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Review Article

Does pediatric traumatic brain injury cause adult alcohol misuse: Combining preclinical and epidemiological approaches

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ABSTRACT

Traumatic brain injury (TBI) is closely interrelated with alcohol use disorders. This is mediated, in part, by the large number of individuals who are intoxicated at the time of their injuries. However, there is also evidence, both preclinically and epidemiologically that TBI, particularly when it occurs early in life can increase the incidence of alcohol use disorders later on. This is extremely important because drinking after TBI has been associated with much poorer long-term outcomes as compared to individuals who do not drink. However, for a number of reasons including potential confounders and a relatively long time between injury and onset of drinking it has been difficult to definitively assign causality. Here, we utilize a framework derived from the toxicology literature to determine whether a causal relationship between pediatric TBI and subsequent alcohol abuse is evident. In order for there to be a high likelihood of a causal relationship between an environmental factor and a health outcome, this framework indicates that an epidemiological relationship be present in humans and that analogous relationship has to exist in a preclinical model system and that the mechanism(s) of action that are identified in the model system must also be plausibly active in humans. In this review we discuss the epidemiological evidence for increased drinking in humans. Further, we discuss, the animal models for increased drinking after TBI and the potential mechanistic insights that have been derived from those animal models. We conclude, based on the framework described, that it is possible that pediatric TBI causes alcohol use disorders in humans.

1. Introduction

Traumatic brain injury (TBI) is closely associated with alcohol use disorders (Corrigan, 1995; Weil et al., 2016a). This is not surprising given the large number of individuals who are intoxicated at the time of their injuries (Corrigan et al., 1995; Taylor et al., 2017). Thus, the population of patients with TBI consists disproportionately of individuals with a history of problem drinking. However, there is emerging evidence that TBI may also play a causal role in alcohol use. Specifically, brain injuries that occur early in life, when alcohol is unlikely to act as the proximate cause of injury, are associated with a greater likelihood of developing alcohol use disorders later in life (Corrigan et al., 2013; Dams-O'Connor et al., 2013; McKinlay et al., 2010). Here we will summarize the extant epidemiological and preclinical evidence that pediatric TBI causes alcohol use disorders (AUD) and describe the classes of evidence that would be necessary to firmly establish causality.

Relationships between TBI and behavioral, somatic, and neurological outcomes have been described epidemiologically in clinical populations, and experimentally in laboratory animals (Bombardier, 2013; Dikmen et al., 1995; Kreutzer et al., 1996; Weil et al., 2016a). The traditional approaches of these two perspectives, each having noted advantages, also fall short of fully addressing the complexity of the human clinical situation. For instance, epidemiological studies have focused on the relative odds of a history of TBI co-occurring with specific, current behaviors or conditions. Elevated risk implies an association, but not causality. Preclinical studies, in contrast, have stripped away the profound heterogeneity of clinical situations and focused on consistent and repeatable injuries in genetically and physiologically similar animals. Generalizability to humans is not a given. Consequently, a large body of clinical and pre-clinical literature exists on which to draw conclusions about TBI outcomes, yet translational interpretation and causality are rarely achievable.

One potential approach to attaining the desired translational outcomes is to consider this body of work within the framework outlined by Robert Koch, who famously laid down a series of postulates in the 1880s that would be required to prove that a particular microbe caused a disease state (Kaufmann and Schaible, 2005; Koch, 1882; Loeffler, 1884). Moreover, they have provided the logical basis for using animal models to provide converging evidence of causality in human disease.

The relationship between a TBI during development and subsequent alcohol misuse clearly differs markedly between the inoculation with a pathogen and development of measurable disease. Moreover, it is not the case that all individuals with these injuries develop AUD *or* that all

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Table 1
Epidemiological studies of the relationship between TBI and alcohol use disorders or other substance misuse.

Study	Method	Alcohol misuse or alcohol use disorder	Other substance misuse
Unknown temporal relationship			
New Haven, Connecticut USA (Silver et al., 2001)	Population survey	Alcohol abuse or dependence AOR[a] = 2.2 (1.7–2.8)	Drug abuse or dependence AOR[a] = 1.8 (1.2–2.5)
2 southeast Australian cities (Anstey et al., 2004)	Population survey	No difference for TBI vs no TBI except young adult females (p = .045)	
Ontario, Canada (Ilie et al., 2015)	Population survey		• Uses marijuana AOR[b] = 2.80 (1.79–4.39) • Uses non-prescription opioids AOR[b] = 2.15 (1.47–3.14) • Current cigarette smoker AOR[b] = 2.90 (1.50–5.59)
Colorado, USA (Whiteneck et al., 2016b)	Population survey	Prevalence of alcohol misuse no different in TBI vs general population.	
Ohio, USA (Bogner et al., in press)	Population survey	• Binge drinking AOR[b] = 1.5 (1.1–2.0) • Heavy drinking AOR[b] = 1.7 (1.1–2.6)	Current cigarette smoker AOR[b] = 1.7 (1.3–2.2)
Known temporal relationship			
Northern Finland (Timonen et al., 2002; Winqvist et al., 2007)	Birth cohort with TBIs through age 16 and outcomes reported at age 33.	Heavy alcohol use no different for childhood TBI vs no childhood TBI	
Christchurch, New Zealand (McKinlay et al., 2014)	Birth cohort with TBIs through age 21 and outcomes at age 25	Alcohol dependence ns for each group: 1st injury 0–5, 6–15, 16-21 years old	• Drug dependence AOR[c] = 2.85 (1.11–7.32) for 1st injury 0–5 years old • Drug dependence AOR[c] = ns for 1st injury 6–15 years old • Drug dependence AOR[c] = 2.55 (1.07–6.12) for 1st injury 16–21 years old
Known Temporal Relationship with Comparison Group			
Sweden (Sariaslan et al., 2016)	Population registry with TBI before age 25 and outcomes through age 33		• Psychiatric hospitalization (including substance use disorders) after age 25 vs unaffected siblings RR = 1.96 (1.82–2.12) • Outpatient psychiatric treatment (including substance use disorders) after age 25 vs unaffected siblings RR = 1.55 (1.48–1.62)
South West England (Kennedy et al., 2017)	Birth cohort (outcomes reported at age 17)	Alcohol use disorder vs orthopedic injured AOR[d] = 1.69 (1.17–2.45)	• Cannabis misuse vs orthopedic injured (ns) • Nicotine dependence vs orthopedic injured (ns)

USA = United States of America, AOR = adjusted odds ratio TBI = traumatic brain injury, ns = non-significant, RR = relative risk.
[a] Adjusted for socio-demographics and health related quality of life variables.
[b] Adjusted for socio-demographics.
[c] Adjusted for socio-demographic factors, early behavioral problems & parental substance abuse.
[d] Adjusted for pre-birth socio-demographic factors, family environment & parenting style and history of criminal activity.

individuals with AUD have a history of TBI. Any potential relationship is obscured by the likely delay between injury and subsequent drinking (especially childhood injury) and a number of potential confounders that could explain the apparent relationship. For instance, a family history of problem drinking would likely increase the likelihood of both childhood TBI and subsequent development of AUD.

The ability to assign a causal relationship between disease onset and the latent development of symptoms is a longstanding diagnostic challenge. For example, cryptic infections, particularly those with a very long delay between infection and the onset of measurable disease, have historically been particularly difficult to assign to a causal pathogen. This difficulty is likely the case for several reasons, first, the long delay allows for an extended period of time during which potentially confounding variables may intervene and obscure the relationship. Second, long delays between infection (or other exposure) and the onset of measurable disease are also usually associated with variability in the degree and timing of disease onset, which can further obscure chains of causality. Finally, experimental modeling of delayed onset diseases are necessarily longer and require more involved experiments to account for that delay (Cochran et al., 2000). Childhood TBI as a cause of later alcohol abuse is very much subject to these obscuring variables. There is relatively little alcohol consumption in pre-adolescent children, so children injured at a very young age may go for more than a decade without exposure to alcohol. During this time individuals with a history of TBI may either appear grossly unaffected *or* exhibit impairments in cognitive and executive function or other persistent sequela. In either case, observers may be less likely to assign casual roles for later alcohol use to previous injuries, either because the individual appeared to have fully recovered by the time alcohol misuse was identified or because causal variables were obscured by the other long-term consequences of their injury.

Here we propose that to fully understand the long-term sequela of pediatric traumatic brain injury we have to utilize the tools of a third, related discipline, toxicology. We will apply a framework proposed by (Adami et al., 2011) for combining preclinical findings with epidemiological results to ask the question, “Does childhood TBI cause adult alcohol misuse?” Clearly TBI is not a toxin, but toxicology uses a set of tools including examination of age of exposure, number and severity of injury and non-linear dose response curves that may be critical for a full understanding of the role of TBI in later outcomes. In this paper, we will briefly describe some of the key epidemiological and preclinical links between TBI and neurobehavioral outcomes and consider how the logic behind toxicological science can help us to better understand causal relationships between earlier developmental TBI and later predisposition toward alcohol.

This exercise is not just academic, because individuals with a history of pediatric TBI do, on the whole, drink more than those without a history (Corrigan et al., 2013; Dams-O'Connor et al., 2013; McKinlay et al., 2010). Moreover, there is substantial preclinical, clinical, and epidemiological data that shows that drinking is predictive of negative outcomes in individuals with a history of TBI (Corrigan, 1995; Karelina et al. 2017). Drinking greatly decreases the likelihood of good rehabilitation outcomes, and is associated with decreased life satisfaction and a much greater likelihood of post-traumatic seizures, psychiatric symptoms, and repeated injuries (Vaaramo et al., 2014; Winqvist et al., 2006). Thus, clinical interventions designed to reduce drinking after

injury have the potential to greatly improve treatment outcomes. However, incorporating proactive approaches to reduce the likelihood of subsequent AUD is not without challenges (Corrigan and Cole, 2008) and would require long term interventions and family education programs since children injured early in life may not develop substance abuse issues for many years. Therefore, it is absolutely critical that we understand whether (and how) TBI increases the likelihood of developing AUD in order to justify the expenditure of limited health care resources toward a potential future comorbidity.

The Adami framework sets up a two-dimensional space to evaluate the evidence for a causal relationship with biological plausibility along the Y axis and epidemiological evidence along the X. A potential causal relationship would only be likely if there is both strong epidemiological evidence for the relationship *and* a plausible biological relationship. In other words, this requires that an analogous mechanism exists in both a model system and in humans. If only one of the two classes of evidence is present then a causal relationship is unlikely.

2. Epidemiological evidence

Table 1 summarizes 10 epidemiological studies in which TBI and alcohol abuse were examined. When other substance abuse was included, those studies were included as well. The Swedish population registry study conducted by Sariaslan et al. (2016) included substance abuse among all psychiatric diagnoses. While the lack of diagnostic specificity limits its utility for the current discussion, the article was included because of the uniqueness of being able to compare children with TBI to unaffected siblings. These studies were generally of three types: (1) population surveys in which a geographic area was systematically canvassed and samples weighted to population characteristics; (2) birth cohorts in which children born in a given time period in a specific geographic region are followed prospectively with periodic data extraction; and (3) population registries in which datasets are combined to allow the relationship between a criterion condition and a subsequent outcome for a population of interest.

Each type of methodology has strengths and weaknesses. Population surveys must rely on self-report for both the TBI history and substance abuse outcome. Generally, weighting is more complex, though that issue has only a minimal impact on the current discussion as we are less concerned about prevalence and more concerned with the co-occurrence between a condition and an outcome. Both birth cohorts and population registries typically only gather data on TBIs that receive medical attention (though in theory a birth cohort could do otherwise) and thus may not be fully representative of all TBIs that people experience, as many mild TBIs do not result in a visit to a clinic, Emergency Department or hospital. The birth cohorts and population registries reported here are also limited in the age range during which the outcomes manifest. While both methods could theoretically follow participants much later in life; those reported to date have stopped at adolescence or young adulthood.

Each of the methods also vary by the extent to which causality can be inferred. Most population surveys are purely cross-sectional and only report that a TBI occurred sometime in the past and a substance use problem is occurring presently. Without information on the age at which the first TBI occurred and the age at which substance misuse began, it is not possible to be certain that TBI preceded misuse and thus could potentially be causative. On the other hand, birth cohorts and registries are specifically limited to those who have incurred childhood TBIs, presumably preceding the use of substances (as noted above). However, as onset of TBI begins to enter into adolescence, confidence assuming TBI preceded substance misuse declines. Even when it is known that TBI precedes substance misuse, causal conclusions are limited by the prospect that both are caused by a third phenomenon. In the case of adult consequences of childhood TBI, one hypothesis is that childhood exposures, whether community factors, familial characteristics or adverse childhood experiences, may account for both injury and substance abuse (Ilie et al., 2014; McHugo et al., 2017; McKinlay et al., 2014). Controlling statistically for these factors is common; however, comparison to unaffected siblings may be a more effective control for this confound. A second hypothesis is that personality characteristics, particularly risk-taking and impulsivity, account for both injury and misuse (Bonow et al., 2019; James et al., 2014). Using an orthopedically injured comparison group to control for this confound is common—the assumption being that both groups have comparable levels of these traits.

2.1. What can be learned from the existing literature?

Evidence from the 10 studies reviewed here provide support for a relationship between TBI and substance use disorders generally, however the evidence for AUD is moderate (i.e., neither strong nor weak). Three of the 7 studies that examined a relationship with alcohol found a significant relationship; and 4 of 5 that examined other addictive substances were positive. Though not shown in the tables, even non-significant results showed trends toward a relationship, suggesting attenuated strength of the methodologies employed may account for some of the non-significant findings. Whiteneck et al. (2016a) also observed that moderate and severe TBIs may have a protective effect on AUD manifestation due to potentially limited access, the presence of medical conditions that preclude alcohol use (e.g., medications for seizures) or the occurrence of headache in response to alcohol consumption. Clinical phenomena such as these will serve to obscure a relationship between TBI and AUD, at least among those with more severe injuries. Finally, considering just the studies of simple associations, the frequent (but not universal) observation that other substance use disorders are associated with TBI (Ilie et al., 2014; McKinlay et al., 2014; Silver et al., 2001) may strengthen support for a dopaminergic mechanism of action.

The two studies that employed comparison groups are best positioned to provide insight into the question of causality. Unfortunately, as noted above, we cannot separate AUD, or even all substance use disorders, from other psychiatric diagnoses in the Swedish registry study (Sariaslan et al., 2016). The birth cohort reported by Kennedy et al. (2017) provides support for a causal relationship independent of risk-taking and impulsivity that is assumed to be shared by those incurring only orthopedic injuries. It is interesting that alcohol but not cannabis misuse or nicotine dependence showed a greater association with childhood TBI, at least at age 17.

3. Biological plausibility

Epidemiological evidence for elevated risk for problem drinking in the pediatric TBI population is moderate and of sufficient clinical importance to justify investigation into mechanisms of action and potential interventions. Moreover, as outlined above there are multiple critical potential confounders and logistical challenges associated with epidemiological investigations into the relationships between TBI and subsequent alcohol misuse. Here, an animal model which can strip away variation in injury type and severity, genetics, drinking history, and other potential variables inherent to epidemiological research can provide both converging phenomenological evidence and allow for mechanistic experiments which are not feasible in humans. Thus, our overall goal for this section, in accordance with the epi-tox framework (Adami et al., 2011), is to describe preclinical evidence of TBI-induced alterations in alcohol-related behavior, address potential biological mechanisms in rodents, and consider whether similar mechanisms could be at play in humans.

3.1. Does TBI increase drinking behavior in experimental animals?

We developed an animal model of drinking after mild pediatric TBI (Weil et al., 2016b). Briefly, mice at 21 days of age were administered a mild, closed-head, concussive impact over the left temporoparietal

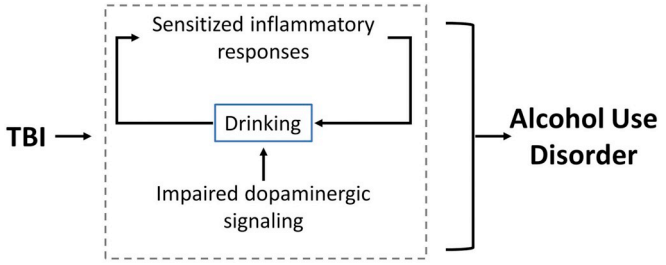

Fig. 1. Simplified schematic summarizing the biological mechanisms that can link traumatic brain injuries during development to subsequent development of alcohol use disorders.

cortex. A separate cohort of mice was injured at 60 days of age or at both 21 and 60 days. This injury produces a brief (1–5 min) period of unconsciousness and virtually no deficits in motor control, affective behaviors or cognitive function. Further, this injury paradigm produces widespread but diffuse axonal degeneration with minimal evidence of frank neuronal death or the formation of a focal lesion. After the injury, mice were returned to standard housing conditions until they were young adults (approximately 70 days of age) and then were tested in a two-bottle choice paradigm with escalating concentrations of unsweetened alcohol (and tap water in the other bottle). Intriguingly, female mice injured at 21 days of age (or at both 21 and 60 days) drank much more alcohol (more than double) than did sham-injured females, females injured only as adults, or males regardless of injury status. This increase in drinking behavior was also associated with increased conditioned place preference responses to intraperitoneal alcohol and was independent of changes in the ability to detect either sweet or bitter solutions. Thus, TBI during juvenile development (but not later in life) increased drinking behavior and did so only in female mice (Weil et al., 2016b).

We were surprised by the strong sex difference in drinking after injury. Female rodents tend to drink more than males under basal conditions (Becker and Koob, 2016; Eriksson and Pikkarainen, 1968) but it was not immediately obvious why the effect of injury was not apparent in males given that there is not strong evidence for large sex differences in drinking in humans and particularly not in that direction. The strain of mice used is not a particularly alcohol preferring one (Schneider, 1973) and one strategy that has been employed to increase drinking behavior in mice is to expose them intermittently to alcohol during adolescence rather than adulthood (Melendez, 2011). Under these conditions male mice that underwent injury early in life exhibited increased alcohol self-administration compared to sham injured animals. Currently, we are investigating the neuroendocrine basis of sex differences in drinking behavior after TBI.

These data are largely in agreement with several other rodent studies either showing increases in alcohol self-administration after injury or only testing animals that had been injured as adults. However methodological variables among the animal studies, including differences in species, injury type and severity, age (at injury and testing), alcohol administration paradigm and history of alcohol exposure, make it difficult to directly compare among them although several patterns do emerge. First, in the acute post-injury period TBI appears to decrease alcohol intake as has been reported frequently in clinical populations and in mice following TBIs (Bombardier et al., 2003; Lowing et al., 2014). Rates of alcohol drinking rebound over time in clinical populations and this is also apparent in rodents. For instance, several groups have exposed animals to alcohol prior to injury, either to train them to perform operantly for alcohol or to establish baseline levels of drinking. Mayeux et al. (2015) reported that lateral fluid percussion injury, performed in adult male rats, increased alcohol responses approximately 50% in an operant self-administration paradigm. Whether this prior exposure is necessary to potentiate drinking behavior remains unspecified but would line up well with the epidemiological evidence demonstrating that pre-injury drinking predicts subsequent alcohol abuse (Winqvist et al., 2006). Similarly, Lim and colleagues report that alcohol self-administration was bimodally distributed after injury, if a median split was performed on sham and blast-exposed rats, the higher drinkers among the blast-exposed group drank approximately 50% more than the high drinkers in sham group (Lim et al., 2015). Finally, mice derived from a high drinking line exhibit reductions from around 30% ethanol to 10% after mTBI drinking alcohol self-administration after injury whereas those from a less alcohol preferring line do not although these animals drink only around 10% of the alcohol under basal conditions as well, suggesting that a floor effect may exist (Poznanski et al., 2018). Taken together these data suggest that TBI cannot induce alcohol drinking in animals that would normally not do so but can greatly increase drinking in animals that because of their age, sex, genetics or individual differences are predisposed to drinking.

3.2. Is there a biological link between pediatric TBI and alcohol drinking?

Traumatic injuries to the developing nervous system both directly damage the brain and can interfere with and alter the trajectory of ongoing neurodevelopmental activities (Giza et al., 2009; Semple et al., 2013). Both human and rodent brains undergo tremendously intricate neurodevelopmental events postnatally, many of which can have profound influences on the vulnerability to subsequent substance use disorders (Enoch, 2011; Eslinger et al., 1992). Thus, there are likely to be many neurobiological mechanisms that couple trauma to drug abuse. We have previously reviewed the neuronal and biopsychosocial processes that could couple TBI to AUD (Karelina et al. 2017; Weil et al., 2016a). Here we will focus on the potential mechanisms that have received the most attention, namely, the evidence that TBI persistently alters central inflammatory signaling and meso-limbic dopamine physiology in both experimental animals and clinical populations with potential implications for the development of substance abuse issues (Fig. 1). These are by no means meant to be either exhaustive reviews of these mechanisms or the only potential links but are described to offer biological plausibility.

3.3. Role of the inflammatory response in TBI

Although traumatic brain injuries can constitute wildly different etiologies and severity, neuroinflammation is a nearly ubiquitous response (Witcher et al., 2015). Moreover, it is becoming increasingly clear that proinflammatory mediators have critical roles in neurodevelopmental processes under physiological conditions (Bilbo and Schwarz, 2009; Merrill, 1992; Schafer et al., 2012) meaning that trauma-induced inflammatory reactions early in life can profoundly disrupt neural development. Additionally, immunological parameters are also persistently altered following early life inflammatory responses with the potential to sensitize immune cells to subsequent inflammatory stimuli such as alcohol (Adams-Chapman and Stoll, 2006; Burke et al., 2016). Additionally, TBI can serve to prime immune cells to exhibit hyperinflammatory responses to subsequent inflammatory events (Fenn et al., 2014; Witcher et al., 2015). Thus, taken together, neuroinflammation that occurs after TBI in children can disrupt fundamental neurodevelopmental processes including neurogenesis, myelination, and synapse formation in circuitry critical to neuronal responses to alcohol (Glynn et al., 2011; Paolicelli et al., 2011).

Neuroinflammatory signaling is directly relevant for alcohol-related behavior as there are bidirectional links between alcohol and inflammatory responses. Neuroinflammatory events in the brain tend to promote drinking behavior. For instance, cellular components of the innate immune system in the brain express pattern recognition receptors called Toll-like receptors (TLRs) that are activated by, among other things, microbe associated molecules (Akira and Takeda, 2004). Activation of TLR3 and TLR4 with the model inflammogens Poly I:C and lipopolysaccharide respectively increases alcohol self-

administration (Blednov et al., 2011; Randall et al., 2019). Conversely genetic deletion of proinflammatory cytokines or administration of anti-inflammatory signaling molecules can reduce drinking behavior in rodents (Blednov et al., 2012). Thus, the ongoing inflammatory responses that are a key sequela of TBI may increase the likelihood of drinking in individuals with a history of TBI (Coleman and Crews, 2018).

Clearly, however, not all individuals who drink misuse the drug or become dependent. TBI-induced inflammatory responses, however, may serve to facilitate the transition toward dependence in part because alcohol is itself proinflammatory and can activate TLRs and lead to the production of other proinflammatory signaling molecules (He and Crews, 2008; Pascual et al., 2011; Vetreno and Crews, 2012). Indeed, individuals with a long history of heavy drinking exhibit evidence of prolonged and extensive neuroinflammatory reactions (He and Crews, 2008), although central inflammatory responses have been described in rodents in response to acute alcohol exposure (Crews et al., 2011). Moreover, alcohol withdrawal is proinflammatory and blockade of cytokine signaling can help reduce the aversive components of withdrawal in rats (Freeman et al., 2012).

For individuals with a history of TBI who exhibit sensitized inflammatory responses, the possibility exists that a vicious cycle could be established (Coleman and Crews, 2018). Specifically, TBI may sensitize or prime the innate neuroinflammatory system, which produces inflammatory responses that can increase drinking behavior, which promotes further neuroinflammation (Coleman and Crews, 2018; Fernandez-Lizarbe et al., 2013; Karelina et al., 2018). Additionally, the increase in incidence of alcohol use disorders could potentially be mediated by promoting early onset of drinking behavior which is a powerful predictor of AUD development (DeWit et al., 2000). We have hypothesized previously that once drinking begins, individuals with a history of TBI could exhibit enhanced inflammatory responses to alcohol itself. Finally, sensitized alcohol responses could also exacerbate the aversive consequences of withdrawal (Weil et al., 2016a; Weil et al., 2016b). Moreover, we recently showed in experimental animals that increases in adolescent drinking behavior in mice after TBI could be blocked with the microglial activation inhibitor minocycline, which suggests that inflammatory responses are necessary for the increase in drinking behavior after injury (Karelina et al., 2018).

3.4. Involvement of dopamine dysregulation after TBI

There is substantial evidence that mesolimbic dopamine is involved in the rewarding aspects of alcohol consumption in both humans and experimental animals (Di Chiara and Bassareo, 2007; Ramchandani et al., 2011). Dopamine concentrations in the ventral striatum rise after ethanol consumption and are correlated with the subjective levels of euphoria in human imaging studies (Boileau et al., 2003). In contrast, various aspects of dopamine physiology, including dopamine synthesis, transporter activity and receptor expression, are generally downregulated in abstinent alcoholics (Heinz et al., 2005; Martinez et al., 2005) and experimental animals withdrawing from alcohol (Diana et al., 1993). Genetic polymorphisms in D2 receptor expression that lead to reduced expression increase the incidence of AUD (Comings et al., 1994). Although there is some conflicting evidence among experimental studies in animals, the majority conclude that dopaminergic physiology is involved in alcohol-related behaviors.

Dopaminergic machinery undergoes substantial maturation and reorganization during juvenile development and thus it would not be surprising if a TBI during this period substantially interfered with homeostatic development of neural circuits. There has been relatively little investigation into dopaminergic outcomes from early life TBI but there is substantial evidence from adult experimental animals that TBI persistently alters dopamine signaling. In general, dopaminergic machinery appears to be acutely upregulated following injury but then eventually settles into long-term reductions in dopamine signaling in rodents (Bales et al., 2010; Bales et al., 2009; Wagner et al., 2005; Wagner et al., 2009). In our juvenile mouse model of mild TBI, animals exhibited reduced locomotor sensitization to amphetamine stimulation in adulthood and reductions in dopaminergic machinery including tyrosine hydroxylase (the rate limiting enzyme in dopamine production) in the ventral tegmental area and further alterations in dopamine transporter and receptor expression throughout the mesolimbic system (Karelina et al., 2017b).

Among humans, there has been comparatively little direct evidence of dopamine dysregulation in TBI survivors. Single photon emission tomography has served as the principal mechanism for identifying post-injury dopaminergic dysfunction. For instance, patients with TBI had reduced dopamine transporter activity and reduced D2 binding in the striatum compared to age matched individuals despite having primary lesion sites outside of the striatum (Donnemiller et al., 2000). More recent studies have correlated reductions in dopamine transporter activity to cognitive and executive dysfunction among moderate-severe brain injured individuals (Jenkins et al., 2018). The imaging evidence of reduced dopaminergic signaling is supported by the widespread use of dopamine-facilitating drugs to treat the cognitive and behavioral consequences of brain injury (Frenette et al., 2012; Sami and Faruqui, 2015).

The precise mechanisms that lead to dopaminergic dysfunction following TBI likely reflect both direct damage to the cell bodies and axons of dopaminergic midbrain neurons, and alterations in the biochemical and neuronal regulation of dopamine release by other neurotransmitter systems including GABA and glutamate (Ding et al., 2001; Hutson et al., 2011; Zandy et al., 2015) in rats. Moreover, as mentioned above it is likely that injuries during development disrupt normal maturation of dopamine circuitry. Finally, inflammatory signaling is strongly-anti-dopaminergic (Felger and Miller, 2012). Thus, it is highly plausible that TBIs, particularly during development, could facilitate the development of drinking and subsequent transition to alcohol abuse by impairing the function of dopaminergic signaling.

These two potential biological mechanisms, primed central inflammatory responses and impaired dopamine signaling, components of which are operative in human patients, both have important potential roles in the development of AUD. Moreover, there is burgeoning but incomplete animal data to support a potential mediational role for these sequelae of TBI in the development of AUD in humans (Merkel et al., 2017; Weil et al., 2016a). More importantly, for the purposes of this paper, we can conclude from these data that the biological plausibility for a causal relationship between TBI and AUD is strong.

4. What future research is needed to establish causality

Our ability to definitively answer the question of whether childhood TBI causes adult AUD would be greatly assisted by elaborations to current research methods. Epidemiological studies should document the age at onset for both TBI and alcohol or other drug misuse. Obtaining information beyond a simple “yes/no” regarding TBI history or “is/is not currently abusing” drugs or alcohol would greatly enhance the utility of these studies. Even population surveys can employ methods to elicit retrospective information about onset. Epidemiological studies should also explore ways to control for characteristics other than just age, gender and race/ethnicity. Comparative groups, especially from the same household or with similar risk factors for injury, are essential to the ability to rule out confounding influences. Finally, all research methods should account for how TBI and alcohol use manifest. Neither phenomena are unitary nor homogenous. Number, severity and recency of TBI, as well as age at occurrence, are important ways to characterize one's lifetime exposure to TBI. Similarly, in addition to onset, alcohol misuse varies by amounts consumed, regularity in the short-term and consistency over time. A richer operationalization of both constructs would likely improve our ability to detect more nuanced relationships.

There are several missing components of the preclinical studies that would provide increased clarity on the relationship between TBI and animal models of AUD. First, most of the work in animals has focused on the role of TBI in alcohol self-administration (either using a two-bottle choice or operant approach). Although willingness to self-administer alcohol is certainly relevant to risk for AUD, more alcohol self-administration is not a model of alcohol dependence. Addiction has been characterized as a multi-stage process with binge and intoxication, followed by withdrawal and negative affect and preoccupation and anticipation all leading to the gradual loss of control over substance taking (Volkow et al., 2016). Most of the preclinical studies have focused on the early stages of the process and have not examined whether injured animals would become dependent on alcohol.

From a mechanistic point of view there are many unanswered questions as to how a physical stimulus at a particular developmental age is coupled to increased propensity to alcohol self-administration and potential dependence. This is of importance because if we understand the basic biology we are more likely to be able to predict which individuals who suffer a TBI may be at elevated risk for AUD and to begin to tailor intervention strategies to this population.

5. Conclusion

Based on the extant, epidemiological and pre-clinical evidence, we consider it possible that pediatric TBI is causally related to alcohol misuse later in life. The specific populations for which this relationship holds true remains largely unspecified but it seems clear that age at injury, severity of injury, sex, and likely other variables can modulate this relationship. The precise mechanisms that link TBI to alcohol misuse in humans remain unspecified and may not represent a single process in all individuals. That being said, however, there is preclinical evidence that TBI can increase drinking in animals via mechanisms that are highly likely to exist in humans. More research at both the epidemiological and preclinical levels will be necessary before this causal relationship can be fully proven or understood.

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