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Featured Article

Does traumatic brain injury hold the key to the Alzheimer's puzzle?

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Abstract

Introduction: Neurodegenerative disorders have been a graveyard for hundreds of well-intentioned efforts at drug discovery and development. Concussion and other traumatic brain injuries (TBIs) and Alzheimer's disease (AD) share many overlapping pathologies and possible clinical links.

Methods: We searched the literature since 1995 using MEDLINE and Google Scholar for the terms concussion, AD, and shared neuropathologies. We also studied a TBI animal model as a supplement to transgenic (Tg) mouse AD models for evaluating AD drug efficacy by preventing neuronal losses. To evaluate TBI/AD pathologies and neuronal self-induced cell death (apoptosis), we are studying brain extracellular vesicles in plasma and (-)-phenserine pharmacology to probe, in animal models of AD and humans, apoptosis and pathways common to concussion and AD.

Results: Neuronal cell death and a diverse and significant pathological cascade follow TBIs. Many of the developing pathologies are present in early AD. The use of an animal model of concussion as a supplement to Tg mice provides an indication of an AD drug candidate's potential for preventing apoptosis and resulting progression toward dementia in AD. This weight drop supplementation to Tg mouse models, the experimental drug (-)-phenserine, and plasma-derived extracellular vesicles enriched for neuronal origin to follow biomarkers of neurodegenerative processes, each and in combination, show promise as tools useful for probing the progression of disease in AD, TBI/AD pathologies, apoptosis, and drug effects on rates of apoptosis both preclinically and in humans. (-)-Phenserine both countered many subacute post-TBI pathologies that could initiate clinical AD and, in the concussion and other animal models, showed evidence consistent with direct inhibition of neuronal preprogrammed cell death in the presence of TBI/AD pathologies.

Discussion: These findings may provide support for expanding preclinical Tg mouse studies in AD with a TBI weight drop model, insights into the progression of pathological targets, their relations to apoptosis, and timing of interventions against these targets and apoptosis. Such studies may demonstrate the potential for drugs to effectively and safely inhibit preprogrammed cell death as a new drug development strategy for use in the fight to defeat AD.

Keywords: Concussion; Alzheimer's disease; Neuropathology; Anecrotic cell death; Preprogrammed cell death; Timing of therapeutic interventions; Drug targets

1. Introduction

Since the identification of the nucleus basalis of Meynert lesion in Alzheimer's disease (AD) brains in 1983, over 3 decades of intensive preclinical investigation and drug candidate evaluations have failed to mitigate the onset of dementia for affected patients [1]. AD investigators are not alone. Neurodegenerative disorders have been a graveyard for hundreds of well-intentioned efforts at drug discovery and development [2,3]. In spite of promising effects in animal models, all attempts at drug arrests of degenerative brain pathologies have failed in clinical trials. No drug has successfully altered the disease course in AD, arrested the pathologies in

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Parkinson's disease (PD), and mitigated the pathological effects from traumatic brain injuries (TBIs) including concussions and course of other neurodegenerative disorders.

After a review of the literature, we concluded earlier that, under current conditions, for scientific [3] and regulatory [4] reasons, development of a clinically effective anti–amyloid β 42 ($A\beta_{42}$)-targeted therapy was unlikely. As a consequence, we considered how AD investigators might turn current research emphases in different directions that potentially offer opportunities to outflank, rather than frontally assault, AD. In general, neurodegenerations, while distinguished by specific pathologies and clinical presentations, share general features; specifically, chronic, slowly unfolding cascades of poorly understood associated pathologies. One potentially promising approach to understanding these shared and probably important contributory pathological sources for disease progression in neurodegenerations may arise from the controversial but frequently reported association between AD and concussion/TBIs [5–9]. Chronic degenerative processes may be difficult to understand in part because of the slow and unpredictable unfolding of events; for example, Aβ deposits have been detected during the fourth decade of life in brains of persons regarded at increased risk of later dementia. Yet, extensive Aβ deposits and neurofibrillary tangles (NFTs) comprising hyperphosphorylated tau (p-Tau), both pathognomonic neuropathological features of AD, have been reported in cognitively unimpaired persons in their eighth and ninth decades of life. Many of the pathologies found in these 5 decades of unfolding AD pathologies have also been reported as present in and unfolding within weeks following TBIs: inflammatory, glutaminergic, oxidative, Aβ, cholinergic, and other environmental stressors of neurons [10,11]. We undertook the opportunity to study, in more depth, TBI as a possible model contributory to better understanding the puzzle of AD. We were motivated to turn in this direction as a result of the overlapping AD/TBI pathologies and the potential advantages from being able to study the interrelations among pathologies during their accelerated unfolding following their provocation by the stressor TBI.

As a result of this turn, we have found a range of potential opportunities deserving further consideration.

- As background, we provide a comparison of known TBI and AD pathologies and claimed clinical associations where patients report a history of TBI preceding the onset of AD.
- These overlaps reveal not only the possibility of identifying, in further studies of TBI, causal interrelations among AD neuropathologies but also a pressing need for plasma-based measures reflecting activities in the brain of these pathologies.
- As a consequence, under Methods and Results/Discussion, we pursue and describe the current potential for evaluating biomarkers derived from plasma extracellular vesicles (EVs; sometimes termed exosomes) expressing neuronal markers for brain origin to better inform AD clinical research about the state of pathologies in patients.
- A third implication from our initial studies of TBI pathologies may be the utilities from using a weight drop animal model for concussive injury as a supplemental assessment of candidate AD drugs.
- The ultimate aim of AD drug intervention is to prevent the onset of dementia due to losses of neurons. We have found that the TBI animal weight drop model provides the opportunity to study AD drug effects on neuronal death occurring secondary to induced pathologies.
- There is a pressing need for plasma biomarkers of brain-specific neurochemical processes. Neuronally and astrocyte-marked EVs show promise as plasma-sourced indicators of brain neurochemical activities.
- As we discuss with EVs, used as an intervention, a drug, in both *in vitro* and *in vivo* animal model studies, serves potentially as both a pharmacological probe and a therapeutic candidate.
- As a result from probing anoxia, weight drop, and AD-related models and *in vitro* mechanisms with (-)-phenserine, we are able to report that the indirect neuroprotective activities of drugs from mitigation of disease pathologies may be capable of countering AD and related neurodegenerations with a direct anti-programmed cell death drug activity.
- Finally, this preliminary evidence from (-)-phenserine probing of various animal models suggests to us the utility of introducing into AD drug development increased uses of small intensively assessed clinical trials. Q4
- Hence, in synopsis, to aid development of AD drug interventions that prevent the onset of dementia due to dysfunction and losses of neurons, the application of a TBI animal model (such as the weight drop model) provides an opportunity to study AD drug effects on neuronal death occurring secondary to induced pathologies. Up till now, most candidate AD drugs gain traction from successes in AD transgenic (Tg) mouse models that represent critical pathologies regarded as responsible for clinical AD. However, interventions against these pathologies have failed when translated into humans in clinical trials; with hundreds of promising preclinical drug candidates failing to arrest the progression of AD over the past decade. The screening of drugs in animal models requires a change, by being more rigorous and including models for alternative pathologies. Inclusion of a TBI model provides accelerated development of neurodegenerative brain pathologies and neuronal compromise and death and can supplement or possibly replace existing models for drug interventions against AD and perhaps other neurodegenerative diseases whose time-dependent process can be evaluated by the use of EV technology that provides a window to the brain.