Commentary

Changing Paradigm in Mild Traumatic Brain Injury Research

Giovanni Grasso* and Alessandro Landi

Section of Neurosurgery, Department of Experimental Biomedicine and Clinical Neurosciences (BIONEC), University of Palermo, Palermo, Italy

Traumatic brain injury (TBI) is a major cause of death and disability among young adults. Recent data show that TBI affects about 1.7 million people annually in the United States (Faul and Coronado, 2015). After TBI, the primary injury produces almost irreparable brain damage. However, recent experimental studies have shown evidence for dynamic brain repair following TBI because endogenous progenitor cells may play regenerative roles in response to injuries (McGinn and Povlishock, 2015). In surviving patients, what plays a critical role in the clinical prognosis is the subsequent secondary injury; without effective treatment, cascades that include glutamatergic excitotoxicity and calcium overload will promote additional brain damage.

Recently, a growing interest in milder forms of TBI has blossomed. These usually involve multiple low-impact injuries, and these injuries are often reported in association with domestic violence, contact sports, or military activities (Galgano et al., 2016; Krawczyk et al., 2013; Landre et al., 2006). Repetitive mild TBI (mTBI) has been associated with deficits in several functional areas, including speed of information processing, memory and attention, and executive functions (McKee et al., 2013), including verbal learning and delayed recall (McKee et al., 2013, 2015). Accordingly, mTBI can be considered a distinct condition with respect to the acute sequelae of concussion or TBI (Gavett et al., 2011). Recent pathological studies have shown the occurrence of morphological changes in the brain following repetitive low-impact traumatic injury events. This includes the progressive development of chronic traumatic encephalopathy (CTE), which is often associated with the deposition of tau protein in the brain parenchyma (Ojo et al., 2016).

Given the unique characteristics of mTBI, the mechanisms and the clinical scenario underlying such a form of TBI are an intense area of study. What has become clear, however, is that the outcome for TBI patients reflects the direct cellular damage caused by the primary impact and the cascade of secondary cellular and molecular responses that are activated following the initial injury. Understanding these processes underlying mTBI is of crucial importance, and experimental models would be helpful. Modeling mTBI, however, has been challenging. In most of the cases, the mild versions of the common experimental models of TBI have been based on less severe degrees of injury. Accordingly, the results do not represent certainly the clinical scenario of human mTBI.

In this issue of the Journal of Neuroscience Research, Zander and collaborators report the first indoor primary blast model, which uses military explosives in a controlled environment. They examined the effects of primary rat neurons and mixed cultures exposed to single and repeated blasts in order to simulate explosive blast-induced mTBI. Their findings clearly show that blast exposure disrupts the integrity of the plasma membrane, leading to the upset of ion homeostasis, formation of reactive oxygen species, and glutamate release. This mTBI model will be useful in studying the underlying pathophysiology of brain injury and in investigating the vulnerability of the injured brain to second insults. Although the study tries to reproduce a real scenario, it must be considered that this is an in vitro study and the results obtained are related to a particular type of explosive in an indoor platform. Accordingly, the effects experienced outside or with a different explosive may be different. Furthermore, injuries experienced by animals or humans will likely differ from the in vitro effects obtained with this model. Therefore, additional studies are necessary to validate the results of this study, and this would only be possible by in vivo studies and a direct comparison with data collected from injured persons or cadaveric analyses.

What we do know is that mTBI sequelae clearly affect the performance in work and leisure activities as long as the brain is injured. Accordingly, given the high incidence of this condition, the economic burden of such pathology is considerable. Military personnel and contact sports athletes who experienced mTBI are at significantly increased risk for adverse occupational outcomes. Translational research and clinical trials focusing on treatments blossoming from experimental research can lead to the development of treatments that truly change the paradigm in the management of TBI.

*Correspondence to: Giovanni Grasso, MD, PhD, Clinica Neurochirurgica, Policlinico Universitario di Palermo, Via del Vespro 129, 90100 Palermo, Italy. E-mail: giovanni.grasso@unipa.it

Received 3 June 2016; Accepted 6 June 2016

Published online 29 June 2016 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/jnr.23803
development of effective actions for counteracting the sequelae of mTBI. However, many researchers have long explored agents with possible beneficial effects following TBI. Although several compounds have been demonstrated to be effective in preclinical models, only some of these have entered clinical development, and some of those that survived early safety trials have been studied in controlled efficacy trials. Despite these efforts, all phase III trials have so far failed to demonstrate efficacy of these agents (Grasso et al., 2016). The pathophysiological heterogeneity of TBI-affected patients and the absence of satisfactory pharmacokinetic investigations necessary to assess optimal doses and timing for administration might have led to the clinical trial failures. Experimental models of TBI are designed to produce a relatively homogeneous type of injury, so they may not be able to reproduce fully all the aspects that are observed in human TBI. This may in part explain why drugs that showed promise in preclinical studies failed in clinical translation. However, in vitro and in vivo models have been crucial in exploring both cellular and molecular mechanisms of human TBI because of the limitations of the clinical setting as well as in developing and characterizing novel therapeutic strategies. To achieve new therapeutic solutions, appropriate experimental paradigms should be designed.

REFERENCES