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An anatomical and physiological basis for the cardiovascular autonomic nervous system consequences of sport-related brain injury

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ABSTRACT

Concussion is defined as a complex pathophysiological process affecting the brain that is induced by the application or transmission of traumatic biomechanical forces to the head. The result of the impact is the onset of transient symptoms that may be experienced for approximately 2 weeks in most individuals. However, in some individuals, symptoms may not resolve and persist for a protracted period and a chronic injury ensues. Concussion symptoms are generally characterized by their emergence through changes in affect, cognition, or multi-sensory processes including the visual and vestibular systems. An emerging consequence of concussion is the presence of cardiovascular autonomic nervous system dysfunction that is most apparent through hemodynamic perturbations and provocations. Further interrogation of data that are derived from continuous digital electrocardiograms and/or beat-to-beat blood pressure monitoring often reveal an imbalance of parasympathetic or sympathetic nervous system activity during a provocation after an injury. The disturbance is often greatest early after injury and a resolution of the dysfunction occurs in parallel with other symptoms. The possibility exists that the disturbance may remain if the concussion does not resolve. Unfortunately, there is little evidence in humans to support the etiology for the emergence of this post-injury dysfunction. As such, evidence from experimental models of traumatic brain injury and casual observations from human studies of concussion implicate a transient abnormality of the anatomical structures and functions of the cardiovascular autonomic nervous system. The purpose of this review article is to provide a mechanistic narrative of multi-disciplinary evidence to support the anatomical and physiological basis of cardiovascular autonomic nervous system dysfunction after concussion. The review article will identify the anatomical structures of the autonomic nervous system and propose a theoretical framework to demonstrate the potential effects of concussive head trauma on corresponding outcome measurements. Evidence from experimental models will be used to describe abnormal cellular functions and provide a hypothetical mechanistic basis for the respective responses of the anatomical structures to concussive head trauma. When available, example observations from the human concussion literature will be presented to demonstrate the effects of concussive head trauma that may be related to anomalous activity in the respective anatomical structures of the autonomic nervous system.

1. Introduction

An association is emerging between the accumulated effects of concussive and sub-concussive head impacts and long-term neurological dysfunction and morbidity. The increasing number of observations and empirical evidence highlights that knowledge gaps for the full implication and manifestation of concussion injuries are as glaring as ever and that consequences to the injury may continue long after the overt symptomatology has resolved. A “silver-lining” to the recognition of these gaps, and the international scale of the estimated concussion occurrence rate of 6 per 1000 people (Cassidy et al., 2004), has been the infusion and acceptance of skills and techniques from new disciplines that not only contribute to our understanding of the concussive sequelae, but also provide a medium through which the injury may be diagnosed, severity/complexity potentially inferred, and time-course to symptom resolution monitored. This collective multi-national, interprofessional effort to address the public health crisis has led to the development and wide-scale adoption of a standardized side-line evaluation for suspected injuries (Mccrory et al., 2013), vigorous guidelines for injury management and the safe return-to-play (RTP) (Broglio

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et al., 2014; Herring et al., 2011; Harmon et al., 2013), and a more informed public and athlete population who expect accountability for safety monitoring and clinical decision making from medical professionals and sanctioning bodies of sports activities and events.

The consensus appreciation for the short and long-term effects of concussion often focus on the presence of subtle to clinically-significant affective disorders (Guskiewicz et al., 2007; Vynorius et al., 2016; Decq et al., 2016; Solomon et al., 2016), cognitive impairment (Broglio et al., 2012; Guskiewicz et al., 2005; Broglio et al., 2009; Rabinowitz and And Levin, 2014) and abnormal sleep patterns (Sullivan et al., 2016; Tkachenko et al., 2016; Kostyun, 2015). However, evidence for multisensory disorders (e.g., vestibular, oculomotor, etc.) being experienced after concussion (Ellis et al., 2016a; Ellis et al., 2015; Samadani et al., 2015), and in 'otherwise healthy' individuals with a prior history of concussion is also becoming apparent (Moore et al., 2014; Ellis et al., 2016b; Valovich Mcleod and Hale, 2015). There is evidence for hypopituitarism, a collection of hormone disorders in which the secretory patterns of one or more hormones along a given axis are abnormal, in post-acute concussion (La Fountaine et al., 2016a; Foley and And Wang, 2012), with chronic exposure to concussive and sub-concussive head impacts (Ives et al., 2007; Tanriverdi et al., 2008), among retired athletes with a history of concussion injuries (Kelly et al., 2014), and in military personnel with blast-induced mild traumatic brain injury (MTBI) (Wilkinson et al., 2012). Pituitary dysfunction can lead to growth hormone deficiency, hypovolemia and other hormone imbalances that may independently or collectively contribute to a reciprocal impairment of distal end organ function presenting in the clinical symptomatology and impact one's quality of life following injury. Thus, the presence of secondary dysfunction in several systems following concussion lends to the argument that other structures and their corresponding functions may also be subject to the acute influences of concussion, and perhaps, remain impaired if the clinical syndrome persists into the chronic, unresolved phase.

It has been suggested that an uncoupling of the cardiovascular (CV) autonomic nervous system (ANS) occurs on multiple levels after a traumatic brain injury (TBI) (Goldstein et al., 1998). The post-TBI uncoupling will most often present as a diminished or situationally (e.g., psychophysiological state) inappropriate efferent neural transmission to the effector organs (e.g., sinoatrial node, peripheral vasculature). However, placing this uncoupling into the context of a "reflex-arc", it must also then be appreciated that efferent responses generated by the CV-ANS are, under normal conditions and independent of advancing age, scaled in magnitude to perturbations by afferent stimuli (e.g., blood pressure/hemodynamic changes, hypercapnia), which suggests that central nervous system (CNS) integration must also be considered with local reflex adjustments. When an individual initiates physiological work that exceeds the resting metabolic state, there is a well-orchestrated series of ANS events that facilitate CV performance. Once the workload is initiated, parasympathetic nervous system (PNS) activity through the vagal nerve (cranial nerve X) is withdrawn from the sinoatrial node permitting the heart rate to increase; the magnitude of which is partially determined by the initial blood pressure changes through the arterial baroreflex. It is believed that this reduced PNS outflow accounts for much of the initial rise in heart rate during exercise. As the intensity and duration of the physiological work continues, sympathetic nervous system (SNS) outflow to the sinoatrial node and myocardium increases, causing a greater rate of discharge and force of contraction in the heart. With further increases of intensity and sustained duration, carbon dioxide and $H+$ ion waste products from cellular metabolism begin to accumulate in the blood causing a shift in pH toward a more acidic state. From here, arterial chemoreceptors located throughout the periphery send afferent signals to the brainstem and an increase in respiratory and heart rate ensues to enhance the off-loading of carbon dioxide from the system and to buffer the blood. This metaboreflex will then drive the system until volitional termination of the work or exhaustion ceases it. The most unique aspect to this sequence of events, is that the transition between states of CV-ANS and metabolic drive vary wildly between individuals and can change within an individual over time as an adaptation to routine physical activity and vigorous conditioning, or with persistent sedentarism, and in the proposed context of concussion, a transient neurological impairment of the ANS (Blake et al., 2016).

With our working appreciation for the CV-ANS, it is not surprising that concussed athletes whose injury have yet to fully resolve will routinely experience intolerance to exertion (e.g., hemodynamic stressors) under free-living conditions or while being evaluated for RTP. Guidelines on RTP, suggests that physical activity be reintroduced in a systematic manner such that the intensity and complexity of exertion be progressively increased toward expected levels of the respective sport performed (Broglio et al., 2014; Herring et al., 2011; Harmon et al., 2013). The limiting feature to progression toward RTP is the re-emergence of concussive symptoms, or evidence of reduced performance from a prior assessment. In other words, exercise intolerance, which may be clinically demonstrated as an abnormal heart rate or blood pressure response compared to controls for a given workload (Kozlowski et al., 2013), should be considered as a symptom of CV-ANS dysfunction following concussion. The review article will identify the anatomical structures of the autonomic nervous system and propose a theoretical framework to demonstrate the potential effects of concussive head trauma on corresponding outcome measurements. Evidence from experimental models will be used to describe abnormal cellular functions and provide a hypothetical mechanistic basis for the respective responses of the anatomical structures to concussive head trauma. When available, example observations from the human concussion literature will be presented to demonstrate the effects of concussive head trauma that may be related to anomalous activity in the respective anatomical structures of the autonomic nervous system.

2. Concussion pathophysiology

2.1. Cellular metabolism

Concussion is defined as a complex pathophysiological process affecting the brain that is induced by the application or transmission of traumatic biomechanical forces to the head resulting in any one, or combination of compressive, tensile, or shear stressors that are reasonably (e.g., compressive) or poorly (e.g., tensile or shear) tolerated by the neural tissue (Aubry et al., 2002; Guskiewicz et al., 2004; Gennarelli, 1993; Schneider, 1973; Cantu, 1997). The concussive insult to the brain results in a hyper-excitable state due to widespread neuronal membrane depolarization (Walker et al., 1944) and is characterized by a significant and indiscriminant outflow of neurometabolites, ionic fluxes (e.g., potassium and calcium) and excitatory neurotransmitters (Giza and Hovda, 2001; Giza and Hovda, 2014). This neurometabolic cascade appears to remain for a period up to 2 weeks after injury perturbing acute and sub-acute cellular physiological processes as the concentrations of excitatory neurotransmitters such as glutamate and the *N*-methyl-D-aspartate (NMDA) act on receptors leading to further/sustained neuronal depolarization with an efflux of potassium and influx of calcium (Giza and Hovda, 2001; Giza and Hovda, 2014), further perpetuating membrane instability. The cellular metabolic disorder arises as prolonged elevations in calcium may diminish oxidative mitochondrial ATP synthesis (Fineman et al., 1993; Osteen et al., 2001) and efforts to restore the resting membrane potential are enacted by the sodium-potassium pump, which requires increasing amounts of energy [e.g., adenosine triphosphate (ATP)] through enhanced glucose metabolism (Giza and Hovda, 2001; Giza and Hovda, 2014). Under normal conditions the brain consumes approximately 20% of ingested calories and oxygen (Clark and Sokoloff, 1999) and the induction of a hypermetabolic and glycolytic state would be accommodated through increases in cerebral blood flow (CBF) by local autoregulation and systemic hemodynamic responses.