LISPRO, an ionic cocrystal of lithium, as a potential novel treatment for Alzheimers disease

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USA

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LISPRO, an ionic cocrystal of lithium, as a potential novel treatment for Alzheimers disease

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NIH (NIA)

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15/05/2016

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1

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Brain Disorders... Dementia... Neurodegenerative... Neurosciences

Research Abstract
DESCRIPTION (provided by applicant): Recently, we were the first to report the crystal structure of an ICC of lithium with an organic anion, salicylic acid, and l-proline (LISPRO). We also found that this change in speciation did not negatively affect the bioactivity of lithium at several endpoints with relevance to the treatment of AD. These clinically relevant endpoints included: increasing inhibitory GSK3ß (Ser9) phosphorylation and decreasing tau hyperphosphorylation in human tau transfected HeLa cells as well as modulating/rebalancing GSK3ß (Ser9/Thr390) phosphorylation and reducing ß-amyloid deposits and levels of tau hyperphosphorylation in Tg2576 mice. In addition, LISPRO treatment promoted anti-inflammatory/Th2 responses and decreased proinflammatory soluble CD40 ligand (CD40L) in the CNS of these mice. Importantly the salicylate group may underlie these added effects not seen with LiCO3. Not only did the cocrystal outperform or match the efficacy of the lithium control at all endpoints but it also produced profound modulation of lithium's pharmacokinetics. Previously, no lithium salts were reported with modulated pharmacokinetics. By incorporating the salicylate anion into the crystal structure, we achieved plateau-like plasma and brain lithium levels out to 48 h in rats. Most importantly LISPRO reduced the toxic plasma level spike seen with Li2CO3 which has been associated with adverse effects. LISPRO could completely abolish this spike and we hypothesize that this will significantly enhance its safety. Further, salicylic aid is the primary active metabolite in aspirin and, unlike current FDA- approved lithium salts, this anion is bioactive and may be synergistic for reducing neuroinflammation associated with AD. In this proposal, we intend to fully characterize LISPRO's therapeutic potential in 3XTg-AD mouse model in the following 3 specific aims: (1) Examine cognitive impairment in 3XTg-AD mice following oral LISPRO treatment – we will examine whether oral administration of LISPRO could improve neurocognition in 3XTg-AD mice using a well established battery of behavioral tests. Further, we will test if this cognitive improvement could be correlated with reductions in AD-like pathology (Aß levels/deposits and NFT formation). (2) Determine AD-like pathological changes in 3XTg-AD mice following oral LISPRO treatment – Following LISPRO treatment, we will sacrifice these mice at several ages to examine AD-like pathological changes, and possible undesirable side-effects including Notch processing and any possible renal impairment. Groups will be compared by their effects on AD-like pathology. (3) Characterize glial activation states ex vivo in young and aged 3XTg-AD mice following oral LISPRO treatment – We will examine LISPRO's ability to promote the M2 phenotype ex vivo in primary microglia isolated from young or aged LISPRO-fed 3XTg-AD mice compared with those fed control diets. These data should be important to begin to understand how LISPRO mechanistically works at the cellular level to reduce AD pathology and cognitive impairment.

Lay Summary
PUBLIC HEALTH RELEVANCE: Alzheimer's disease (AD) is a chronic, progressive dementia associated with impairment in memory and behavior. It currently accounts for about 70% of all dementias and onset typically occurs in mid-late life. The frequency doubles every five years after age 60, increasing from a prevalence of about 1% in individuals aged 60 years to about 40% among those aged 85 years or greater. Thus this disease is a clear healthcare problem for all individuals living past the age of 60. In terms of healthcare costs, it's estimated that the toal

direct and indirect costs related to AD alone are, on a per-patient basis, some $91,000 over the course the illness. In this proposal, we intend to fully characterize the therapeutic potential of n ICC of lithium with an organic anion, salicylic acid, and l-proline (LISPRO) in 3XTg-AD mouse model. These studies could lay the foundation for AD clinical trials with LISPRO in the near future.

Further information available at:

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United States of America

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Alzheimer's disease & other dementias

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