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Submitter Details:

Affiliation: INDUSTRY

Status: Civilian, Other (Non-Government)

Name: Dr. Denis Kay

Primary Email: dkay@alphacognition.com

Secondary Email: dgkay@neurodyn.ca

Phone: 1 902 314 0776

Organization: Alpha Cognition Inc
Vancouver, British Columbia V6B 6L2
Canada

Presenter Details:

Affiliation: INDUSTRY

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Primary Email: dkay@alphacognition.com

Secondary Email: dgkay@neurodyn.ca

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Organization: Alpha Cognition Inc
Vancouver, British Columbia V6B 6L2
Canada

Co-Authors Detail:

Denis Kay[1], Michael Chopp[2], Haiyan Pang[3], Zheng Gang Zhang[2], Ye Xiong[3]
[1]ALPHA Cognition Inc, Vancouver, BC, CA.

[2]Neurology, [3]Neurosurgery, Henry Ford Health System, Detroit, MI, USA

Abstract Details:

Breakout Session: Traumatic Brain Injury Treatment for Early Combat, In-theater Administration

Submission Category: Oral Presentation

Title: ALPHA-1062 Reduces Phospho-Tau Deposition, is Neuroprotective and Enhances Restoration of Sensory, Motor and Cognitive Performance in a Preclinical Model of Moderate Traumatic Brain Injury

Abstract:

Introduction:
Traumatic brain injury (TBI) is an especially important health problem for US military service members & Veterans. For Veterans of Operation Iraqi Freedom/Operation Enduring Freedom/Operation New Dawn (OIF/OED/OND), TBI accounts for the majority of combat casualties, with more than 85% diagnosed as mild-TBIs (mTBIs). Although most mTBI resolves over time, the percentage cases that progress to a chronic phase, sometimes termed ‘post concussion syndrome’ is estimated to be between 10 & 25%. Finally, a history of TBI is associated with increased risk of developing Alzheimer’s disease. A recent

assessment of 350,000 US veterans found that mTBI was significantly associated with more than a 2-fold increase in the risk of dementia diagnosis. Thus, mTBI can result in significant long-term morbidity.
Following mTBI there are significant pathological changes in CNS metabolic & cellular functions that include mitochondrial dysfunction, blood-brain-barrier (BBB) disruption which can be widespread, impairment of neurogenesis, chronic inflammation, oxidative stress, excitotoxicity, & apoptosis. The complexity & diversity of these secondary injury mechanisms may require neuroprotective approaches to target multiple delayed injury factors rather than targeting any single factor.
Rationale for the use of ALPHA-1062: ALPHA-1062 is a lipophilic, essentially pharmacologically inert, pro-drug of the Alzheimer's disease cognitive enhancer galantamine (Razadyne/Reminyl). Following intranasal administration ALPHA-1062 rapidly crosses the nasal mucosa, gains access to the blood compartment & thence the CNS where it is activated by de-esterification to galantamine. This route of administration bypasses first pass metabolism & reduces systemic [gastrointestinal] side effects.
ALPHA-1062 has been demonstrated both during pre-clinical development, & in Phase 1a & 1b single ascending dose & multiple ascending dose studies, to deliver galantamine to the brain with apparent greater tolerability than oral galantamine. In the Phase 1 studies ALPHA-1062 administration, at pharmacologically effective doses, was found to be safe & well tolerated, & exhibited evidence of cognitive benefit with improved focus/attention documented in both healthy young & elderly subjects.
ALPHA-1062's active metabolite galantamine, exhibits both acetylcholinesterase inhibition & nicotinic receptor sensitization, & has previously been demonstrated in pre-clinical models to decrease damage to the BBB following TBI, reduce neuroinflammation, decrease glutamate toxicity, activate cell survival signaling pathways, & enhance neurogenesis.
By exerting multiple effects that are beneficial to the injured brain, we believe that ALPHA-1062 will have a better opportunity to be successful in treating TBI than c&idates that only address one aspect of the pathophysiology resulting from TBI.
Here we report the results of a study designed to assess the efficacy of intranasally administered ALPHA-1062 in a controlled cortical impact (CCI) model of moderate TBI in rats.

Materials & Methods:
Young adult male Wistar rats (2-3 months) received an CCI injury that consisted of a single impact at 4.0 m/sec, 2.5 mm deformation to the left parietal cortex. This model of TBI consistently leads to deficits on motor, sensory, & cognitive functional tests. Following injury, animals were then administered ALPHA-1062 at 4.5 mg/kg or vehicle (purified water as treatment control) intranasally (IN), with treatment initiated 2 hr after injury & continued twice (6 h interval) daily for 35 days. A third cohort was surgically prepared for TBI but not subjected to injury (sham controls). Treatment was initiated relatively soon following injury as we believe that the earliest practical intervention, followed by sustained treatment with an adequate level of ALPHA-1062 will have the greatest impact in preventing or blunting the development of TBI pathophysiology. Although aggressive, this time window for intervention is similar to that employed in the treatment of soft tissue trauma, as well as stroke.
Following TBI, functional recovery was assessed by a series of sensorimotor & cognition tests. Sensorimotor assessment began one day following CCI & was repeated weekly throughout the 35-day study. These tests consisted of a foot fault test (locomotor skill assessed), an adhesive removal test (both sensory & motor function assessed), & a modified neurological severity score (motor, sensory, balance & reflex functions assessed). During the last week of the study animals were assessed for spatial learning & memory function, using a modified Morris water maze (MWM), & recognition memory by a novel object recognition test. Both tests are sensitive measures of hippocampal function.
Evidence of neuroprotection & increased neurogenesis was assessed histologically & by immunohistochemistry (IHC). All rats were sacrificed after the last MWM test 35 days after TBI, & brain tissue was subjected to the following histological analyses, determination of: lesion volume (H&E), neuronal cell loss in injured cortex & hippocampus (NeuN IHC), total Tau & pTau burden (Tau/p-Tau IHC), neuroblast number (doublecortin IHC) &, newborn neurons (NeuN/BrdU double label IHC). To label proliferating cells bromrodeoxyuridine (BrdU), had been administered to all animals for seven days starting at one day post CCI). Detailed methodology for all methods described here can be found in: Zhang Y, et al., J. Neurotrauma. 38:1535–1550 (2021).
Statistical analysis: All data are presented as the mean ± standard deviation.Using one-way or two-way analysis of variance (treatment x time), differences between means were considered statistically significant when p was < 0.05.

Results:
In comparison to the vehicle (purified water) treatment control, ALPHA-1062 treatment initiated 2 hr post injury & continued twice daily for 35 days: 1) significantly improved sensorimotor functional recovery assessed by foot-fault, adhesive removal & modified neurological severity tests; 2) significantly improved cognitive functional recovery measured by the novel object recognition & modified MWM tests at 5 weeks after injury. ALPHA-1062 treatment additionally provided clear evidence of

neuroprotection, resulting in; 3) significantly reduced lesion size (decrease of 28%), 4) significantly reduced neuronal cell loss in the cortex & hippocampus of the injured side, 5) Significantly enhanced neurogenesis including augmentation of doublecortin positive neuroblasts as well as BrdU/NeuN positive new neurons in the Dentate Gyrus of the hippocampus, 6) significant reduction of p-Tau burden s in the cortex & hippocampus of the injured side [without changes in total-Tau] 7) ALPHA-1062 did not significantly alter the body weight over the 35-day study indicating a lack of toxicity. This was consistent with other preclinical experience with this dose range of intranasally administered ALPHA-1062.
Importantly, the extent of the functional recovery was such that in both cognition tests, & in the foot fault & adhesive removal tests, the performance of the ALPHA-1062 treated animals was indistinguishable from that of the sham (uninjured) animals. Again, in the quantitation of cell loss ALPHA-1062 provide sufficient neuroprotection that the cell numbers in the cortex & hippocampus of the injured side of the brain were indistinguishable from those determined for uninjured animals.

Conclusions.
Initiating treatment with ALPHA-1062 at 2 hr following a moderate TBI, followed by 35 days BID significantly: (i) provided neuroprotection & stimulated neurogenesis, when compared to vehicle treatment alone. (ii) improved sensorimotor & cognitive functional recovery, when compared to vehicle treatment alone. (iii) decreased p-Tau burden observed suggesting the potential for ALPHA-1062 treatment following TBI, to reduce one the pathological drivers of the elevated risk of dementia in TBI patients.

Disclaimer: The research reported here was supported financially by ALPHA Cognition Inc (ACI) through a research contract awarded to the Henry Ford Health System (Detroit, MI). ACI staff participated in the design of the study only. ACI staff were not involved in the conduct of the experimental research, the data analysis or preparation of the study report.

Learning Objectives

1. Learn that treatment with ALPHA-1062 at 2 hr following a moderate TBI, followed by 35 days of BID treatment, in rodents significantly; provided neuroprotection, reduced p-Tau burden and stimulated neurogenesis, when compared to vehicle treatment alone.
2. Recognize that ALPHA-1062 treatment significantly improved sensorimotor and cognitive functional recovery in a rat contusion model of TBI, when compared to vehicle treatment alone.
3. Understand that the reduced p-Tau burden observed following ALPHA-1062 treatment has the potential to reduce one the pathological drivers of the elevated risk of later life dementia development in TBI patients.

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