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The Neurobiological Effects of Repetitive Head Impacts in Contact Sports

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Abstract

It is now recognized that repetitive head impacts (RHIs) in sport have the potential for long-term neurological impairments. In order to identify targets for intervention and/or pharmacological treatment it is necessary to characterize the neurobiological mechanisms associated with RHI. This review aims to summarize animal and human studies that specifically address Blood Brain Barrier (BBB) dysfunction, abnormal neuro-metabolic and neuro-inflammatory processes as well as Tau aggregation associated with RHIs, including soccer and other collision sports. Additionally, we examine the influence of physical activity and genetics on outcomes of RHI, discuss of methodological considerations, and provide suggestions for future directions of this burgeoning area of research.

Introduction

In recent years there has been increasing public concern regarding adverse effects of of repeated head impacts in soccer, as well as other contact sports, on brain health. In addition to overt concussions, contact sport athletes such as football, soccer, hockey players and boxers are exposed to repeated sub-concussive head impacts. Sub-concussive impacts to the head have been defined as “cranial impacts that do not result in a known or diagnosed concussion on clinical grounds” (p 1236) (Rodrigues, Lasmar, & Caramelli, 2016). It is now widely recognized that both repetitive concussive (Lipton et al., 2013) and sub-concussive impacts (Bailes, Petraglia, Omalu, Nauman, & Talavage, 2013) are associated with neuropsychological impairments.

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A comprehensive understanding the underlying neurobiological mechanisms associated with repetitive concussive and sub-concussive head impacts is essential to identify points of intervention and potential drug targets. Accordingly, the purpose of this review is to summarize evidence regarding several putative neurobiological mechanisms underlying adverse effects of concussive and sub-concussive repetitive head impacts (RHIs) in contact sports. Specifically, we will review the animal and human studies that examine neurobiological mechanisms relevant to brain injury including Blood Brain Barrier (BBB) dysfunction, abnormal neuro-metabolic and neuro-inflammatory processes as well as Tau aggregation in RHI (Mannix et al., 2014; Vynorius, Paquin, & Seichepine, 2016).

2. Blood Brain Barrier in repetitive head impacts

The Blood Brain Barrier (BBB) refers to endothelial tight junctions and glia components that separate the brain tissue from the peripheral vasculature. Breakdown of the BBB following Traumatic Brain Injury (TBI) is biphasic. An immediate BBB disruption due mechanical damage of the endothelium may be followed by a chronical disruption caused by ongoing neurochemical processes such as inflammation. Sequela of BBB disruption include cerebral edema and consequent increased intracranial pressure as well as precipitation of the coagulation cascade which can impede cerebral blood flow to the local injured site (Lipton, et al., 2013; Webbe and Ochs, 2003; Witol, 2003).

Animal studies

Few experimental animal studies have examined the effects of concussive RHIs on BBB integrity. In their recent review of the pathophysiological mechanisms of RHIs, Fehily and Fitzgerald (2017) illustrate that the current evidence of BBB disruption in rodent models of RHI is variable; two of six the studies they reviewed found evidence of BBB damage while the remainder identified no changes in BBB integrity. However, as described by the authors, divergent findings may be attributable to the time point at which rodent brains were analyzed after the final impact was delivered. Specifically, studies that sacrificed rodents more acutely showed no evidence of BBB damage (Choe, 2016).

Clinical studies

Serum S-100B, a calcium binding protein in the CNS, is commonly considered a biomarker of BBB integrity (Chodobski, Zink, & Szmydynger-Chodobska, 2011). S-100B has been measured in athletes at high risk for RHIs including boxers, American football players and soccer players. In an early study of amateur boxers, Graham et al. (2010) reported elevated serum levels of S-100B immediately following a 5-minute match in boxers who received mostly punches to the head but not in boxers who predominantly sustained impacts to the body (Fehily and Fitzgerald, 2017). On the other hand, Neselius et al. (2013) reported no elevation of S-100B in the serum of Olympic boxers 1–6 and 14 days after completing at least 47 boxing bouts (Blyth et al., 2011; Kanner et al., 2003). These divergent findings are likely attributable to the different time points in which S-100B was measured following injury.

Three studies, of two independent samples, have examined the association between RHIs and S-100B in American football players. Using an overlapping sample, Marchi et al. (2013) and Puvenna et al. (2014) reported increased levels of S-100B in non-concussed football players following a college level game. Additionally, they found a significant positive association between number of head impacts, estimated using a self-reported metric, and post-game levels of S-100B (Graham MR et al., 2011). Similarly, in their study of Division III football players, Rogatzki et al. (2016) reported an increase in pre vs. post-game S100-B levels due to sub-concussive RHIs (Neselius et al., 2013).

Literature examining the association of S100-B and sub-concussive RHIs from soccer heading has employed various experimental designs. Stalancke et al.'s group has reported, in both male (Marchi et al., 2013; Puvenna et al., 2014) and female (Rogatzki et al., 2016) elite soccer players, elevated post-game S-100B levels. In a much larger study of elite soccer players, Straume- Naesheim et al. (2008) reported an increase in post-practice S-100B in players who conducted a mean of 18.9 headers during a practice. Interestingly, S-100B was also significantly elevated in the players who participated in high intensity exercise but did not head the ball, which the authors suggest may be attributable to the effects of physical activity on BBB integrity (Stalnacke, Tegner, & Sojka, 2004). On the other hand, studies conducted in a controlled setting, where players are instructed as to how many headers to complete within a specific time interval, have reported no effect of heading on levels of S-100B (Stalnacke, Ohlsson, Tegner, & Sojka, 2006).

3. Neurometabolic effects of repetitive head impacts

Concussions cause a "neuro-metabolic cascade" of events. In brief, the rapid acceleration-deceleration forces perturb ion levels across cellular membranes and causes an unorganized release of neurotransmitters. Resultant activation of the sodium-potassium pump increases the utilization of glucose. This immediate hypermetabolic state is succeeded by a hypo-metabolic state that can last for weeks post-injury (Straume-Naesheim TM, Jochum M, Dvorak J, & R., 2008).

Animal studies

Rodents models of repetitive concussion suggest that there exists a vulnerable period during which additional cranial impacts confer worse metabolic outcomes. In their seminal studies, Vagnozzi et al. (2008) measured markers of mitochondrial, oxidative and nitrosative stress in rats that received injuries spaced 1– 5 days apart. They reported that metabolism was most robustly impaired when an additional concussion was induced 3 days after the first (Dorminy et al., 2015; Otto M et al., 2000; Stalnacke and P, 2008). Moreover, Prins et al. (2013) demonstrated that another concussion given within the time frame of glucose hypo-metabolism extended the period of metabolic and behavioral recovery in rats (Barkhoudarian, Hovda, & Giza, 2011; Giza and Hovda, 2014; Giza; and Hovda, 2001).

Clinical studies

Human studies have used Magnetic Resonance Spectroscopy (MRS) to evaluate levels of N-acetyl aspartate (NAA), a biomarker of neuronal metabolism (Tavazzi et al., 2007; Vagnozzi

et al., 2007). A small longitudinal study by Vagnozii et al. (2008) measured NAA in singly and doubly concussed adult athletes. They reported that NAA declined following concussion. Singly concussed athletes recovered their depressed NAA within 30 days but doubly concussed athletes, who sustained a second injury within 15 days of their first, required 45 days for NAA levels to return to baseline (Prins, Alexander, Giza, & Hovda, 2013). On the other hand, Johnson et al. (2012), who cross-sectionally examined asymptomatic student athletes with a recent (< 30 day) history of 1, 2, or 2+ concussion compared to controls, found a trend towards higher NAA in the genu of the corpus callosum associated with multiple concussions. The authors suggest that this paradoxical finding of higher NAA may be attributable to the fact that multiply concussed athletes took significantly longer to become asymptomatic and hence were scanned at a later point following injury (Signoretti, Vagnozzi, Tavazzi, & Lazzarino, 2010).

Two longitudinal studies examined NAA levels pre vs. post season in non-concussed hockey and football players, respectively. Chamard et al. (2012) reported that non-concussed female, but not male, hockey players demonstrated lower levels of NAA at season completion (Vagnozzi et al., 2008), which they attributes to the effect of sub-concussive RHIs on brain metabolism. On the other hand, Poole et al. (2014), who measured brain metabolites in non-concussed high school football players at multiple times over the course of the season found no longitudinal changes in NAA (Johnson et al., 2012). The inconsistent findings associating sub-concussive impacts to changes in NAA are likely attributable to the heterogeneities in study populations examined.

Two cross-sectional studies have compared NAA levels in contact sport athletes to non contact sport athletes (e.g. running, dancing). Koerte et al. (2015) found that NAA levels in professional soccer players, absent of reported lifetime concussions, did not significantly differ from non-contact sport athletes (Chamard et al., 2012). In keeping with these findings, Churchill et. al. (2017) found that compared to non-contact sport athletes, football players, but not soccer players, demonstrated significant reductions NAA; however, contact sports athletes (i.e. soccer players) showed no alterations in NAA (Poole et al., 2015). Overall, these results suggest that NAA may not be a sensitive biomarker for neurometabolic manifestations of sub-concussive RHIs may vary based on the type of contact sport (e.g. football vs. soccer) and the nature of the force incurred. Future work is necessary to characterize the magnitude of exposure to RHIs required to alter NAA and its clinical significance, if any.

4. Neuro-immune in repetitive head impacts

In recent years, there has been growing interest in the role of neuro-inflammatory mechanisms in both degenerative and repair processes following a mTBI. For a complete description of mechanisms of neuroinflammation in TBI refer to (Koerte et al., 2015) and (Churchill, Hutchison, Di Battista, Graham, & Schweizer, 2017). In brief, the neuro-inflammatory response to trauma in the brain includes acute recruitment of neutrophils and monocytes to site of injury. Soon after, resident microglia are activated to release either pro-inflammatory cytokines (M1 phenotype), which damage neurons, or anti-inflammatory cytokines (M2 phenotype) that function in tissue repair (Chiu et al., 2016).

Animal studies

Most animal studies of neuroinflammation associated with RHIs have used immunohistochemistry to characterize the extent of Glial Fibrillary Acidic Protein (GFAP) and Ionized calcium adaptor molecule 1 (Iba-1) which respectively quantify the extent of astrogliosis and microgliosis. In their recent review, Fehily and Fitzgerald (2017) demonstrate that astrogliosis and microgliosis are most consistently observed in rodent brains when injuries are induced 24-hr apart but less so at longer time intervals (C. A. McKee and Lukens, 2016).

Only two studies have explored the cytokine response following RHIs. Gao et al. (2017) measured cytokine levels (TNF-a and IL-6 and IL-10) in singly and multiply concussed rats at 1,3,7,14 and 30 days' post injury. They reported that compared to rodents exposed to a single concussion, multiply concussed rodents showed increased pro-inflammatory (TNF-a and IL-6) and decreased anti-inflammatory (IL-10) cytokine levels at all time points, however, this response was most pronounced 7 days after the last injury (Kumar and Loane, 2012). This group also published a study that demonstrated that compared to non- injured control animals, rats who sustained repetitive concussions showed elevated TNF-a, that peaked at 1 week following the last injury as well as elevated IL-6 and IL-10 which both peaked at 2-weeks post-injury (Fehily and Fitzgerald, 2017). These preliminary studies suggest that cytokines are dynamically altered following RHIs; however, more work is needed understand how these cytokines interact to effect outcomes.

Clinical studies

Clinical studies of the neuroinflammatory response to RHI are limited, given the inherent challenges associated with accessing the CNS in vivo. DiBatissta et al. (2016) reported elevated levels of peripheral cytokines in university athletes (including soccer players) with a history of multiple concussions who did not have a systemic inflammatory condition (Gao et al., 2017). Moreover, Shahim et al. (2017) recently reported elevated levels of GFAP in the CSF of professional athletes exposed to a mean of 5.5 lifetime concussion compared to controls (Bai et al., 2017). Furthermore, Studies using a novel Positron Emission Tomography (PET) imaging ligand, [^{11}C] a \DPA-713 proposed to reflect microglial activation, have recently demonstrated widespread neuro-inflammation in young (Di Battista et al., 2016) and old NFL football players as compared to controls (Shahim P et al., 2017). Overall, these early investigations suggest that neuro-inflammation plays an important role in RHIs but much more research is necessary to understand the clinical time course of inflammation in RHIs.

5. Tau aggregation in repetitive head impacts

Development of Chronic Traumatic Encephalopathy (CTE) has emerged as a major concern in individuals exposed to RHIs, particularly in professional athletes. As a post mortem diagnosis, the pathognomonic lesions in CTE are perivascular phosphorylated aggregates of the microtubule associated protein, Tau, located deep within the sulci of the cerebral cortex (Coughlin et al., 2017).

Animal studies

In their recent review, Edwards et. al. (2017) summarized studies that have utilized animal models of repetitive concussions to explore pathophysiological consequences from misfolded protein aggregates including Tau. As the authors illustrate, despite the heterogeneity in experimental designs, models of repetitive concussions consistently demonstrate elevated phosphorylated Tau (p-Tau) (Coughlin et al., 2015).

Clinical studies

CTE has been detected in the deceased brains of a contact sport athletes; most commonly in American football players but also in soccer players, other athletes and combat veterans (A. C. McKee et al., 2016). Recently have researchers been able to measure *in-vivo* levels of peripheral Tau; however, it is still unclear if peripheral tau is an accurate biomarker for tau deposition in the brain.

An aforementioned study by Neselius et al. (2013) of Olympic boxers demonstrated significant elevations in plasma total tau 1–6 days after at least 47 bouts, which returned to normal after a 14 period of no boxing activity (Fehily and Fitzgerald, 2017). Three studies have examined peripheral tau levels in football players exposed to both concussive and sub-concussive RHIs. Stern et. al. (2016) identified higher extracellular levels of plasma exsosomal tau in former NFL football players enriched for exposure to RHIs as compared to a group of controls (A. C. McKee et al., 2009). Alosco et al. (2017) did not identify a difference in plasma total tau levels when NFL players were compared to controls, but reported the estimated number of lifetime head impacts in players was positively associated their plasma levels of Tau (Neselius, et al., 2013). Similarly, DiBattista et al. (2016) reported that athletes engaged in sports with purposeful contact (e.g. hockey and football players) showed elevated levels of plasma tau compared to athletes engaged in sports with unintentional contact (e.g. soccer and basketball players). The authors suggest that these findings may be indicative of the fact that sub-concussive RHI may be more likely to cause Tau deposition than repeated concussions (Stern et al., 2016).

Kawata et al. (2018) examined pre vs. post practice plasma total tau levels in Division I football players exposed to sub-concussive impacts. These authors observed increased Tau concentrations following practice; however, Tau was not associated with number or magnitude of head impacts, measured using a mouth-gaurd equipped with an accelerometer. Interestingly, these authors report that levels of tau were most prominently elevated after a practice with fewer head impacts, which they posit may be reflect the effects of physical activity on BBB integrity or gylmphatic clearance (Alosco et al., 2017).

6. Potential confounders and effect modifiers of RHI

Physical Activity as potential confounder

It is well known that physically activity improves brain function and can slow the progression of age-related memory decline and dementia (Di Battista, et al., 2016). Moreover, studies have demonstrated that physical activity is associated with increased levels of NAA (Kawata et al., 2018) and S-100B (A. C. McKee, Daneshvar, Alvarez, &

Stein, 2014; Tremblay, Pascual-Leone, & Theoret, 2017) as well as reduced neuroinflammation (Erickson et al., 2012; Gonzales et al., 2013). Despite these apparent benefits, no study to date has yet attempted to disentangled the beneficial effects of exercise from the adverse effects of RHI on brain health. Moreover, in light of recent evidence that strenuous exercise can have adverse neuropsychological effects (Straume-Naesheim TM, et al., 2008) it will be essential for future studies to consider the intensity of exercise as a potential confounder.

Genetics as a potential effect modifier

Apolipoprotein E (APOE) is the most commonly studied Single Nucleotide Polymorphism (SNP) in mTBI. Researchers have pointed to impaired neurite outgrowth and cytoskeletal integrity (Svensson, Lexell, & Deierborg, 2015) as well as more oxidative stress and inflammation (Pawlukiewicz, Yengo-Kahn, & Solomon, 2017) as potential mechanisms underlying APOE-ε4 associated neuronal damage. Although a meta-analysis (Huang and Mahley, 2014) found that presence of APOE-ε4 is not associated with worse outcomes from a concussion, an updated investigation is warranted.

Few studies have explored the role of APOE-ε4 on RHI. An early study by Jordan et.al. (1997) demonstrated that compared to APOE-ε4 negative professional boxers, APOE-ε4 positive boxers exposed to a high number of bouts were more likely to develop symptoms associated with chronic brain injury (Jofre-Monseny, Minihane, & Rimbach, 2008). Likewise, Kutner et al. (2000) demonstrated that older aged current professional football players with APOE-ε4 allele performed worse on tasks assessing general cognitive function (Zhou et al., 2008). This evidence suggests that APOE-ε4 may be associated with worse outcomes from RHIs; however, it is imperative for future work to directly examine the effect modification of APOE-ε4 on the association between number of sub-concussive impacts, such as soccer heading, and outcomes.

Emerging evidence suggests that other SNPs including Brain Derived Neurotrophic Factor Val 66 Met (Jordan et al., 1997), COMT Val 158Met (Kutner, 2000), and Dopamine DRD2 C6957T (McAllister et al., 2012; Narayanan et al., 2016; Wang et al., 2018) may modify outcomes from concussions. However, to our knowledge, no study to date has examined the role of these candidate SNP as moderators of outcomes from repeated head impacts, which may have important implications for personalized exposure-risk assessment and screening interventions in soccer players and other individuals exposed to RHI. Moreover, Genome Wide Association Studies (GWAS) may reveal uncommon genes and gene-gene interactions associated with adverse outcomes; however, it will be important for future researchers to standardize methodologies to accumulate a sample size sufficient to conduct GWAS studies.

7. Methodological Considerations and Future Directions

It is still unclear how animal models of RHIs directly translate to human pathology given the differences in anatomical structure and protein expression patterns (Winkler et al., 2017; Winkler et al., 2016). Likewise, elements of animal experiments including the use of stereotaxic frames and anesthesia as well as the protracted frequencies at which repeated impacts are delivered make it difficult to translate animal models to human contexts (Yue et

al., 2017). To establish true synergy between animal and human studies future research will benefit from applying consistent designs and conditions to animal and human experiments.

Most studies have addressed multiple concussions and only few studies have explored the effect of repeated subconcussive impacts on neurobiological outcomes. A critical question for researchers exploring the effects of repeated head impacts on clinical outcome is how to best characterize exposure. Quantifying the number of head impacts necessary to cause adverse neurobiological outcomes in human subjects poses many challenges. Most studies we have reviewed that examined outcomes from RHI relied on self-report of exposure which may be limited by recall bias. Several of the studies reviewed here rely upon the presumption that contact sport athletes and other vulnerable populations are exposed to numerous bouts of sub-concussive events that accumulate over their career, and do not quantify or even estimate magnitude of exposure. Only one self- report metric of repetitive impact exposure has been externally validated (Ojo, Mouzon, & Crawford, 2016). Such well-characterized method, however, will be essential to determine the number of sub-concussive events necessary to incite irrevocable neurobiological and functional decline. Fewer studies have utilized kinematic instrumentation, such as wearable accelerometers, which may provide a more accurate assessment of the biomechanics of RHI. Nonetheless, these devices limited in their current use given their lack of external validity and their divergent use of biomechanical parameters (Angoa-Perez et al., 2014).

Many studies reviewed here have utilized novel biomarkers of neurological injury mechanisms but there are limitations to these assays that must be considered. As Thelin et al. (2017) discuss, studies supporting the use of S100-B as a marker for BBB integrity are limited by sample size and inappropriate controls (Catenaccio et al., 2016). Furthermore, although studies reviewed here have utilized Quanterix Simoa's peripheral tau assay as a biomarker, it is necessary for future large scale clinical trials to discern the sensitivity and specificity of this assay in detecting effects of repetitive concussive and sub concussive head impacts.

8. Conclusions

The neurobiological consequences of RHIs is an important area of ongoing research which will ultimately aid in identifying subclinical and potentially reversible markers of injury, which can be used for screening and may provide new targets for therapeutic intervention. Formulating definitive conclusions from the articles reviewed here is hindered by both the paucity of studies as well as their methodological heterogeneity; however, the overall findings in this review support the notion that RHIs are associated with neurobiological consequences including disruption of the BBB, abnormal neurometabolism, neuroinflammation and aggregation and deposition of tau. Future work, applying valid, reliable and most importantly consistent methodologies is necessary to fully characterize the effects of RHIs as well as the level of exposure necessary to precipitate neurobiological perturbations and that confer risk for irreversible neurobiological effects and ultimately functional manifestations. To fully understand these association between RHIs and abnormal neurobiological outcomes, it is imperative for researchers to address potential confounds such as physical activity and consider the effect modifying role of genetics factors on

individual risk. Such knowledge can inform public health interventions to screen and protect vulnerable players as well identify treatment targets that can be addressed to prevent persistent clinical impairment.

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