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Review article

The potential for animal models to provide insight into mild traumatic brain injury: Translational challenges and strategies

Sandy R. Shultz[a,*,1], Stuart J. McDonald[b,1], Cole Vonder Haar[c], Alicia Meconi[d], Robert Vink[e], Paul van Donkelaar[f], Chand Taneja[d], Grant L. Iverson[g], Brian R. Christie[d]

[a] Department of Medicine, The Royal Melbourne Hospital, The University of Melbourne, Parkville, VIC, Australia
[b] Department of Physiology, Anatomy and Microbiology, La Trobe University, Melbourne, VIC, Australia
[c] Department of Psychology, The University of British Columbia, Vancouver, BC, Canada
[d] Division of Medical Sciences, The University of Victoria, Victoria, BC, Canada
[e] Division of Health Sciences, The University of South Australia, Adelaide, SA, Australia
[f] School of Health and Exercise Sciences, The University of British Columbia Okanagan, Kelowna, BC, Canada
[g] Department of Physical Medicine and Rehabilitation, Harvard Medical School, Spaulding Rehabilitation Hospital, Home Base, A Red Sox Foundation and Massachusetts General Hospital Program, and MassGeneral Hospital for Children™ Sports Concussion Program, Boston, MA, USA

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ABSTRACT

Mild traumatic brain injury (mTBI) is a common health problem. There is tremendous variability and heterogeneity in human mTBI, including mechanisms of injury, biomechanical forces, injury severity, spatial and temporal pathophysiology, genetic factors, pre-injury vulnerability and resilience factors, and clinical outcomes. Animal models greatly reduce this variability and heterogeneity, and provide a means to study mTBI in a rigorous, controlled, and efficient manner. Rodent models, in particular, are time- and cost-efficient, and they allow researchers to measure morphological, cellular, molecular, and behavioral variables in a single study. However, inter-species differences in anatomy, morphology, metabolism, neurobiology, and lifespan create translational challenges. Although the term "mild" TBI is used often in the pre-clinical literature, clearly defined criteria for mild, moderate, and severe TBI in animal models have not been agreed upon. In this review, we introduce current issues facing the mTBI field, summarize the available research methodologies and previous studies in mTBI animal models, and discuss how a translational research approach may be useful in advancing our understanding and management of mTBI.

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* Corresponding author at: Office 1.02, Melbourne Brain Centre Department of Medicine, The University of Melbourne Parkville, VIC, 3050, Australia.
E-mail address: sshultz@unimelb.edu.au (S.R. Shultz).
[1] Co-first authors.

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1. Introduction

This review is based on topics covered in the 2015 International Behavioral Neuroscience Society symposium titled "From the lab bench to the field: translational research approaches for investigating mild traumatic brain injury (mTBI)." Mild injuries to the brain occur during athletic participation, daily life, and military service. There is a broad range of injury severity within the mTBI classification range, from sporting injuries that involve modest biomechanical forces and clinical symptoms that resolve within hours, to injuries sustained in high-speed motor vehicle accidents that result in macrostructural damage to the brain and that abut the moderate TBI classification range. The biomechanical forces that result in mTBI are believed to initiate a pathophysiological cascade in the central nervous system that is heterogeneous in nature but can involve a combination of inflammatory, metabolic, neuronal, and axonal abnormalities or changes (Blennow et al., 2012; Carroll et al., 2004; Giza and Hovda, 2014; Jordan, 2013). Mild injuries to the brain are associated with large adverse effects on balance and cognition within the first 24 h (Broglio and Puetz, 2008), often extending well into the first week following injury (Dougan et al., 2014; Williams et al., 2015), and these deficits improve and typically resolve within the first month after injury in athletes (Cancelliere et al., 2014) and within three months of injury in civilians (Rohling et al., 2011). A subgroup, however, report symptoms long after injury (Carroll et al., 2014). The clinical symptoms and problems in the initial days following mTBI might be caused in large part by cellular, sub-cellular, and molecular pathophysiology that cannot be currently measured in clinical settings. The cause of persistent symptoms, however, is likely multifactorial and a biopsychosocial perspective is needed to better understand and predict clinical outcomes (Iverson et al., 2012). A number of studies have also found the presence of postconcussion-like symptoms in healthy individuals (Iverson and Lange, 2003; Wang et al., 2006), suggesting that post-concussion symptoms are neither specific nor reliable indicators of mTBI. Because of the variable clinical presentation of mild brain injuries, there have been efforts to identify more sensitive, reliable, and/or objective indicators of brain injury and recovery, such as serum biomarkers, microstructural changes in white matter, neurometabolic alterations and differences in neurochemistry, and functional physiological changes in neural networks.

1.1. Blood biomarkers

Blood biomarkers may be helpful for mTBI diagnosis, monitoring injury progression and recovery, and providing pertinent information about ongoing pathophysiological changes to guide management (Zetterberg et al., 2013). There are a number of potential blood-based biomarkers that may be sensitive to the neuronal and glial cell loss, metabolic abnormalities, neuroinflammation, axonal injury, and other pathophysiological changes associated with mTBI (see Zetterberg et al., 2013 for a comprehensive review on fluid biomarkers for mTBI). Briefly, initial studies report increased levels of S100 calcium-binding protein B (S100B), glial fibrillary acidic protein (GFAP), tau, galectin 3, matrix metalloproteinase 9, occludin, plasma soluble cellular prion protein, calpain-cleaved αII-spectrin N-terminal fragment (SNTF) and decreased levels of copeptin in plasma and/or serum at various acute and subacute post-mTBI time points (Metting et al., 2012; Pham et al., 2015; Shahim et al., 2014; Shan et al., 2016; Siman et al., 2013; Siman et al., 2015). Other studies demonstrate the potential of microRNA as a blood biomarker in mTBI (Redell et al., 2010; Sharma et al., 2014). However, longitudinal studies that have assessed blood biomarkers in mTBI patients to validate their diagnostic and prognostic usefulness are limited (Zetterberg et al., 2013). Furthermore, the lack of standardized methods to quantify some blood biomarkers, and the need for either baseline measures for each individual or validated cut-off points, are additional limitations (Zetterberg et al., 2013).

1.2. Neuroimaging

Advanced magnetic resonance imaging (MRI) techniques have been developed that could be sensitive to pathophysiological changes that occur in the injured brain, and might contribute to cumulative and long-term effects of repeated mTBIs (Baugh et al., 2012; Hunter et al., 2012; Jeter et al., 2013). Diffusion MRI measures are sensitive to axonal injury and have been utilized in previous studies to identify abnormalities in the white matter tracts of mTBI patients at acute, sub-acute, and chronic post-injury time points (Dimou and Lagopoulos, 2014; Dodd et al., 2014; Gardner et al., 2012; Lancaster et al., 2016; Shenton et al., 2012; Wilde et al., 2015; Xiong et al., 2014). For example, a recent study used diffusion MRI to serially examine white matter changes at 24 h and 1 week after a sports-related concussion (Lancaster et al., 2016). Diffusion MRI revealed that the concussed group exhibited widespread changes compared with control subjects 24 h after the concussion. Furthermore, at one-week follow up the differences in these diffusion measures were even more widespread. Notably, although the concussed group reported more symptoms and worse cognitive performance than a control group at 24 h, there were no significant differences on these measures one week later despite the presence of the diffusion MRI abnormalities.

Magnetic resonance spectroscopy (MRS) provides measurements of brain metabolites that may be affected by mTBI including N-acetylaspartate, glutathione, glutamate, and myo-inosotol (Gardner et al., 2014; Johnson et al., 2012a; Tremblay et al., 2014; Vagnozzi et al., 2010, 2008; Xiong et al., 2014). A multicenter MRS study examined 40 concussed athletes, as well as 30 healthy subject controls at 3, 15, 22, and 30 days post-injury for the determination of *N*-acetylaspartate, creatine, and choline (Vagnozzi et al., 2010). Concussed patients had the most significant alteration of metabolite ratios at day 3 post-injury. These neurometabolic changes gradually recovered, and by 30 days post-injury all concussed athletes had their metabolite ratios return to values detected in controls. Self-reported symptoms in the patients resolved between 3 and 15 days after concussion.

Susceptibility-weighted imaging (SWI) is a technique that exploits differences in magnetic susceptibility between tissues, and is sensitive to microhemorrhages that might occur in some people as a result of mTBI (Huang et al., 2015; Kenney et al., 2016; Wang et al., 2014). Huang et al. (2015) compared the frequency of microbleeds identified by SWI in 111 patients with mTBI