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Featured Article

Blast traumatic brain injury–induced cognitive deficits are attenuated by preinjury or postinjury treatment with the glucagon-like peptide-1 receptor agonist, exendin-4

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Abstract

Background: Blast traumatic brain injury (B-TBI) affects military and civilian personnel. Presently, there are no approved drugs for blast brain injury.

Methods: Exendin-4 (Ex-4), administered subcutaneously, was evaluated as a pretreatment (48 hours) and postinjury treatment (2 hours) on neurodegeneration, behaviors, and gene expressions in a murine open field model of blast injury.

Results: B-TBI induced neurodegeneration, changes in cognition, and genes expressions linked to dementia disorders. Ex-4, administered preinjury or postinjury, ameliorated B-TBI–induced neurodegeneration at 72 hours, memory deficits from days 7–14, and attenuated genes regulated by blast at day 14 postinjury.

Conclusions: The present data suggest shared pathologic processes between concussive and B-TBI, with end points amenable to beneficial therapeutic manipulation by Ex-4. B-TBI–induced dementia-related gene pathways and cognitive deficits in mice somewhat parallel epidemiologic studies of Barnes et al. who identified a greater risk in US military veterans who experienced diverse TBIs, for dementia in later life.

Keywords: Exendin-4; Blast injury; Traumatic brain injury; Neurodegeneration; Alzheimer's disease; Parkinson's disease; Behavioral deficits; Gene expression; Glucagon-like peptide-1

1. Introduction

Traumatic brain injury (TBI) is a significant cause of disability and death worldwide, particularly among military forces serving in modern combat operations. It is estimated that approximately 19.5%–22.8% of all returning deployed US troops suffer exposure to blast and/or concussive TBI [1], with the total number of such injuries estimated to be as high as 320,000 [2]. Blast TBI is defined as an injury imposed on the brain after a blast detonation of an explosive

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device. Currently, there are four classifications of "blast" injury; (1) primary injury that is caused solely by the changes in atmospheric air pressure producing compression and expansion of tissues and fluid filled regions of the brain. (2) Secondary injury caused by objects turning into projectiles that strike the heads of individuals. (3) Tertiary injury occurs when individuals themselves are turned into projectiles and they collide with other objects and or people. Finally, (4) quaternary injuries are related to blast-induced burns, smoke inhalation, and other environmental factors [3]. Furthermore, blast traumatic brain injury (B-TBI), similar to concussive-TBI, manifests different levels of severity, from mild (as is the case for our model presently described) to moderate and severe. Based on data made from military sources, mild TBI (mTBI) events are far more common than moderate and severe TBIs [1,4]. Personnel that experience TBI present with an increased vulnerability to the development of chronic neurodegenerative dementia-related disorders [5]. Because of the large numbers of military individuals that have experienced a TBI, these findings suggest that in the near future there may be an epidemic of early onset dementia.

In recent years, advances in our knowledge of the molecular mechanisms that regulate the health and survival of neurons, together with an understanding of key pathways induced by TBI that lead to neuronal dysfunction and death [6–8], are being applied to the development of experimental drugs with properties potentially beneficial for TBI treatment, whether concussive or blast related. Primary brain injury is induced by the immediate insult to the head, likely as a consequence of mechanical forces inducing shearing and compression of neuronal and vascular tissue at the time of trauma, as well as rotational head acceleration. A cascade of pathologic events may then follow that leads to further secondary brain injury that takes place from minutes to days after the trauma [9]. Edema, ischemia, inflammatory responses, free-radical generation, elevated excitatory neurotransmitters (e.g., glutamate excitotoxicity), loss/disruption of synaptic connections, and DNA damage [6–10] lead to neuronal dysfunction, dendritic and synaptic loss and, when cellular damage is sufficiently profound, apoptosis [11–16]. Such factors may then exacerbate inflammatory processes to trigger the development of a self-propagating adverse cycle of events [17–20].

Counterbalancing apoptotic pathways leading to cell death are biochemical cascades that promote cell survival [21,22]. To this end, we have been studying cell survival/neuroprotection consequent to G-protein–coupled receptor (GPCR) activation, specifically focusing on the glucagon-like peptide-1 receptor (GLP-1R) and its long-acting peptide analogs [23], epitomized by exendin-4 (Ex-4) [24,25], that are of clinical relevance in type-2 diabetes mellitus [24,25] and neurodegenerative disorders [23,26–29]. Receptors for GLP-1 have been found in the brain; specifically throughout the cerebrum, including the cerebral cortex, hippocampus, substantia nigra, as well as pituitary, olfactory bulb, and within spinal cord and peripheral nerves [23,30,31]. In light of the numerous commonalities existing across neurodegenerative disorders and their occurrence in TBI, we recently demonstrated that a GLP-1R agonist Ex-4 acting via GLP-1R stimulation significantly mitigates the biochemical and behavioral sequela of concussive TBI [32–34].

In the present investigation, our goals were to assess mouse hippocampal and cortical neurodegeneration and hippocampal gene expression changes at an early time point after open field B-TBI in mouse. Additional goals were to study changes in behavioral performance at a later time point in the continuum of events following blast injury and hippocampal gene expression. We observed evidence of B-TBI–induced neurodegeneration, altered gene expression that were associated with dementia-related molecular pathways, and cognitive deficits. Significantly, we describe how treatment with Ex-4 before or after injury attenuates the development of B-TBI–induced neurodegeneration, memory impairments, and in large part prevents injury-induced changes in hippocampal gene expression. These studies suggest that this agent and likely similar drugs acting via the GLP-1R may have potential utility as therapeutic treatments for blast-induced traumatic brain injury in humans.

2. Materials and methods

2.1. Animal studies

A series of parallel animal studies were undertaken where Ex-4 was administered before (48 hours before) and after (2 hours after) a B-TBI or a sham procedure. (1) Hippocampal and cortical neurodegeneration was evaluated on day 3 after blast. (2) Animal cognition and anxiety-like behaviors were evaluated over a period of 7 days starting on day 7 after blast. (3) Hippocampal complementary DNA (cDNA) microarray gene expression studies were performed on day 3, at this time animals were administered Ex-4 preinjury or postinjury, and on day 14, where animals were administered Ex-4 as a pretreatment.

Male ICR mice weighing 30–40 g were kept five per cage under a constant 12-h light-dark cycle, at room temperature (22 ± 2°C). Food (Purina rodent chow) and water were available *ad libitum*. Each mouse was used for one experiment and for one time point only. The Ethics Committee of the Sackler Faculty of Medicine approved the experimental protocol (M-11-086), in compliance with the guidelines for animal experimentation of the National Institutes of Health (DHEW publication 85–23, revised, 1995). The numbers of animals per treatment group for the assessment of neurodegeneration, gene expression and animal cognition, were selected based on experience from prior studies [16,33,35,36], and specific numbers are provided in the following. All attempts were made to minimize both the numbers of mice used for our studies and their suffering. All experimental manipulations were conducted during the light phase of the light-dark cycle. At the time of animal euthanasia, a two-stage method