

Exercise Intervention in Traumatic Brain Injury

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Mini Review

Physical exercise offers a unique, non-pharmacological, non-invasive yet habit-strengthening, intervention that integrates different schedules/branches, whether of an endurance or resistance type that may be 'tailored' for both individuals who have suffered brain trauma and healthy individuals. In any case, it presents a critical requirement for an "empowered" lifestyle. The necessity of individuals' activity regime is linked to the assurance of normal, healthy developmental trajectories for structure and function over the complete lifespan of individuals, as evidenced from global public health physical activity guidelines. It restores the healthy homeostatic regulation of stress, cognitive-emotional affective status and the balance of the hypothalamic-pituitary adrenal axis together the amelioration or reversal of performance deficits observed in neurocognitive tasks under conditions of neurologic or psychiatric disorder. Under conditions mechanical infliction, exercise protects against vascular risk factors that include hypertension, diabetes, cellular inflammation and aortic rigidity through inducing direct changes to cerebrovasculature that involve beneficial changes in cerebral blood flow, angiogenesis and redemption from vascular disease which imply optimal brain plasticity. Essentially, physical exercise, maintained regularly even daily, may underpin the scaffolding constructions of the brain's adaptive process by facilitating the reinforcement and reinstatement of existing networks, circuits and pathways that, although damaged, provide the substrate for reconstruction following injury [1]. For rehabilitative measures following injuries to the brain exercise has proven useful although caution must be maintained since premature initiation of a program may aggravate symptoms and retrogress outcome [2]. A single session of exercise, independent of intensity, was found to induce a positive outcome for traumatic brain injury (TBI) patients, by (i) increasing positive feelings and (ii) reducing negative feelings [3]. Physical activity/exercise may ameliorate mitochondrial dysfunction, neuronal loss, reduce neuroinflammation, and facilitate recovery after brain injury.

Brain trauma, whether mild, moderate or severe, depending on cause and severity, may be accompanied by headache, of varying intensity, dizziness, loss of consciousness, blurred vision, hearing impediment, confusion, memory loss, seizure activity, paralysis and coma as the first-noticed symptoms,

with expectation of damage to blood-brain-barrier integrity, accelerated apoptosis and excitotoxicity. All of these signs and symptoms in various combinations, intensities, locations and stages will determine the extent of short-term and long-term destruction of physical, motor, cognitive, behavioral and emotional domains. Analyses of individual diagnoses from 57 studies meeting the inclusion criteria indicated that individuals presenting previous TBI showed higher odds (risk) of Alzheimer's disease, Parkinson's disease, mild cognitive impairment, depression, mixed affective disorders, and bipolar disorder compared with those individuals without TBI [4]. TBI may be presented as primary and secondary injury responses; the former represents immediate mechanical damage that appears at the moment of impact, and involves brain contusion, laceration, haemorrhage, axon transection and diffuse axonal injury whereas the latter, which progresses over hours, days and months, represents glutamate excitotoxicity, ionic gradient disturbances, metabolic disruption, mitochondrial dysfunction, reactive oxygen species formation, neuroinflammation and hypoxic-ischemic damage [5,6]. The secondary responses naturally exacerbate the primary responses [7,8]. Physical exercise exerts multiple interventional effects upon the destructive effects of TBI that extend from anti-apoptotic effects through reinstatement of cerebrovascular integrity to augmentation of neuroplasticity at cellular, circuit, regional and behavioral levels with greater dividends arising from the proactive implementation over the reactive initiation [9]. In this regard, delaying the initiation of exercise schedules ought to be avoided since complete rest exceeding three days is less advantageous to patient recovery, gradual resumption of pre-injury activities and exercise programs are warranted as soon as tolerated (with the exception of activities that contain a high mild TBI exposure risk), and supervised exercise programs may benefit patients with persistent symptoms [10]. Holland and Schmidt (2015) [11] have outlined the various factors, static (e.g. age, intellectual ability/education) and dynamic (e.g. exercise), that promote resilience following TBI over multiple domains of function, including cognition, emotional regulation, health, wellness and well-being, stress-coping, daily behavioral activities, etc. The notion of resilience is multifaceted, incorporating an individual's ability to properly adapt to stressful situations and injuries, including TBI, and adversity through the lifespan. Physical exercise influences recovery and

promotes resilience following TBI through mobilizing a variety of psychobiological/physiological processes [12-15] and may be compared with other types of neural activation progression from a viewpoint of cerebral integrity [16-18].

Animal models of TBI are designed so that each model produces a relatively homogeneous type of injury, regarding age, sex, genetic background, and the injury parameters which are well-controlled. In this regard, any particular animal model may not be able to represent completely all the aspects of secondary injury development that are observed in cases of human TBI, which may explain, at least partially, why therapeutic drugs that were indicative in preclinical studies failed within the reality of clinical studies [19]. Similarly, animal models of rehabilitative measures after TBI must be considered according to these constraints [20]. Nevertheless, much important information emerges from the preclinical laboratory. Using an animal model TBI, Taylor and colleagues (2015) [21] studied the effects of a 6-week exercise period, prior to TBI, upon (i) post-TBI behavioral responses in mice, and (ii) exercise-induced elevations of the neuroprotective molecules vascular endothelial growth factor-A and erythropoietin and heme oxygenase-1 in the sensorimotor cortex and hippocampus. They observed that pre-TBI exercise reduced post-TBI sensorimotor and cognitive deficits concurrent with increased vascular endothelial growth factor-A in the hippocampus, heme oxygenase-1 microRNA in the cortex and hippocampus and erythropoietin in the cortex. Similarly, Hu and colleagues (2015) [22] have shown that microRNA 21, involved in aspects of protection for cancer and heart disease, was active in neuroprotection provided by voluntary running-wheel activity following TBI treatment. Preconditioning, i.e. pre-TBI, voluntary running-wheel exercise was shown to reduce TBI-induced lesion size, attenuate neuronal loss in the hippocampus, cortex, and thalamus, and decrease microglial activation in the cortex. Furthermore, pre-TBI exercise activated the brain-derived neurotrophic factor pathway prior to the trauma and amplified the injury-dependent increase in heat shock protein 70 expression, thereby attenuating key apoptotic pathways [23]. These latter processes included reduction in CCI-induced up-regulation of proapoptotic B-cell lymphoma 2 (Bcl-2)-homology 3-only Bcl-2 family molecules (Bid, Puma), decreased mitochondria permeabilization with attenuated release of cytochrome c and apoptosis-inducing factor, reduced apoptosis-inducing factor translocation to the nucleus, and attenuated caspase activation. In the light of these neuroprotective actions, voluntary physical exercise may serve to limit the consequences of TBI.

Finally, there is a paucity of information regarding exercise-related epigenetic processes in horses. DNA methylation is a key mechanism for regulating gene expression in response to environmental changes and exercise alters methylation patterns. Gim and colleagues (2015) [24] observed that after 30 min of running exercise, 596 genes were hypomethylated and 715 genes were hypermethylated in the superior horses, whereas in the inferior horses, 868 genes were hypomethylated and 794 genes were hypermethylated. These genes were analyzed based on gene ontology (GO)

annotations and the exercise-related pathway patterns in the two horses were compared. After exercise, gene regions related to cell division and adhesion were hypermethylated in the superior horse, whereas regions related to cell signaling and transport were hypermethylated in the inferior horse. In the context of TBI, it may be considered that brain injury poses an adverse environment and as noted previously exercise offers a positive epigenetic environment. Taken together, the consensus of the evidence reported above implies that the 'pre-emptive' utilizations of exercise programs ought to be standard among guidelines for health and well-being administrations.

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