AMINOPHENOLIC AMYLOID-BETA ANTIAGGREGANTS, A SERIES OF COMPOUNDS DEVELOPED FROM 3-HYDROXYANTHRANILIC ACID: A MECHANISM OF ACTION STUDY

ARTICLE *in* ALZHEIMER'S AND DEMENTIA · JULY 2014

Impact Factor: 12.41 · DOI: 10.1016/j.jalz.2014.05.637

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Conclusions: These preliminary data show a weak-to-moderate but significant association between dual-task gait performance and cognitive function in community-dwelling patients with AD. Whether this dual-task cost can be reduced by exercise is investigated in the ADEX study.

P1-395 AMINOPHENOLIC AMYLOID-BETA ANTIAGGREGANTS, A SERIES OF COMPOUNDS DEVELOPED FROM 3-HYDROXYANTHRANILIC ACID: A MECHANISM OF ACTION STUDY

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Background: Amyloid-beta (Aβ) is implicated in the neurodegeneration associated with Alzheimer's disease (AD). In its monomeric form, Aβ is non-toxic, but soluble oligomeric aggregates of Aβ are believed to be the chief mediators of neurotoxicity. Aβ antiaggregants have been shown to prevent peptide oligomerization and soluble oligomer formation. Accordingly, novel Aβ antiaggregants have garnered interest as putative therapeutics in AD. **Methods:** 3-Hydroxyanthranilic acid (3HAA), a kynurenine metabolite of tryptophan, was identified via an in silico screen of molecules endogenous to the human brain; these results were confirmed using an in vitro thioflavin-T (ThT) binding assay. Simple functional changes in 3HAA produced an analogue series that retained antiaggregant properties in the ThT assay. As such, the diversity space of 3HAA was explored to better understand structural and functional requirements to afford antiaggregant ability. A series of aminophenolic antiaggregant molecules were developed using bioisosteric, alkyl and aryl substitutions. Analogue development was supplemented with molecular modeling (MM). Several nuclear magnetic resonance (NMR) techniques were used to gain insight into the mechanism of action for novel aminophenolic antiaggregants including: DOSY, wLOGSY, trNOESY, and STD-NMR. Studies were conducted using full Aβ 1-40 as well as several smaller peptides contained within the sequence of Aβ. **Results:** Several potent aminophenol antiaggregants were synthesized, showing excellent Aβ antiaggregant activity per ThT. NMR studies and preliminary MM suggest that the K 16 L 17 V 18 F 19 motif of Aβ is the region at which aminophenol antiaggregant interaction occurs; this motif is different from other classes of antiaggregant molecules we have developed, thereby suggesting that 3HAA may be a starting point for novel chemical entities (NCEs) with Aβ antiaggregant activity. **Conclusions:** A novel class of aminophenol antiaggregants was synthesized that possess excellent Aβ antiaggregant activity in vitro; these molecules may serve as an excellent platform for further development of drug-like NCEs which may serve as Aβ antiaggregants.

P1-396 CYSTEINE PROTEASE INHIBITOR, E64D, OF CATHEPSIN B REDUCES PGLU-ABETA AND ABETA, AND IMPROVES MEMORY DEFICITS IN THE APPLON MOUSE MODEL OF AD

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Background: Pyroglutamate amyloid-beta peptides (pGlu-Abeta) are particularly pernicious forms of Abeta. pGlu-Abeta and full-length Abeta peptides accumulate in Alzheimer's disease (AD) brains, leading to severe memory deficits. pGlu-Abeta peptides are N-terminally truncated forms of full-length Abeta peptides with modification of the N-terminal glutamate to form pGlu-Abeta(3-40/42). The prominent presence of pGlu-Abeta in AD brains and involvment pGlu-Abeta to initiate formation of oligomeric neurotoxic Abeta forms may be key in AD. Our recent research indicates the key role of the alternative beta-secretase cathepsin B (CatB) in the production of pGlu-Abeta and Abeta (Hook et al., 2014, in press; Kindy et al., 2012), suggesting that inhibitors of CatB can reduce pGlu-Abeta and Abeta. Therefore, this study investigated the cysteine protease inhibitor E64d, that inhibits CatB, for its effectives in reducing Abeta peptide forms and improving memory deficits in APPLon AD mice, which express APP-695 and have the wild-type (wt) beta-secretase activity present in most AD patients. **Methods:** APPLon mice were administered E64d (oral), using E64d prepared in the food chow. Memory deficits were then assessed by the Morris water maze test. Brain tissue samples were measured for levels of pGlu-Abeta and flAbeta peptides by ELISAs, and amyloid plaque load was assessed by quantitative immunohistochemistry. **Results:** E64d treatment reduced brain levels of pGlu-Abeta(3-40/42), flAbeta(1-40/42), and pGlu-Abeta/Abeta plaque load in APPLon mice. E64d treatment of APPLon mice with CatB gene knockout resulted in similar level of Abeta peptide reduction,. Notably, E64d resulted in substantial and significant improvement in memory deficits. **Conclusions:** Administration (oral) of the cysteine protease inhibitor E64d to APPLon mice resulted in decreased brain levels of pGlu-Abeta and flAbeta, decreased amyloid plaque load, and substantial improvement in memory deficits. E64d is known to be safe in patients, based on extensive clinical trials in Japan for muscular dystrophy. These data strongly suggest that the E64d type compound(s) will be useful as therapeutic drug candidates for treating AD patients.

P1-397 SUVN-G3031: A NOVEL AND POTENT HISTAMINE H3 RECEPTOR ANTAGONIST FOR POTENTIAL TREATMENT OF COGNITIVE DEFICITS

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Background: H 3 receptors play a critical role as neuromodulators through their widespread distribution in the central nervous system. Blockade of this receptor augments the pre-synaptic release of both histamine and other neurotransmitters including acetylcholine from cholinergic neurons. Currently, several H 3 receptor antagonists/inverse agonists are in different stages of clinical trials for the potential treatment of narcolepsy, cognitive impairments associated with Alzheimer's disease, Parkinson's disease, schizophrenia and attention deficit hyperactivity disorder. **Methods:** In vitro affinity and selectivity profile was assessed in suitable systems. Pharmacokinetic and brain penetration was evaluated in male Wistar rats. In-vivo receptor occupancy was carried at various dose levels using non-radiolabled tracer. SUVN-G3031 was evaluated in H 3 agonist induced dipsogenia assay and rat models of cognition like object recognition task, T-maze and Morris water maze task. Effect of SUVN-G3031 on histamine and acetylcholine modulation in brain was studied using microdialysis. Toxicity profile of SUVN-G3031 was evaluated in rodents/ non rodents and In vitro models. **Results:** SUVN-G3031 is one of the lead molecules with hKi of 8.7 nM and has more than 100 fold selectivity against the related GPCRs. SUVN-G3031 exhibited desired pharmacokinetic property and brain penetration. This molecule exhibited an excellent separation between H 3 affinity and hERG ion channel inhibition. SUVN-G3031 blocked R-α-methylhistamine induced water intake and increased tele -methylhistamine levels in brain and cerebrospinal fluid. Treatment with SUVN-G3031 significantly reversed time induced memory deficit in novel object recognition test & T-maze task and scopolamine induced memory deficit in Morris water maze task. A single oral administration resulted in H 3 receptor occupancy up to 85% in rats and significantly raised acetylcholine and histamine levels in the cortex. SUVN-G3031 was well tolerated in toxicity studies in animals with wide margin of safety and is non mutagenic. **Conclusions:** SUVN-G3031 displayed desired efficacy, safety, pharmacokinetic and metabolic