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Review

The neurobiological effects of repetitive head impacts in collision sports

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ABSTRACT

It is now recognized that repetitive head impacts (RHI) 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 RHI in collision sports. Additionally, we examine the influence of physical activity and genetics on outcomes of RHI, discuss methodological considerations, and provide suggestions for future directions of this burgeoning area of research.

1. Introduction

In recent years, there has been an increasing public concern regarding the adverse effects of repeated head impacts (RHI) in collision sports on brain health. In addition to overt concussions, collision sport athletes (e.g. American football, soccer, hockey players and boxers) are frequently 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) (Bailes et al., 2013). It is now widely recognized that both repetitive concussive (Mannix et al., 2014; Vynorius et al., 2016) and sub-concussive impacts (Lipton et al., 2013; Webbe and Ochs, 2003; Witol, 2003) are associated with functional impairments.

A comprehensive understanding of 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 (RHI) in collision sports. Specifically, we will review the animal and human studies that examine neurobiological mechanisms that have been previously examined in head injuries, including Blood Brain Barrier (BBB) dysfunction, abnormal neuro-metabolic and neuroinflammatory processes as well as Tau aggregation (Choe, 2016).

2. Blood Brain Barrier in repetitive head impacts

The Blood Brain Barrier (BBB) refers to endothelial tight junctions and glial 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 (Chodobski et al., 2011).

2.1. Animal studies

Few experimental animal studies have examined the effects of concussive RHI on BBB integrity. In their recent review of the pathophysiological mechanisms of RHI, 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 (Fehily and Fitzgerald, 2017).

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2.2. Clinical studies

Serum S-00-B, a calcium binding protein in the CNS, is commonly considered a biomarker of BBB integrity (Blyth et al., 2011; Kanner et al., 2003). S100 -B has been measured in athletes at high risk for RHI including boxers, American football and soccer players. In an early study of amateur boxers, Graham et al. (2011) reported elevated serum levels of S-100B immediately following a 5-min match in boxers who received mostly punches to the head but not in boxers who predominantly sustained impacts to the body (Graham et al., 2011). On the other hand, Neselius et al. (2013) reported no elevation of S100-B in the serum of Olympic boxers 1–6 and 14 days after completing at least 47 boxing bouts (Neselius et al., 2013). These divergent findings are likely attributable to the different time points in which S100-B was measured following injury.

Three studies, of two independent samples, have examined the association between RHI and S100-B in American football players. Using an overlapping sample, Marchi et al. (2013) and Puvenna et al. (2014) found a significant positive association between number sub-concussive RHI, estimated using a self-reported metric, and post-game levels of S100-B (Marchi et al., 2013; Puvenna et al., 2014). Similarly, in their study of Division III American football players, Rogatzki et al. (2016) reported an increase in pre vs. post-game S100-B levels in players due to sub-concussive RHI (Rogatzki et al., 2016).

Literature examining the association of S100-B and sub-concussive RHI from soccer heading has employed various experimental designs. Stalancke et al.'s group has reported, in both male (Stalnacke et al., 2004) and female (Stalnacke et al., 2006) elite soccer players, elevated post-game S100-B levels. In a much larger study of elite soccer players, Straume-Naesheim et al. (2008) reported an increase in post-practice S100-B—in players who conducted a mean of 18.9 headers during a practice. Interestingly, S100-B 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 (Straume-Naesheim et al., 2008). 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 S100-B (Dorminy et al., 2015; Otto et al., 2000; Stalnacke and Sojka, 2008).

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 cause 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 (Barkhoudarian et al., 2011; Giza and Hovda, 2014; Giza and Hovda, 2001).

3.1. Animal studies

Rodents models of repetitive concussions suggest that there exists a vulnerable period during which additional cranial impacts confer worse metabolic outcomes. In their seminal studies, Vagnozzi et al., 2007 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 (Tavazzi et al., 2007; Vagnozzi et al., 2007). 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 (Prins et al., 2013).

3.2. Clinical studies

Human studies have used Magnetic Resonance Spectroscopy (MRS) to evaluate levels of N-acetyl aspartate (NAA), a biomarker of neuronal metabolism (Signoretti et al., 2010). A small longitudinal study by Vagnozzi et al. (2008) measured NAA in singly and doubly concussed adult athletes. They reported that NAA declined following concussion (s). 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 (Vagnozzi et al., 2008). 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(s) 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 (Johnson et al., 2012).

Two longitudinal studies examined NAA levels pre vs. post season in hockey and American 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 (Chamard et al., 2012), which they attributed to the effect of sub-concussive RHI on brain metabolism. On the other hand, Poole et al., 2014, who measured brain metabolites in non-concussed high school American football players at multiple times over the course of the season found no longitudinal changes in NAA (Poole et al., 2014). 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 collision sport athletes to non- collision sport athletes (e.g. runners and dancers). Koerte et al. (2015) found that NAA levels in professional soccer players, absent of reported lifetime concussions, did not significantly differ from non-collision sport athletes (Koerte et al., 2015). In keeping with these findings, Churchill et al. (2017) found that compared to non-collision sport athletes, American football, but not soccer players, demonstrated significant reductions in NAA (Churchill et al., 2017). Overall, these results suggest that neurometabolic manifestations of RHI may vary based on the type of collision sport (e.g. American football vs. soccer) and the nature of the force incurred. Future work is necessary to characterize the magnitude of exposure to RHI 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 neuroinflammatory mechanisms in both degenerative and repair processes following a mTBI. For a complete description of mechanisms of neuroinflammation in TBI refer to (Chiu et al., 2016) and (McKee and Lukens, 2016). 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 (Kumar and Loane, 2012).

4.1. Animal studies

Most animal studies of neuroinflammation associated with RHI 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-h apart but less so at longer time intervals (Fehily and Fitzgerald, 2017).

Only two studies have explored the cytokine response following RHI. Gao et al. (2017) measured cytokine levels (TNF-a, 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 (Gao et al., 2017). This group also published a study that demonstrated that compared to non-injured control animals, rats who sustained RHI 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 (Bai et al., 2017). These preliminary studies suggest that cytokines are dynamically altered following RHI; however, more work is needed understand how these cytokines interact to effect outcomes.

4.2. Clinical studies

Clinical studies of the neuroinflammatory response to RHI are limited, given the inherent challenges associated with accessing the CNS in vivo. Di Battista et al. (2016) reported elevated levels of peripheral cytokines in university athletes with a history of multiple concussions who did not have a systemic inflammatory condition (Di Battista et al., 2016). 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 (Shahim et al., 2017). Furthermore, Studies using a novel Positron Emission Tomography (PET) imaging ligand, [^{11}C]DPA-713 proposed to reflect microglial activation, have recently demonstrated widespread neuroinflammation in young (Coughlin et al., 2017) and old (Coughlin et al., 2015) NFL football players as compared to controls. Overall, these early investigations suggest that neuroinflammation plays an important role in RHI but much more research is necessary to understand the clinical time course of inflammation in RHI.

5. Tau aggregation in repetitive head impacts

Development of Chronic Traumatic Encephalopathy (CTE) has emerged as a major concern in individuals exposed to RHI, 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 (McKee et al., 2016).

5.1. Animal studies

In their recent review, Edwards III 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 Tau (Edwards III et al., 2017).

5.2. Clinical studies

CTE has been detected in the deceased brains of a collision sport athletes; most commonly in American football players but also in soccer players, other athletes and combat veterans (McKee et al., 2009). Recently, researchers have 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 levels 1–6 days after at least 47 bouts, which returned to normal after a 14 period of no boxing activity (Neselius et al., 2013). Three studies have examined peripheral Tau levels in American football players exposed to concussive and sub-concussive head RHIs. Stern et al. (2016) identified higher extracellular levels of plasma exosomal Tau in former NFL football players enriched for exposure to RHI as compared to a group of controls (Stern et al., 2016). Alosco et al. (2017) did not identify a difference in plasma total Tau levels when NFL players were compared to controls, but reported that the estimated number of lifetime head impacts in players was positively associated their levels of Tau (Alosco et al., 2017). Similarly, Di Battista et al. (2016) reported that athletes engaged in sports with purposeful collision (e.g. hockey and American football players) showed elevated levels of Tau compared to athletes engaged in sports with unintentional collision (e.g. soccer and basketball players) (Di Battista et al., 2016).

Kawata et al. (2018) examined pre vs. post practice plasma total Tau levels in Division I American football players exposed to concussive and sub-concussive RHIs. 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 (Kawata et al., 2018).

6. Potential confounders and effect modifiers of RHI

6.1. 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 (McKee et al., 2014; Tremblay et al., 2017). Moreover, studies have demonstrated that physical activity is associated with increased levels of NAA (Erickson et al., 2012; Gonzales et al., 2013) and S100-B (Straume-Naesheim et al., 2008) as well as reduced neuroinflammation (Svensson et al., 2015). 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 (Pawlukiewicz et al., 2017) it will be essential for future studies to consider and explicitly measure fitness and the intensity of exercise as a potential confounder.

6.2. Genetics as a potential effect modifier

Apolipoprotein E (APOE) is the most commonly studied Single Nucleotide Polymorphism (SNP) in concussions. Researchers have pointed to impaired neurite outgrowth and cytoskeletal integrity (Huang and Mahley, 2014) as well as more oxidative stress and inflammation (Jofre-Monseny et al., 2008) as potential mechanisms underlying APOE-ε4 associated neuronal damage.

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 (Jordan et al., 1997). Likewise, Kutner (2000) demonstrated that older aged current professional American football players with APOE-ε4 allele performed worse on tasks assessing general cognitive function (Kutner, 2000). This evidence suggests that APOE-ε4 may be associated with worse outcomes from RHI; 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 (McAllister et al., 2012; Narayanan et al., 2016; Wang et al., 2018), catechol-O-

methyltransferase Val 158Met (Winkler et al., 2017; Winkler et al., 2016), and Dopamine DRD2 C6957T (Yue et al., 2017) may modify outcomes from concussions. However, to our knowledge, no study to date has examined the role of these candidate SNPs as moderators of outcomes from RHI, which may have important implications for personalized exposure-risk assessment and screening interventions in athletes 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 RHI directly translate to human pathology given the differences in anatomical structure and protein expression patterns (Ojo 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 (Angoa-Perez et al., 2014). 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 sub-concussive 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 collision sport athletes are exposed to numerous bouts of sub-concussive events that accumulate over their career, and do not quantify or even estimate magnitude of exposure. To date, only a one self- report metric of repetitive impact exposure has been externally validated (Catenaccio et al., 2016). Such well-characterized methods, 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 (King et al., 2016).

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 (Thelin et al., 2017). 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 RHI 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 RHI 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 RHI as well as the level of exposure necessary to precipitate neurobiological perturbations that confer risk for irreversible neurobiological effects and ultimately functional manifestations. To fully understand these association between RHI 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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