Experimental Neurology 267 (2015) 13–17

Contents lists available at ScienceDirect

Experimental Neurology

journal homepage: www.elsevier.com/locate/yexnr

Commentary

It might be time to let cooler heads prevail after mild traumatic brain injury or concussion

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Introduction

Few conditions in medicine have garnered more recent interest in the lay press than mild traumatic brain injury (mTBI) or concussion. For decades, investigation into the pathobiology and therapy of TBI has often been viewed by the neuroscience community as "too messy to understand" or "lacking a clear relationship between anatomical injury and behavioral consequences" and has been carried out largely by a limited number of dedicated investigative groups, primarily (albeit not exclusively) focused on the challenging problem of severe TBI.

However, the acute and sub-acute consequences of mTBI in settings such as sports concussion or combat casualty care have been recognized to represent an enormous public health problem, and the recent realization that mTBI and/or repetitive mTBI may serve as occult triggers to the development or exacerbation of a number of important conditions across the spectrum of neurodegenerative disease including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, chronic traumatic encephalopathy, and possibly others, has produced a maelstrom of interest and both pre-clinical and clinical investigation that–for the field of TBI—is long overdue (DeKosky et al., 2013; Robertson et al., 2014; Skolnick et al., 2014; Smith et al., 2013; Kochanek et al, 2015). This epiphany in the field of mTBI has produced a golden age of investigation with many new realizations, and exciting potential opportunities to develop novel therapies, and has been driven in part by a welcome surge in financial support for this research particularly from both the United States Army, and the National Institutes of Health (Diaz-Arrastia et al., 2014a,b; Kochanek et al., 2011; McMahon et al., 2014). There is, thus, new hope for the successful development of novel therapies across the severity and phenotypic spectra of TBI that will reduce the acute and chronic morbidity, and/or mortality that is currently observed, and also for the identification of therapies that might stop chronic neurodegenerative diseases from developing after TBI. In this issue of *Experimental Neurology*, Titus and co-workers (Titus et al., 2015), from the laboratory of Dr. Dalton Dietrich, who has been a leading investigator in the area of hypothermia in experimental brain injury for decades, provide us with another logical, simple, and somewhat frightening observation in mTBI—yet one that might have considerable clinical consequence.

Imposed hyperthermia exacerbates cognitive deficits after mTBI in rats

Using an established parasagittal fluid percussion injury model of mTBI in adult rats and carefully selecting a threshold injury level that bordered on the margin of producing cognitive deficits, Titus and co-workers (Titus et al., 2015), imposed a 4 hour and 15 minute period of a clinically relevant level of hyperthermia (approximately 39 °C) using external warming with heat lamps and demonstrated that concomitant hyperthermia imposed at an early time after mTBI produced or unmasked behavioral deficits. Cue and contextual fear conditioning were assessed at 1 week after injury and impaired performance on escape latency to find the hidden platform in Morris water maze testing assessed at 2 weeks after injury. Work by investigators in this same laboratory had previously reported that mild hyperthermia increased cortical, hippocampal, and white matter damage (Sakurai et al., 2012). In that prior study, the hyperthermic exposure was somewhat less severe in duration than in the current work, namely 2 h and 15 min, beginning 15 min before the injury, rather than 4 h and 15 min. In the current study, Titus et al. (Titus et al., 2015) further expand upon their findings of increased cognitive deficits from a hyperthermic exposure after mTBI by demonstrating that promptly cooling the rat back to normothermia after a total of 30 min of hyperthermic exposure (namely, hyperthermia for 15 min before and 15 min after injury) ameliorated the cognitive deficits. They also observed that mTBI produced deficits in working memory as assessed at 3 weeks after injury that curiously were neither worsened by the hyperthermic exposure nor influenced by cooling the rat back down to a normothermic temperature level at 15 min after injury using the aforementioned experimental paradigm in their model.

Targeted temperature management after acute brain injury—the contemporary standard of care in neurocritical care

Recognizing that fever can exacerbate secondary brain injury, and that fevers are extremely common in patients after acute brain injury, it has in general terms become standard care in neurocritical care to

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http://dx.doi.org/10.1016/j.expneurol.2015.02.019

attempt to impose targeted temperature management after a variety of types of acute brain injury, including severe TBI, stroke, and cardiac arrest, among others (Bohman and Levine, 2014). It is clear, though, that some controversy still exists and randomized trials are lacking (Kochanek et al., 2012; Lord et al., 2014). This approach is most consistently utilized in patients who are comatose with severe insults—in that setting targeted temperature management can be readily applied and titrated with either surface or catheter based cooling systems to preempt the development of fever (Mayer et al., 2004; Puccio et al., 2009). Indeed, prompt treatment of fever with intravenous iced saline administration is even used in some settings in patients with acute brain injury given the concern over exacerbation of damage by elevated body temperature (Fink et al., 2012). It is also well known that brain temperature is generally slightly higher than body temperature, although the relationship between brain and body temperature can be complex during clinical care (Smith et al., 2011). The magnitude of the detrimental effect of hyperthermia on the injured brain is surprisingly powerful. For example, in the setting of hypoxic–ischemic brain injury in newborns, Laptook et al. (2008) reported that each 1 °C increase in body temperature during the initial 72 h post-resuscitation increased the odds for a poor outcome (death or disability) 3.6–4 folds. Similarly, in a recent study, a targeted temperature management strategy with a goal of clamping adult patients at 36 °C to meticulously prevent fever after cardiac arrest was as effective as mild hypothermia to a level of 33 °C in improving outcome (Nielsen et al., 2013). Germane to the work of Titus et al. (2015), parallel associations between fever and poor outcome after severe TBI have also been reported in both adults and children (Bao et al., 2014; Natale et al., 2000). Although the exact mechanism(s) by which fever exacerbates secondary damage in TBI remain unclear, there are a number of candidate mechanisms, among which inflammation seems to represent a likely contributor (Whalen et al., 1997). In this work by Titus et al. (2015), the hyperthermic state was present at the time of injury—a situation that very likely represents a more concerning scenario than the development of a fever in the hours or days after TBI, as is seen in neurocritical care. Hyperthermia at the time of injury would be expected to be able to increase acute metabolic demands during the period of acute excitotoxicity and early low cerebral blood flow that is well documented in both pre-clinical models and the clinical condition (Bouma et al., 1992; Bryan et al., 1995; Bullock et al., 1998; Palmer et al., 1993). Note that this scenario is quite different from pre-conditioning with heat, where hyperthermia is imposed hours (classically 24 h) prior to the insult—inducing neuroprotective mediators such as heat shock proteins (Chen et al., 1996). Indeed, chronic heat exposure for one month prior to closed head injury in rats was shown to be protective resulting in reductions in both brain edema and blood brain barrier injury versus TBI alone (Shohami et al., 1994). With application of hyperthermia at the time of injury, excitotoxicity, inflammation, and other mechanisms such as oxidative stress appear to be highly sensitive to temperature early after TBI as shown in several clinical reports (Bayir et al., 2004; Globus et al., 1995; Wagner et al., 2004), and may also contribute to the exacerbation of damage by early hyperthermia. But not all secondary injury or repair mechanisms are robustly influenced by manipulation of brain or core temperature (Salonia et al., 2010; Su et al., 2012). As previously noted, acute hyperthermia also magnifies inflammatory cell influx into the injured brain as shown in an early work by Whalen et al. (1997) and later by Thompson et al. (2005) and hyperthermia may also magnify inflammatory mediator production by activated microglia in the injured brain including increases in TNFα and nitric oxide, and P38 kinase activation (Matsui et al., 2012). This could be particularly relevant in the setting of combat casualty care given that mTBI from blast injury has been shown to be accompanied by important cerebral and extracerebral inflammatory responses (Cernak, 2010) even in the absence of neuronal death (Kochanek et al., 2013). Finally, it remains to be determined whether or not hyperthermia actually needs to exacerbate tissue damage to produce these more delayed effects on cognitive outcome, as observed by Titus et al. (2015) or whether, for example, alterations in cell signaling by hyperthermia are sufficient to disrupt memory processing at a later time point after mTBI.

It also should be recognized that in the clinical setting of neurocritical care, patients are generally not subjected to a forced hyperthermic exposure with heat lamps or heating pads, rather they experience fever—triggered by endogenous pyrogens. These are two very different scenarios, the former is generally felt to be much more deleterious and associated with a stress response (Sharma and Hoopes, 2003) while in the latter, there is a re-set of the hypothalamic temperature set point (Saper, 1998). With regard to sports concussion, one would argue that the approach taken by Titus et al. (2015) actually mimics the clinical condition, since unlike the development of fever after severe or moderate TBI in the neurocritical care setting, imposed hyperthermia is more representative of what is occurring during vigorous athletic training or combat casualty care (discussed further below).

Hyperthermia is common in the setting of mTBI and concussion

As pointed out by Titus et al. (2015), body temperatures can significantly rise in individuals during periods of strenuous activity such as exercise, participation in sporting events, and in military operations (Goosey-Tolfrey et al., 2008; Nybo, 2008; Ozgünen et al., 2010), and indeed, the development of heat stroke during summer football practice is well described with an estimate of over 9000 heat related illnesses in high school athletes alone annually (Yard et al., 2010). These data do not include younger athletes or take into consideration either college or professional athletic participation. It is potentially quite important that the highest rate of heat illness is in football players, and the month of August—during the rigors of training camp—has the greatest heat illness rate. Given the possibility that concurrent concussions, mTBI, or repetitive concussions could be occurring in these young athletes (such as during football or soccer practice) one can begin to understand the potential ramifications of the work of Titus et al. (2015) and the need to expand our understanding of the impact of alterations in temperature beyond the setting of severe brain injury. Myriad questions are raised by this work in this regard, ranging from—is there an analogous relationship between acute hyperthermia after mTBI or concussion and secondary cognitive or histological derangements—and other mTBI sequelae—such as posttraumatic stress disorder, depression or other mood disturbances, vestibular disturbances or other pathologies? Similarly, how does hyperthermia at the time of a concussion or mTBI impact a subsequent TBI—or multiple concussions? Does hyperthermia at the time of mTBI or early thereafter more robustly set into motion neuroinflammation than mTBI or repetitive mTBI alone—possibly strengthening the link between mTBI and neurodegenerative disease? What is the temporal window of "opportunity" for hyperthermia to produce detrimental effects after mTBI? Might there also be a role for mild therapeutic hypothermia to reverse those sequelae? And from the standpoint of pediatric brain injury, given the importance of repetitive mTBI among young athletes and in other setting such as abusive head trauma (the shaken baby syndrome), what are the consequences of hyperthermia after mTBI in the developing brain? These along with a vast number of other unknowns related to hyperthermia, mTBI and sports concussion, now emerge as important questions for the field—questions that deserve to be explored. It is difficult to imagine that hyperthermia at the time of mTBI is not deleterious—the question is likely how significant its clinical impact may be and how to best deal with it given the many scenarios that are likely to be involved.

Targeted normothermia or beyond after mTBI or concussion

If hyperthermia after mTBI is shown to be associated with enhanced morbidity, accelerated or increased prevalence of neurodegenerative disease, or other deleterious consequences in the clinical setting, it will be necessary to determine whether that knowledge is sufficient to

prompt the implementation of strategies to induce normothermia in the immediate post injury period in patients with concussion or mTBI—or whether a randomized controlled trial would be needed to prove therapeutic efficacy of such an approach. As has been the case in neurocritical care, concerns over potential harm to patients by allowing hyperthermia to remain untreated in the face of established brain injury have made it difficult to create equipoise for such a trial. However, given that induction of normothermia might be much more complex in the field setting of sports concussion than in the highly controlled neurocritical care environment such a trial might be feasible or viewed as necessary. However, as pointed out by Titus et al. (2015), cooling strategies to influence athletic performance have already been implemented (Siegel et al., 2012; Tyler et al., 2013) and thus, the technical challenges of implementation of targeted temperature management in the setting of sports concussion with hyperthermia might not represent a major hurdle. And in this setting the target is simply a return to normothermia which is the goal and represents a much more readily achievable target than mild hypothermia—which produces shivering and cold stress in conscious patients, and requires administration of sedatives (Hostler et al., 2010). Although somewhat beyond the scope of the work of Titus et al. (2015), even with the aforementioned challenges, the question of the potential use of mild therapeutic hypothermia in mTBI or concussion is also worthy of consideration. Indeed mTBI and concussion represent insults that deserve, in general, a much enhanced investigation of the potential utility of acute neuroprotective strategies—a concept that was recently reviewed (Kochanek et al., 2015). mTBI or concussion may be much more able to be manipulated successfully by acute therapies than severe TBI—where clinical trials have generally failed. Pre-clinical investigations across a menu of models of varying severities may be helpful in this regard (Kochanek et al., 2011).

Exacerbation of cognitive deficits by hyperthermia after mTBI: limitations and concerns

There are a number of limitations in the work by Titus et al. (2015) that merit discussion. First, 4 h is a rather prolonged period of hyperthermia—one that is generally somewhat beyond what would be seen clinically. That the prior work by this group (Sakurai et al, 2012) showed that 2 h of hyperthermia exacerbated injury in a similar temporal exposure after mTBI suggests that even shorter exposures are also deleterious. Indeed the duration of exposure to hyperthermia that is deleterious remains to be defined—and is likely not a single number given the many TBI phenotypes and complicating cerebral and extracerebral factors that are operating. Nevertheless, 4 h is a relatively long duration for a temperature of 39 °C. A second potential limitation is that in the work by Titus et al. (2015) cooling was initiated 15 min after the injury—which might be challenging to implement clinically. In vitro electrophysiology studies in hippocampal slices show that warming to 41 °C increases CA3 depolarization and spontaneous action potentials within minutes (Kim and Connors, 2012). CA3 is a well-known target in TBI. The time window for successful mitigation of the deleterious consequences remains to be defined, and could be dependent on many factors such as severity of the injury, degree of the hyperthermia, or genetic predisposition, among others.

Another potentially important question that remains unanswered is whether hyperthermia in the setting of mTBI actually exacerbates damage, or simply accelerates damage. Data supporting the latter possibility include pre-clinical studies with mild hypothermia showing that relatively acute effects on neuroprotection, for example, can disappear when much more protracted follow-up is used (Colbourne et al., 1997). Whether hyperthermia has similar but opposite temporal kinetics compared to mild hypothermia (i.e., does heating the injured brain simply speed up the evolution of secondary injury—or does it actually increase the damage) deserves additional exploration.

Whenever temperature is manipulated, whether or not extracerebral effects are playing a role also can be difficult to determine. The authors did an excellent job in controlling and/or reporting acute physiological variables during the experiments. However, even though there were no statistically significant differences between groups, subtle and/or unappreciated differences might be important given that autoregulatory mechanisms in brain can be lost even in mTBI (Strebel et al., 1997). Finally, as discussed by the authors, the use of anesthetics could contribute to the vulnerability of the traumatically injured brain to secondary injury and complicate interpretation. However, isoflurane—as used in this report—has been shown to be neuroprotective particularly early after injury (Statler et al., 2000, 2006), and thus it is possible that these studies could actually be underestimating the deleterious potential clinical impact of hyperthermia in the acute phase after mTBI or concussion—which occurs in the absence of anesthesia.

The genetic nexus between hyperthermia, cancer and microRNA: a link to mTBI?

Prolonged mild hyperthermia may exacerbate cell death and/or ultimate dysfunction in the injured brain. Little is known about that risk in the setting of mTBI where axonal injury has been shown to prevail rather than overt neuronal death. However, hyperthermia in the absence of severe trauma has been explored and applied in oncology where it is clinically used to treat cancer, often combined with chemotherapy to augment cell death (Wust et al., 2002). Ostensibly, discussing cancer here, in the context of mTBI, may seem tangential—yet the reality is that the pathomechanisms of hyperthermia are the same regardless if activated to kill cancer or inhibited to save neurons after TBI. Thus, a new frontier in hyperthermia induced brain tumor therapy involves injecting magnetic microbeads directly into the CNS and then subjecting them to alternating magnetic fields, creating localized heat at the tumor site (Maier-Hauff et al., 2007). Incredibly, killing brain tumor cells by this method is enhanced via attaching lethal-7a microRNAs (let-7a miRNA) to the magnetic nano-particles (Yin et al., 2014). That suggests that hyperthermia has the capacity to alter biological potency of miRNAs such as let-7a. Might this relate to hyperthermia in the setting of mTBI? Serum miRNAs increase in mTBI patients and may alter gene functions which might in turn affect recovery (Redell et al., 2010). Remarkably, let-7i miRNA has been shown to endogenously increase after mild blast TBI in rat (Balakathiresan et al., 2012) as well as other miRNAs after mTBI using a weight drop model of closed head injury (Sharma et al., 2014). Low temperature is also known to affect miRNAs in the setting of TBI. Separate work from Dr. Dietrich's group shows that that 4 h of cooling (33 °C) alters expression of many endogenous miRNAs after FPI (Truettner et al., 2011). It remains to be determined whether or not hyperthermia affects miRNAs, such as by altering their levels and/or gene regulation, which could ultimately influence secondary injury mechanisms or outcomes after mTBI. Work by Titus et al. (2015) lays the necessary groundwork to potentially explore those as well as many other exciting questions in mTBI, and to further unravel the molecular biochemistry mediating acute hypothermia induced toxicity.

Conclusions

This work by Titus et al. (2015) from the laboratory of Dalton Dietrich at the University of Miami represents another important and timely report by this group on the potential impact of temperature on the injured brain. The use of mild hypothermia and/or targeted temperature management has revolutionized neonatal neurocritical care, impacted the neurocritical care of comatose adults after cardiac arrest, and the care of patients with a variety of other acute neurological insults such as severe TBI, stroke, spinal cord injury and subarachnoid hemorrhage. If temperature control is important to mTBI and concussion, it

could have a substantial impact on mTBI outcomes, and in a very high risk group for the occurrence of multiple concussions. This seminal work throws down the gauntlet on an important area of future investigation and one very worthy of answers as we capitalize on the golden age of TBI research.

Acknowledgments

We thank the NINDS/NIH (1R21NS088145—TCJ), NS087978 (PMK), and the United States Army W81 XWH-10-1-0623 and W81XWH-14-2-0018 (PMK) for support.

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