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Review article

Elucidating opportunities and pitfalls in the treatment of experimental traumatic brain injury to optimize and facilitate clinical translation

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ABSTRACT

The aim of this review is to discuss the research presented in a symposium entitled *"Current progress in characterizing therapeutic strategies and challenges in experimental CNS injury"* which was presented at the 2016 International Behavioral Neuroscience Society annual meeting. Herein we discuss diffuse and focal traumatic brain injury (TBI) and ensuing chronic behavioral deficits as well as potential rehabilitative approaches. We also discuss the effects of stress on executive function after TBI as well as the response of the endocrine system and regulatory feedback mechanisms. The role of the endocannabinoids after CNS injury is also discussed. Finally, we conclude with a discussion of antipsychotic and antiepileptic drugs, which are provided to control TBI-induced agitation and seizures, respectively. The review consists predominantly of published data.

1. Introduction

With an estimated ten million traumatic brain injuries (TBI) reported annually worldwide, the World Health Organization predicts that TBI will surpass many diseases as the major cause of death and disability by the year 2020 (Langlois et al., 2006; Hyder et al., 2007; Faul and Coronado, 2015; Coronado et al., 2015). Further, the economic impact of acute and long-term care was estimated at $61 billion in the U.S. in 2000 by the Centers for Disease Control and Prevention (CDC) (Faul et al., 2007), and approximately $40 billion in Europe in 2010 (Olesen et al., 2012).

Approximately 75% of reported TBIs are mild and are typically referred to as diffuse TBI or concussion, as determined by a Glasgow Coma Scale (GCS) score of 13–15 (Thurman et al., 1999; Grossman et al., 2010). Mild TBIs are generally caused by sporting accidents, falls, motor vehicle crashes, and domestic violence (Faul and Coronado, 2015). By definition, TBI results in mechanical damage occurring due to the torsion and deformation of the brain as it rapidly moves within the skull. The signature pathology of diffuse TBI is diffuse axonal injury (DAI), which refers to the physical shearing of axons and the sequelae of events that lead to axon disconnection from the cell body; a pathology that is disseminated throughout the brain while being located adjacent to healthy tissue (McGinn and Povlishock, 2016).

The remaining 25% of TBIs consist of focal, penetrating, and combined (diffuse + focal) injuries. Focal injuries can occur from epidural and subdural hematomas and gross tissue damage resulting in focal

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lesions that are characterized by cell death and contusion. According to the CDC, deaths from TBI are down 7%, but there are currently 5.3 million Americans living with disabilities directly related to the TBI. Improved safety equipment and improved acute medical treatment have contributed to the worldwide trend for an increased population of TBI survivors. Unfortunately, with limited treatments available, many patients live out the rest of their lives with disabilities associated with the TBI. With such a large population affected by TBI, symptom management and optimization of rehabilitation are paramount for medical professionals.

1.1. Types of rehabilitation for post-concussive symptoms and TBI-related disabilities

Acute and persisting post-concussive symptoms (PCS) after various forms of TBI are composed of somatic (e.g., headache, dizziness, light and sound sensitivity, balance and vision problems), cognitive (e.g., memory, executive function, confusion), and affective (e.g., anxiety, sleep disorders, emotionality) deficits. Most patients recover from PCS within 1–3 weeks. However, for 15–20% of the TBI population, PCS persist for months and even longer (McAllister 1992; Alves et al., 1993; McAllister et al., 2001; Ragnarsson, 2002; Radhakrishnan et al., 2016). After a TBI that requires hospitalization, the prevalence for persisting (at least 1 year) somatic, cognitive, affective, and motor deficits increases to over 43% of survivors (Selassie et al., 2008). Moreover, several studies indicate that females are more likely to have persistent symptoms after mild TBI (Farace and Alves, 2000; Bazarian et al., 2010; Mott et al., 2012; Iverson and Pogoda, 2015; Silverberg et al., 2015). In particular, headaches and dizziness (Farace and Alves 2000), loss of confidence (Colantonio et al., 2010), depression (Bay et al., 2009), and anxiety (Liossi and Wood, 2009) are quite common. This finding is troubling given that females make up approximately 41% of the TBI population in the United States. The true incidence of persisting PCS is unknown as many TBI patients do not seek medical care likely because they do not identify the injury as the etiology of their symptoms (Langlois et al., 2006).

Despite the growing awareness of persisting PCS and TBI related disabilities, especially in the athletic community, treatments are limited and mainly consist of symptom-specific pharmacological and rehabilitation approaches (Radhakrishnan et al., 2016). Rehabilitation for this population includes cognitive-behavioral therapy, attention and strategy training, emotional therapy, re-socialization, cervicovestibular and oculomotor rehabilitation, and tactile stimulation (Mittenberg et al., 1996; Cicerone et al., 2005; Rohling et al., 2009; Silverberg et al., 2013; Schneider et al., 2014; Broglio et al., 2015; Gertler et al., 2015; Parianen Lesemann et al., 2015). It is recommended that therapists approach each patient individually as success of rehabilitation is impacted by the type of injury, gender, age, nutrition, pre- and post-morbid conditions, polytrauma, and overall attitude and level of determination of each patient. Also, the timing, duration, intensity, and type of rehabilitation can largely influence success (Kay et al., 1992; Ponsford et al., 2000; Yen and Wong, 2007; Cook et al., 2008; Bazarian et al., 2010; Purohit et al., 2013; Thomas et al., 2015).

In general, cognitive deficits and impairments refer to any deficiency in cognitive processes that impact intellectual performance and abilities in comparison to pre-injury status. Most affected after TBI are memory, information processing, attention, and executive function (Bondi et al., 2014a, 2015). Cognitive-behavioral therapy provides educational materials, therapist-guided symptom management strategies, and guidance toward resumins pre-injury activities. Patients adhering to the recommended guidelines reported decreased duration, frequency, and severity of symptoms (Mittenberg et al., 1996; Miller and Mittenberg, 1998). Attention and strategy training improves mild memory impairment, attention deficits, and communication deficits by teaching and practicing strategies to compensate for residual effects rather than depending on restoration of original function (Cicerone et al., 2005).

Therapies dedicated to affective disorders after TBI are often focused on mitigating apathy, anxiety, anger, aggression, frustration, and depression that can impede overall rehabilitation efforts and social interactions brought about by adapting to injury-induced deficits (McDonald and Flanagan, 2004). Thus, in a subsequent section of this review, a discussion of drugs that are aimed at managing agitation and aggression will be discussed. Rehabilitation includes mechanisms for managing stress, setting realistic goals, and emotional support. For the latter, therapists recommend that the family also be educated on injury-induced emotional instability and strategies to demonstrate support of the patient. Often, temporary use of pharmacological treatments are recommended to facilitate learning of new strategies (Vaishnavi et al., 2009).

In addition to persisting cognitive and affective PCS, somatic symptoms include sensory hypersensitivity to light and sound, vestibular (i.e., dizziness and imbalance) and ocular-motor impairments, such as gaze instability, visual fatigue, and visual motion sensitivity (Ventura et al., 2016). Cervicovestibular rehabilitation is a newer approach that uses a combination of vestibular rehabilitation and cervical spine physiotherapy in patients with symptoms of dizziness, neck pain, and headaches (Schneider et al., 2014). Other approaches to vestibular rehabilitation after mild TBI for balance and sensory integration are non-aerobic exercise interventions and computerized dynamic posturography, a test of balance that evaluates the sensory input from the feet and legs involving vision and vestibular function. Posturography is used for diagnosis, tracking of patient progress, and aiding the therapist in designing an individual rehabilitation program (Lin et al., 2015). Oculomotor training includes the use of eye patches, penlights, mirrors, lenses, and prisms to improve the performance of ocular muscles (Broglio et al., 2015). Regardless of the type of rehabilitation, education, support, and regular monitoring are key to long-term success (Dittmar, 1997).

For severe TBIs that involve focal lesions, motor rehabilitation may also be necessary. The severity of deficits can range from a coma state to loss of fine articulation of peripheral appendages. To avoid atrophy and muscle shortening brought about by immobility in coma patients, passive stretching is recommended for at-risk muscles. For the greater range of severity, a degree of physical, occupational, and speech therapy may be necessary for the return of daily activities and work. Rehabilitation may take the form of task-oriented motor training, gait correction, resistance training, or constrained-induced movement therapy (Cimolin et al., 2012).

1.2. Animal models of TBI

There are several models of experimental TBI that replicate many aspects of the human condition (Kline and Dixon, 2001; Cernak, 2005; Morganti-Kossmann et al., 2010; Marklund and Hillered, 2011; Osier and Dixon, 2016). Specifically, the fluid percussion (FP) and controlled cortical impact (CCI) are the most widely used, but weight-drop and blast are rapidly gaining momentum. Each has been modified over time to increase validity toward specific aspects of the clinical situation, with concussion, contusion, diffuse axonal injury (DAI), and hemorrhage being the primary pathological features of interest (Xiong et al., 2013). The pathological outcomes from FP injury can be produced by varying the placement of the craniectomy and the fluid pulse. For example, if the craniectomy is placed along the midline suture, the result is a diffuse brain injury in both hemispheres (Dixon et al., 1987; McIntosh et al., 1987), whereas a lateral craniectomy results in a 'mixed pathology,' containing a focal brain injury with a diffuse component (McIntosh et al., 1989; Thompson et al., 2005). To better replicate the susceptibility of athletes to repetitive concussion, repetitive mild TBI models are becoming more available. An extensive table of repetitive TBI models can be found in an excellent review by Brody et al. (2015). The CCI injury model consists of a direct impact delivered to the