methods:** This study was designed to evaluate the effects of CLA and linseed oil on activity of PLA_2 subtypes ($iPLA_2$, $sPLA_2$ and $cPLA_2$) in rat brain. Forty-eight Wistar rats (75 ± 10 days-old) received by gavage 1.1 ml/day of the following treatments, for 30 days: 1) Control (saline solution); 2) CLA supplement; 3) sunflower oil (SO) and 4) linseed oil (LO). The CLA supplement contained 60% of total CLA (30% of trans-10 cis-12 and 30% of cis-9 trans-11) as methyl esters. SO and LO contained 65% of linoleic acid and 50% of α-linolenic acid and were used as a source of n-6 and n-3 PUFA, respectively. After 30 days, animals were decapitated and samples of hippocampus and frontal cortex were collected to perform PLA_2 subtypes activity essays. Results were analyzed by ANOVA followed by Tukey-test and differences were declared significant at $P<0.05$. **Results:** Activity of $iPLA_2$ in the cortex increased by 160 and 145% ($P<0.05$) in LO when compared with SO and control, respectively. However, activities of $sPLA_2$ and $cPLA_2$ were unaltered by treatments in the cortex. In the hippocampus, there were no differences among treatments for both $iPLA_2$ and $sPLA_2$, but activity of $cPLA_2$ increased by 262, 210 and 400% ($P<0.01$) in CLA when compared with LO, SO and Control (0.16 vs. 0.061, 0.076 and 0.040 pMol/mg prot/min, respectively). **Conclusions:** Our results suggest a nutraceutic potential of linseed oil and CLA for prevention and/or inhibition of Alzheimer's disease progression.

P2-225 CHARACTERIZATION OF INOSITOL TRANSPORTERS AS A METHOD FOR DRUG DELIVERY TO THE CNS

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Background: One challenge to designing drugs for targeting CNS diseases is to develop compounds that when given orally, cross the blood-brain barrier to reach their target sites in the brain. One design strategy is to develop drugs that can cross into the brain using a known transport system. myo-Inositol is able to cross into the brain using the inositol transporters, of which there are three: one hydrogen/myo-inositol cotransporter (HMIT) and two sodium/myo-inositol cotransporters (SMIT1, SMIT2). Our laboratory has previously shown that scyllo-inositol, ELND005, is able to both prevent and reverse Alzheimer's disease pathology in the TgCRND8 mouse model of Alzheimer's disease. We have also shown, using gas chromatography/mass spectrometry, that ad libitum treatment of mice with scyllo-inositol results in a significant increase in the brain levels of scyllo-inositol in both TgCRND8 and non-Tg littermates (Fenili et al, 2007, J Mol Med). **Methods:** Competitive transport assays have been developed to examine the minimal binding requirements for transport by the three known inositol transporters in astrocytic and neural cell lines. Inositol, simple sugars and related compounds, 20 in total, were used to define the structural features required for active transport. Further the relative expression of the transporters as a function of age and disease progression was analyzed in the cortex, hippocampus, septum and cerebellum using QPCR. **Results:** Across all brain regions analyzed the expression level of the transporters were HMIT > SMIT1 > SMIT2. This result did not vary with age or disease phenotype. **Conclusions:** All three inositol transporters are expressed in the brain, with a similar pattern of expression being observed regardless of brain region.

P2-226 PUBLIC SUPPORT FOR AN ANNUAL TAX INCREASE TO PROVIDE ACCESS TO AN ALZHEIMER'S DISEASE MEDICATION IN CANADA

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Background: In Canada, the cost of Alzheimer's disease (AD) medications is mainly borne by patients and caregivers. The primary objective of this study was to measure the Canadian general public's support for a program of unrestricted access to AD medications. The secondary objective was to identify determinants of support for the program. **Methods:** A national sample of 500 Canadians, aged 18 years or older, was randomly recruited to participate in a computer-assisted telephone interview. The sample was stratified by income. Participants were presented with a set of randomly-ordered scenarios describing a hypothetical, new AD medication. The efficacy of the medication was varied by scenario: the medication was alternately described as modifying the symptoms of cognitive decline or actually halting disease progression. The adverse effects profile was also varied in the scenarios: no adverse effects or a 30% chance of some adverse effects. For each scenario, participants were asked whether they supported an annual increase in personal income taxes to fund unrestricted access to the AD medication.