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Animal models of traumatic brain injury

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INTRODUCTION

Affecting over 1.7 million people in the US each year, traumatic brain injury (TBI) is now recognized as a major health issue (Faul et al., 2010). This includes the personal burden endured by survivors and their families and also the significant economic burden at an estimated annual cost of over $76 billion in the US alone (Finkelstein et al., 2006). Furthermore, TBI may also be a risk factor for the later development of neurodegenerative disorders, including Alzheimer's disease (AD) (Mortimer et al., 1985, 1991; Graves et al., 1990; Molgaard et al., 1990; O'Meara et al., 1997; Salib and Hillier, 1997; Schofield et al., 1997; Guo et al., 2000; Plassman et al., 2000; Fleminger et al, 2003; Johnson et al., 2012). Despite this huge impact on society, no treatment has been shown to be efficacious though there have been multiple phase III clinical trials (Narayan et al., 2002; Menon, 2009). While the reasons for these failures are complex, the clinical relevance of animal models of TBI used in drug development has been a major point of criticism and reflection (Marklund and Hillered, 2011).

TBI in humans is characterized by a vast spectrum of evolving neuropathologies. In acute severe TBI, heterogeneous pathologies span varying degrees of brain swelling, hemorrhage, contusions, diffuse axonal injury (DAI), and ischemia (Graham et al., 2002). Although the pathologic substrates of mild TBI are not well characterized, they appear to be more homogeneous, predominantly encompassing a mild degree of DAI (Blumbergs et al., 1994, 1995; Browne et al., 2011). Moreover, while evolving pathologies were previously thought to resolve within months of TBI, it is now recognized that degenerative and inflammatory changes can continue to progress even decades after injury (Chen et al., 2009; Johnson et al., 2012, 2013b). This diverse nature of human TBI highlights the challenges of developing clinically relevant animal models, with an emerging consensus that no one model is sufficient.

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Countless animal TBI models have been developed over several decades to address either general or specific clinical conditions. Historically, these experimental TBI models were categorized broadly as “focal,” including those that induce cerebral contusions, edema, and hematomas, or “diffuse” with pathologic features comprising more widespread vascular injury, ischemia, general brain swelling, and DAI. However, this stark distinction is falling out of use since it is now recognized that few “focal” models actually induce exclusively localized pathology. Additionally, the variation in the character and extent of pathologies between models of “diffuse” TBI models are too great to be captured under one heading. Instead, more recent descriptions of TBI models address key pathologic features and/or injury severity, with the caveat that many other changes may also be present. For this chapter, we will use this general approach to discuss experimental models based on their principle neuropathologic features.

For TBI model development and use, there are cautionary tales of missteps in the past regarding terminology and interpretation of “clinically relevant” aspects of experimental TBI models. For example, whereas some rodent models are described as producing “severe TBI,” the injured animals are able to ambulate, eat, and groom within hours of TBI, clearly very different from severe TBI in humans. Likewise, there has been debate whether the term “DAI” is appropriate to describe axonal pathology in rodents from both a mechanistic and anatomic perspective (described in more detail below) (Johnson et al., 2013b). Clarity regarding clinically relevant features of animal TBI models is particularly important for the preclinical development of TBI therapies. Indeed, considering that there have been many therapies shown to be efficacious in rodent models of TBI that did not subsequently translate in clinical trials, there has been intense interest in examining the sources of this disparity and plotting a course forward.

Due to the extensive range of models of TBI, this chapter will focus on models of *dynamic* closed-head traumatic brain injury, and will not include models of penetrating, ablation, lesion injury or quasi-static injury such as prolonged compression injury. Rather, this chapter aims to address the clinical relevance and general utility of various categories of established animal TBI models. For the development of these models, important consideration of the injury biomechanics is essential to mimic the spectrum of TBI neuropathology.

BIOMECHANICS OF TRAUMATIC BRAIN INJURY

The viscoelastic nature of the brain appears to be a major liability in the face of rapid head accelerations. Under normal daily activities, the brain easily accommodates any transient tissue deformations, returning to its resting geometry unharmed. However, under very rapid or *dynamic* mechanical loading conditions, the viscoelastic brain behaves stiffer, causing damage in regions of high strain (Holbourn, 1943, 1945; Strich, 1961; Smith et al., 1999; Smith and Meaney, 2000). For tissue injury, the *dynamic* component refers to the mechanical pulse being applied within 50 milliseconds (ms) (Smith and Meaney, 2000; Smith et al., 2003), a feature that is typically adopted in animal models of TBI.

To mirror the clinical circumstances, acceleration forces are utilized in some animal models to rapidly deform brain tissue. Translational or linear accelerations that impact the skull or

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brain can produce intracranial pressure gradients and movement of the brain relative to the inner surface of the skull. The magnitude of the peak intracranial pressure depends directly on the level of translational acceleration, while the amount of skull–brain movement is less sensitive to the acceleration magnitude. The local skull distortion and propagation of stress waves through the brain from the point of impact and gross movement of the brain direct the form of brain damage. Common pathologic consequences resulting from this mechanical injury include extradural hematomas, surface contusions, and intracerebral hemorrhage, typically near the site of contact.

Rotational acceleration of the brain can be triggered by translational forces impacting the head, inducing rotation, or even in the absence of head impact such as in motor vehicle crashes where rapid head movements of a restrained occupant can occur. Head rotational acceleration causes various brain regions to undergo differential shear, tensile, and compressive forces that cause tissue deformation at high strain rates (Meaney et al., 1995). The amount of shear strain is related not only to the amount of rotational acceleration, but also to the presence of intracranial dural compartments (e.g., falx, tentorium cerebri) and direction of motion. These inertial forces are responsible for the most pronounced types of damage encountered in nonmissile head injury, including acute subdural hematoma resulting from the tearing of subdural bridging veins and DAI (Graham et al., 2002).

One common misperception of TBI biomechanics is the mechanism of “coup and contrecoup” injuries, referring to surface contusions on opposing hemispheres. This mechanism is commonly portrayed in videos on TBI information websites showing the brain bouncing back and forth within the skull due to head impact. However, while brain contusions may indeed be caused near sites of head impact, there is little evidence to support a simple bouncing concept. Rather, the transferred forces from head impact can induce rapid shifting of the brain surface, which causes some brain regions to impinge on the skull, thus resulting in additional contusions. The constructive interference of stress waves through the skull may also maximize the stress on the brain surface opposite the impact point, but this stress point may also occur at other points where skull thickness changes dramatically.

The relative extent of contact versus inertial forces determines the character and extent of focal and diffuse brain pathologies in human TBI (Fig. 8.1). With the exception of hematomas, most other focal pathologies are typically found to be coincident with diffuse injuries, such as DAI (Adams et al., 1982, 1989, 1991; Graham et al., 1995). In contrast, DAI can occur in isolation even in some cases of severe TBI (Graham et al., 2002).

For humans, the size of the brain is also critical in TBI since high mass effects between regions of tissue can create high strains during dynamic brain deformation, with the brain literally pulling itself apart during rapid accelerations. By comparison, the same forces applied to a smaller brain will induce lower strains with less injury (Holbourn 1943, 1945; Margulies et al., 1990). Accordingly, for several animal models of TBI, injury parameters must be scaled up relative to brain size to create the same mechanical loading of brain tissue that occurs in human TBI (Holbourn, 1943, 1945; Margulies et al., 1990; Thibault et al., 1990; Meaney et al., 1995). For example, accelerations had to be increased 500% for a 140 g

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baboon brain and 630% for a 90 g pig brain to induce the same tissue strains leading to DAI in humans (Ommaya et al., 1967; Smith et al., 1997a).

This tenant of scaling injury parameters according to brain size has created debate with regards to the validation of models of head rotational acceleration in small animals, primarily rodents. Indeed, the inertial forces necessary to produce equivalent tissue strains in the less than 2 g rat brain appear to be unachievable, with accelerations approaching 8000% of what is needed to mirror tissue strains human TBI (Meaney et al., 2001). Additionally, it has been argued that the term, "DAI," as characterized as axon pathology spread throughout large white matters domains, should be limited to humans and large animal models with relatively large gyrencephalic brains (Johnson et al., 2013b). Nonetheless, many rodent head impact models of TBI clearly induce axonal pathology, identified as swollen axonal profiles in regions of white matter (e.g., corpus callosum, brainstem) (Nilsson et al., 1977; Nilsson and Nordstrom, 1977; Feeney et al., 1981; Dixon et al., 1987, 1991; McIntosh et al., 1987, 1989; Shapira et al., 1988; Smith et al., 1995; Shreiber et al., 1999a, b).

Overall, the interplay between TBI biomechanics and resultant pathology is critical to the development of clinically relevant animal models of TBI.

CONTUSION MODELS OF TRAUMATIC BRAIN INJURY

In the clinical setting "focal TBI" is used to describe a spectrum of pathologies regardless of the biomechanical nature of injury. This includes intracerebral and intracranial hemorrhage, as well as one of the most common pathologies of moderate-severe TBI, cortical contusion. In contrast, in the laboratory, models of "focal" TBI in the vast majority of cases represent pathologies resulting from a blow to the head. Indeed, virtually all "focal" TBI models are more specifically cortical contusion models with or without more widespread neuropathology. Several species have been used to model cerebral contusion including cats (Sullivan et al., 1976), sheep (Grimmelt et al., 2011), ferrets (Lighthall, 1988), nonhuman primates (Ommaya et al., 1966), and pigs (Durham et al., 2000; Alessandri et al., 2003; Grate et al., 2003; Manley et al., 2006; Zhang et al., 2008; Missios et al., 2009). However, primarily for reasons of convenience and economic viability, mice and rats have been by far the most widely used species.

Currently, four general techniques are used to produce experimental focal brain injury in rodents: weight drop (Nilsson et al., 1977; Nilsson and Nordstrom, 1977; Feeney et al., 1981; Shapira et al., 1988), fluid percussion (FP) (Dixon et al., 1987; McIntosh et al., 1987, 1989) (Fig. 8.2), rigid indentation (Smith et al., 1995; Dixon et al., 1991) (Figs. 8.2, 8.3), and dynamic cortical deformation (DCD) (Shreiber et al., 1999a, b), all of which typically employ mechanical forces to produce dynamic deformation of brain tissue over the course of approximately 10–30 ms (Smith and Meaney, 2000). Notably, weight drop, FPI, and rigid indentation all depend upon impact forces applied directly to the brain or skull of the animal. As the name implies, weight drop models employ weights that are dropped through a guiding apparatus to generate an impact either on the closed cranium, a metal plate fixed to the cranium, or through a craniectomy directly on to the dural surface. Fluid percussion models of brain injury use rapid propagation of a pressure wave through fluid across a sealed

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column into the closed or open cranial cavity. Rigid indentation a pneumatically driven impactor to deform the brain through a craniectomy, at a prespecified velocity and depth, and is commonly referred to as controlled cortical impact (CCI). More recently, various groups have employed CCI directly onto the closed skull in attempts to model more mild and diffuse forms of TBI, often using repetitive injury paradigms (Creed et al., 2011; Shitaka et al., 2011; Bennett et al., 2012; Mouzon et al., 2012, 2014; Hylin et al., 2013). However, given the pliable nature of the skull in rodents, it is unclear to what extent there is a compressive component to these injuries.

In contrast to direct impact models, dynamic cortical deformation is a more “pure” model of contusion injury which has been used both in rodents (Shreiber et al., 1999a, b) and pigs (Zhang et al., 2008). Specifically, a focal and expanding contusion is generated via the application of negative pressure to an exposed region of cerebral cortex. Head motion is restricted in these models and tissue deformation from all four techniques may be adjusted to generate a reproducible spectrum of injury severity.

Not surprisingly, the predominant histopathologic feature of the described models is a focal cortical contusion (Cortez et al., 1989; Smith et al., 1995; Hicks et al., 1996). Histopathologically, contusions typically appear hemorrhagic, necrotic and over time, undergo cavitation, with their boundaries consisting of a glial limitans (Cortez et al., 1989; Soares et al., 1995; Hicks et al., 1996). However, with the exception of DCD, these models all display, to some extent, more widespread pathologic changes both ipsilateral and contralateral to the impact site. Specifically, disruption of the blood–brain barrier, well beyond the contused region (Cortez et al., 1989), with associated post-traumatic vasogenic cerebral edema (Marmarou and Shima, 1990; Soares et al., 1992; Tanno et al., 1992) has been observed (Fig. 8.3). Similarly, neuronal loss and axonal pathology has been observed in regions distant to the contusion site (Dixon et al., 1991; Pierce et al., 1996). Notably, many of these models depend upon a prior craniectomy, which unless sealed may also act as a decompressive craniectomy post-trauma, potentially affecting outcome.

Importantly, it has been shown that tissue loss resulting from experimental contusions produced by focal impact models in rats and mice gradually increases over time, resulting in a dramatic atrophy persistent for even up to 1 year following injury (Bramlett et al., 1997; Bramlett and Dietrich, 2002; Smith et al., 1997b; Dixon et al., 1999; Nakagawa et al., 1999, 2000; Loane et al., 2014) (Fig. 8.4). This may be of particular clinical importance, since brain injury in humans has been associated with progressive neurodegenerative disorders (Johnson et al., 2010; Smith et al., 2013). Microglial and macrophage proliferation and/or recruitment have also been demonstrated in impact models of trauma.

While predominantly found at the site of maximal contusion in the days following injury, microglia are also present in large numbers throughout regions demonstrating blood–brain barrier disruption, including the hippocampus and thalamus (Soares et al., 1995). Astrocytosis, apparently due to hypertrophy rather than proliferation, has also been observed in many regions both proximal and distal to the site of contusion. In addition, leukocytosis has been observed following experimental injury in rats, initially as an increase in neutrophils lining the vasculature in the injured cortex, and by 24 hours post-trauma,

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neutrophils are observed migrating into the contusion and surrounding tissue, but not as widely as the glial response (Soares et al., 1995). Intraparenchymal infiltration of neutrophils is then followed by a significant increase in the presence of parenchymal macrophages (Soares et al., 1995). In addition to the acute phase post-trauma, animal models have more recently been shown to replicate the chronic microglial activation that has been shown to be a feature with long-term survival in human TBI (Johnson et al., 2013a). Specifically, Loane et al. showed persistent microglial activation in association with progressive brain atrophy up to 1 year following controlled cortical impact in mice (Loane et al., 2014). As such, these models may provide important insights as to potential mechanisms of chronic progressive neurodegeneration.

MODELS OF TRAUMATIC AXONAL INJURY

Axons in the white matter appear to be especially vulnerable to damage due to the dynamic deformation that occurs in human TBI. Indeed, DAI is thought to be one of the most common and important pathologic features of TBI (Adams et al., 1982, 1989, 1991; Graham et al., 1995; Johnson et al., 2013b). Therefore, there is great interest in using relevant animal models of TAI in TBI research.

Currently the clinical diagnosis of DAI following TBI is based on the presence of immediate loss of consciousness and/or cognitive dysfunction in the absence of an intracranial mass lesion. In severe TBI, altered neurotransmission due to damage to axons following diffuse injury has been suggested to produce primary coma in contrast to secondary coma resulting from compressive injury. Diagnosis of DAI, other than through histopathologic examination at postmortem, has remained a major challenge. As a consequence of its microscopic and disseminated nature, the axonal pathology of DAI is not directly discernible with standard noninvasive techniques such as conventional computed tomography (CT) or magnetic resonance imaging (MRI) (Mittl et al., 1994), although increasing evidence suggests that diffusion tensor imaging may have utility for detecting axonal pathology (Hunter et al., 2012) (for further detail please refer to Ch 17). Yet, in current clinical practice, this “stealth” pathology is often missed or regarded as a diagnosis of exclusion based on symptoms in the absence of overt changes with conventional neuroimaging. To further complicate matters, the term “diffuse axonal injury” is itself somewhat of a misnomer, since technically the distribution is not diffuse but is instead stereotypically multifocal, preferentially involving midline white matter tracts such as the corpus callosum, internal capsules, brainstem, and cerebellar peduncles (Adams et al., 1989, 1991).

A primary outcome of dynamic deformation of white matter tracts during trauma is the interruption of axonal transport, resulting in accumulation of transported materials leading to axonal swellings within just hours of trauma (Povlishock and Becker, 1985; Christman et al., 1994; Smith et al., 1999). Commonly, swellings appear in a periodic arrangement along the length of an axon at the site of injury, classically referred to as “axonal varicosities,” or as a large single swelling at a disconnected axon terminal described as an “axonal bulb” (previously referred to as a “retraction ball”) (Cajal, 1928; Rand and Courville, 1946; Strich, 1956; Adams et al., 1982, 1984; Povlishock et al., 1983, 1999; Povlishock and Becker, 1985; Adams et al., 1989; Povlishock, 1992; Chen et al., 1999; Smith and Meaney, 2000; Smith et

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al., 2003; Povlishock and Katz, 2005). The histopathologic gold standard for the identification of DAI is achieved via immunohistochemistry to visualize damaged axons accumulating the amyloid precursor protein (APP) (Gentleman et al., 1993; Sherriff et al., 1994). With this as a clinical framework, the following models have been developed to recapitulate the clinical and histopathologic features of DAI.

Gyrencephalic models of diffuse axonal injury

Few clinically relevant models of DAI in gyrencephalic animals have been characterized. This reflects the difficulty of developing a model system that replicates the dynamics of diffuse injury, such as the inertial loading conditions produced in automotive crashes or at the moment of head impact (Smith et al., 2003). Indeed, only two animal models have been shown to replicate the key clinical features of DAI. These “inertial” injury models were initially characterized in nonhuman primates, utilizing nonimpact head rotational acceleration to produce coma in association with diffuse axonal damage (Gennarelli et al., 1982). In this seminal study, the axonal damage produced by this model was found most prominently in midline structures in a similar distribution to that observed following human inertial, nonimpact brain injury (Gennarelli et al., 1982). More specifically, this model was shown to produce a spectrum of injury, including acute subdural hematoma (disruption of bridging vessels) and/or tissue tears in central white matter, often in association with gliding contusions in the parasagittal gray–white matter junction. DAI was found throughout the white matter in both hemispheres, the brainstem, and the cerebellum. Nonhuman primates were originally chosen for this experimental model due to their large brain mass, which as described above, allows for the development of high strain between regions of tissue.

The wide spectrum of pathology produced by rotational-acceleration head injury in the nonhuman primate was found to depend on the exact nature of the biomechanical profile of the injury. For example, rapid rotational acceleration in the sagittal plane produces subdural hematomas, whereas slower acceleration in the coronal plane produces DAI (Gennarelli et al., 1982). These data were the first to conclusively link dynamic mechanical deformation of the brain during trauma with the selective pathology of DAI. Moreover, Gennarelli and colleagues found that DAI was responsible for immediate and prolonged post-traumatic coma, independent of a mass lesion. This important finding was directly extrapolated to transform the clinical diagnosis of DAI in TBI patients.

More recently, a porcine model of rotational acceleration brain injury has been developed, using young adult miniature swine (Ross et al., 1994; Meaney et al., 1995) (Fig. 8.5), which have a brain mass of approximately 70–100 g. This new animal model was established through the initial use of physical model experiments utilizing miniature swine skulls filled with surrogate brain material that were subjected to scaled rotational acceleration. Analysis of point-by-point deformations of the surrogate brains at differing accelerations established experimental parameters predicted to produce DAI in miniature swine (Smith et al., 1997a, 2000). Specifically, pure impulsive head rotation in the coronal plane was produced over 4–6 ms. Peak coronal plane rotational accelerations were found to range from $0.6–1.7\times10^5$ rad/s^2. Rotational acceleration, set at these parameters, was sufficient to consistently produce axonal injury throughout the white matter, particularly subcortically. However, to date, no

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tissue tears or gliding contusions have been observed. Notably, studies using this model demonstrated that the plane of head rotational acceleration in reference to the brainstem is critical in determining the induction and duration of loss of consciousness following injury. Specifically, rotation transverse to the brainstem was associated with coma, whereas equivalent rotation circumferential to the brainstem was not (Smith et al., 2000; Browne et al., 2011). Even at mild parameters of injury, loss of consciousness was induced following rotations transverse to the brainstem (Browne et al., 2011). The duration of loss of consciousness or coma following injury was directly related to the extent of axonal pathology in the brainstem, indicating brainstem damage is a key anatomic substrate for immediate loss of consciousness in TBI (Smith et al., 2000). However, when the brainstem was relatively spared, even extensive axonal pathology throughout the hemispheric white matter produced little or no loss of consciousness. Thus, while there is a link between DAI and immediate post-traumatic loss of consciousness, it appears that the distribution, rather than the overall extent, of axonal pathology is important in determining consciousness immediately following TBI (Browne et al., 2011).

Although the nonhuman primate and porcine rotational acceleration models of brain injury produce axonal damage without impact, translational forces from contact loading may also initiate inertial injury leading to axonal injury, as discussed above.

Rodent models of traumatic axonal injury

The majority of direct impact models (induced through contact loading) in rodents have typically produced axonal injury predominantly proximal to the contusion site. However, as noted, more widespread and severe axonal pathology has been observed in variations of these models (Dixon et al., 1991; Pierce et al., 1996), including fluid percussion injury performed in the midline. The demonstration of axonal damage in regions of contusion, presumably due to primary damage, is not surprising. However, the origin of axonal injury in distant structures, such as the hippocampus and thalamus, is unlikely due to primary mechanical deformation but rather secondary neurochemical injury.

More recently, the widely recognized Marmarou model of impact acceleration in rats has been described as resulting in diffuse brain injury (Marmarou et al., 1994). In this model, a weight is dropped onto a plate fixed to the rat’s cranium. However, while previous weight-drop models described the head as being fixed or positioned on a hard surface (Shapira et al., 1988; Chen et al., 1996), in this adaptation the head was not fixed and was allowed to rotate downward. It has been suggested that this motion, in combination with the impact, results in overt widespread damage to axons (Marmarou et al., 1994). However, there has been concern that the term “acceleration” in this case may be confusing with regards to the biomechanics of injury as they relate to human TBI. With estimates of the acceleration occurring in this model (Li et al., 2011), it is difficult to envision how DAI can occur from acceleration alone in rodents due to brain anatomy and size. It is perhaps these factors that account for the inability to replicate the clinical syndrome of DAI, particularly prolonged alterations in consciousness, using rodent models. Nonetheless, due to their expediency, rodent models of TBI have been instrumental in identifying mechanisms of TAI, such as proteolytic cascades. Moreover, the Marmarou model is becoming the most widely used

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model of TAI and has proved useful in the evaluation of therapies targeting TAI such as FK506 and ciclosporin (Singleton et al., 2001; Okonkwo et al., 2003; Marmarou and Povlishock, 2006).

ANIMAL MODEL OF BLAST-INDUCED TRAUMATIC BRAIN INJURY

The incidence of blast-induced traumatic brain injury (TBI) has risen markedly in recent military engagements (Phillips and Richmond, 1991; Okie, 2005; Warden, 2006; Hoge et al., 2008). Blast exposures are often complex events, and may induce multiple types of TBI by direct impact including penetrating injuries and rapid acceleration-deceleration injuries from being thrown or struck by objects. Thermal or chemical insults can also play a role (DePalma et al., 2005; Moore et al., 2009). However, the role of “pure” or primary blast injury caused by the propagation of rapid pressure waves remains unclear. Specifically, the relative contribution of primary blast versus inertial forces in closed-head TBI is currently debated both clinically and even under experimental conditions (Saljo et al., 2010; Garman et al., 2011; Goldstein et al., 2012). Indeed, since most real-world cases of blast are complicated with other forms of TBI, there is currently no clinical neuropathologic data in humans who have experienced “pure” blast injury. This is a major limitation when attempting to generate appropriate models. Nonetheless, in attempts to simulate field conditions, animal models of blast TBI have directly utilized explosive material or experimental shock tubes to approximate blast conditions. Direct explosive models have used a range of high explosives, with exposure being “open-field” absent walls/obstructions (e.g., 360° radius), “closed-field” within a defined space, and/or within “complex environments” consisting of partial walls/obstructions and vehicle surrogates. Various species have been examined including: rodents (Kaur et al., 1995, 1997), nonhuman primates (Lu et al., 2012), and pigs (Bauman et al., 2009; de Lanerolle et al., 2011). To complement these efforts, in-laboratory blast testing has been performed using shock tubes, which are typically cylindrical tubes where rats (Cernak et al., 2001a, b; Saljo et al., 2001, 2002a, b, 2011; Long et al., 2009; Readnower et al., 2010; Cullen et al., 2011; Garman et al., 2011; Park et al., 2011), mice (Cernak et al., 2011; Koliatsos et al., 2011), and ferrets (Rafaels et al., 2012) have been exposed to blast-like pressure wave propagation driven by compressed gas (e.g., air, nitrogen, helium). Other studies have employed explosive charge-driven shock tubes (Saljo et al., 2000; Reneer et al., 2011). To date, researchers have not standardized shock tube paradigms (e.g., gas versus chemical explosives, tube design), species, location of the specimen, use of body shielding, and head mobility, all of which may greatly alter the nature of the injury. This may, in part, explain the variations in reporting of thresholds and pathologies between laboratories.

The described neuropathology of blast TBI to date includes neuronal degeneration, gliosis, demyelination, microvascular disruption, and/or transient blood–brain barrier compromise (Saljo et al., 2000; Cernak et al., 2001b; Saljo et al., 2002a; Kato et al., 2007; Leung et al., 2008; Dewitt and Prough, 2009; Long et al., 2009; Readnower et al., 2010; Lu et al., 2012). Neuronal stress, apoptosis, and atypical accumulations of phosphorylated heavy neurofilamant have also been reported (Saljo et al., 2000, 2002a). In addition, widespread reactive astrocytosis and inflammation, including microglial activation and neutrophil infiltration, have been observed within hours and persisting for weeks post blast (Kaur et al.,

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1995, 1997; Saljo et al., 2001; Readnower et al., 2010). Interestingly, despite early predictions that blast TBI would result in DAI, this has not yet been observed in animal models.

MODELS OFACUTE HEMATOMA

Acute intracranial hematoma is an extremely common consequence of TBI. In particular, acute subdural hematoma frequently occurs due to tearing of the bridging veins and acute epidural hematoma most commonly occurs secondary to rupture of the middle meningeal artery. Despite the relative frequency of these pathologies they are comparatively poorly studied, perhaps as a result of their primary management being neurosurgical evacuation. Nonetheless, several models have been reported that largely depend upon the introduction of autologous blood to the subdural or epidural space in rodents or larger animals (Ganz and Zwetnow, 1988; Miller et al., 1990; Tsuchida and Bullock, 1995; Sasaki and Dunn, 2001; Balikci et al., 2008; Wang et al., 2010). One group simulated the compressive effects of epidural hematoma in dogs using an inflatable balloon within the epidural space (Ebmeyer et al., 1998).

GENETIC MANIPULATION AND MODELS OF TRAUMATIC BRAIN INJURY

While the biomechanics and associated pathologic outcomes of TBI models limit their relevance to the heterogeneous human condition, a distinct advantage of mouse models, in particular, is the ability to manipulate their genetic background. These techniques have permitted important insights regarding individual responses to injury and the mechanisms that drive them. Important examples include mechanistic evaluations of the role of the apolipoprotein E allele 4 ($ApoE_4$) (Hartman et al., 2002; Crawford et al., 2009; Ferguson et al., 2010; Mannix et al., 2011; Bennett et al., 2013; Namjoshi et al., 2013; Rodriguez et al., 2013), a known predictor of poor outcome from TBI clinically (Teasdale et al., 2005). In addition, transgenic animals have provided important insights regarding the pathologic accumulation of proteins associated with chronic neurodegenerative disease, including amyloid beta and tau (Murai et al., 1998; Smith et al., 1998; Nakagawa et al., 1999, 2000; Hartman et al., 2002; Uryu et al., 2002; Yoshiyama et al., 2005; Abrahamson et al., 2006, 2009; Loane et al., 2009; Tran et al., 2011a, b, 2012).

CONCLUSION

To date the vast majority of animal models of TBI, and particularly those used for pharmacologic evaluations, have been impact models resulting in cerebral contusion in rodents. While these models have been instrumental in advancing understanding of many mechanisms of TBI, their limitations are numerous and may be critical with regard to preclinical drug testing. In particular, rodent models may not recapitulate basic biomechanical mechanisms of human injury. In addition, interlaboratory variability in the execution of TBI models has also been an area of concern. To address this, the National Institute of Neurological Disorders and Stroke (NINDS) is in the process of developing common data elements (CDE) to standardize data collection and analysis from preclinical models and thus facilitate appropriate comparison of results. Specifically, a detailed set of

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elements representing the animal characteristics, history, and assessments/outcomes are outlined. In addition, the numerous model-specific elements (e.g., impactor angle or craniectomy size in CCI) will be listed.

Nonetheless, various models have been important tools for the development of potentially translatable techniques for both the detection and clinical monitoring of TBI patients. Examples include preclinical testing of advanced neuroimaging techniques (Mac Donald et al., 2007; Bennett et al., 2012), biomarker discovery (Siman et al., 2004; Haskins et al., 2005), and neurocritical care monitoring, including microdialysis (Schwetye et al., 2010; Friess et al., 2011, 2012). As such, these models have replicated many specific features of human TBI and enhanced context with clinical relevancy will facilitate the further elucidation of the mechanisms and treatment of injury.

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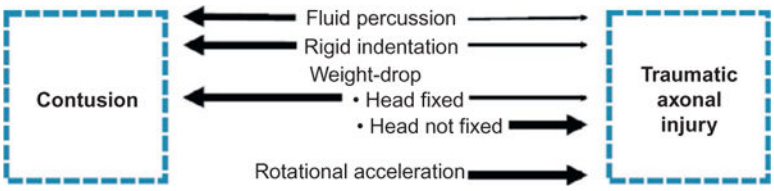

Fig. 8.1.

Diagram outlining the relative pathologies induced by various models of traumatic brain injury. Arrow thickness denotes the predominance of contusion injury versus traumatic axonal injury.

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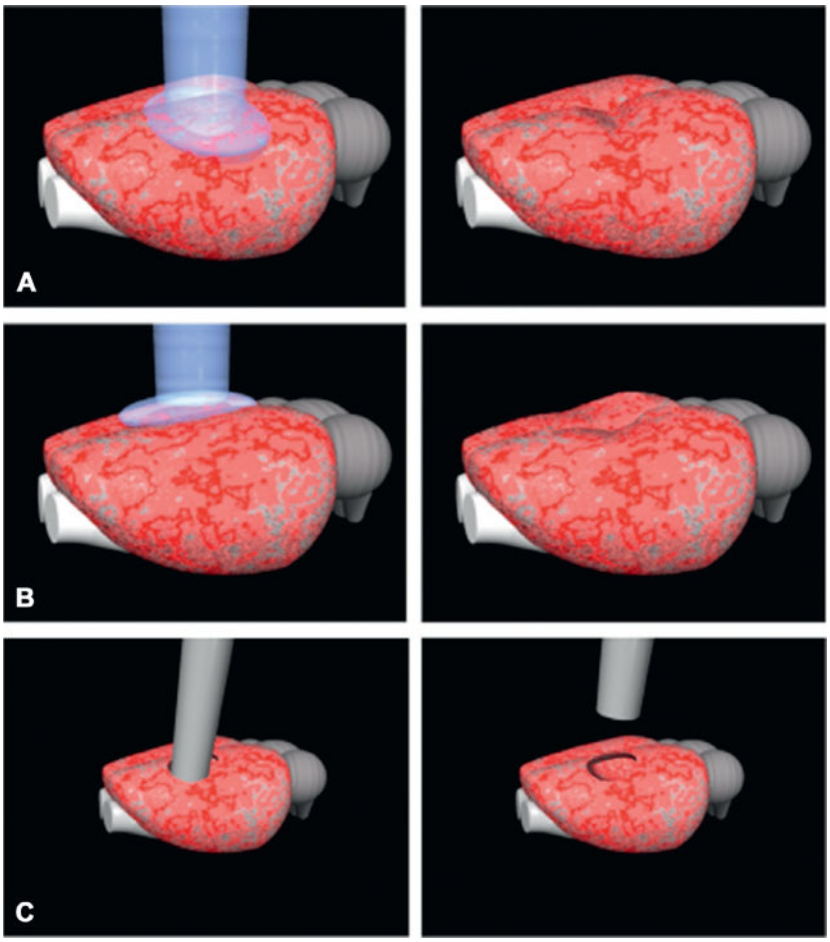

Fig. 8.2.

Schematic displaying the (**A**) lateral and (**B**) midline fluid percussion injury model of traumatic brain injury in rats, and (**C**) the rigid indention/controlled cortical impact model in mice. (3D rendering of image courtesy of John A. Wolf, Ph.D., University of Pennsylvania.)

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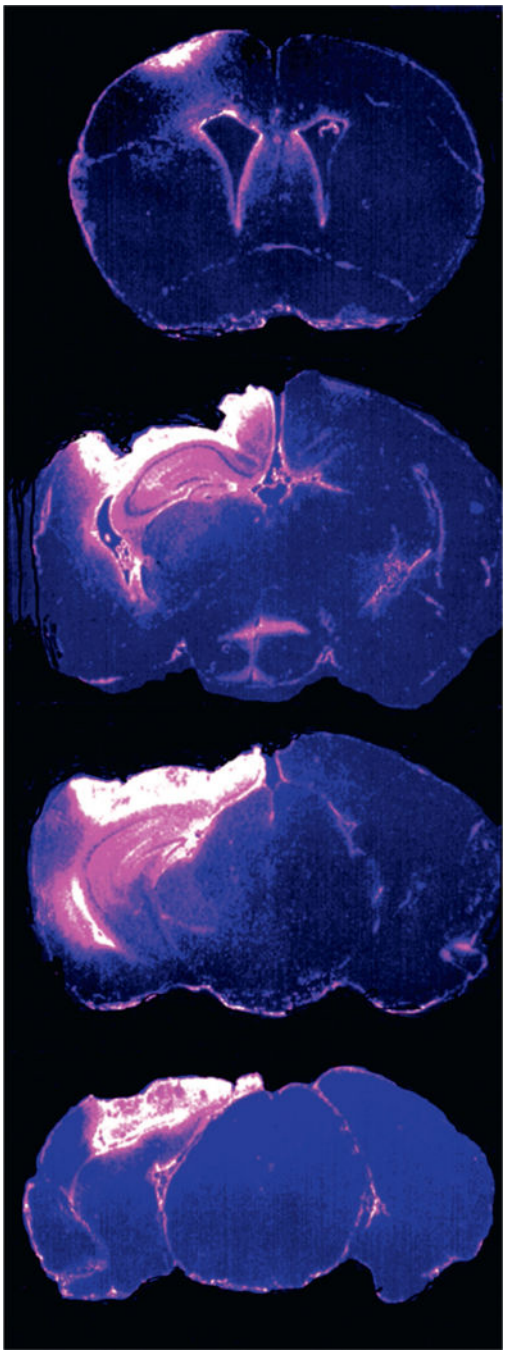

Fig. 8.3.

Representative sections of a mouse brain showing IgG extravasation 48 hours following the controlled cortical impact model of traumatic brain injury. This demonstrates marked blood–brain barrier disruption caused by this model.

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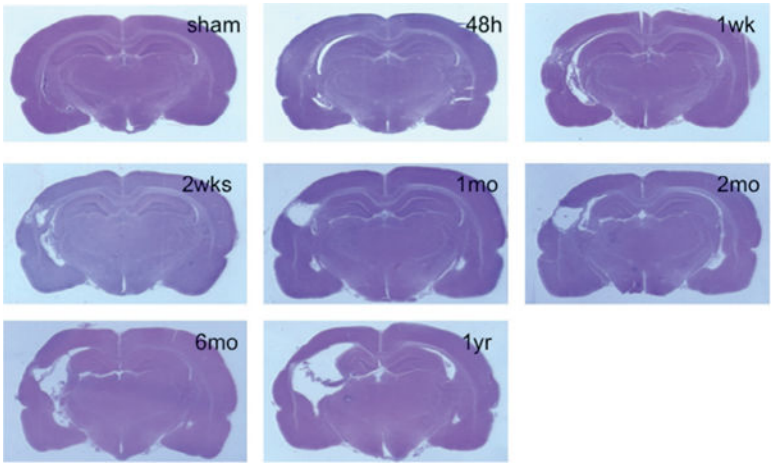

Fig. 8.4.

Representative micrographs showing progressive brain atrophy from 48 hours to 1 year following lateral fluid percussion injury in a rat.

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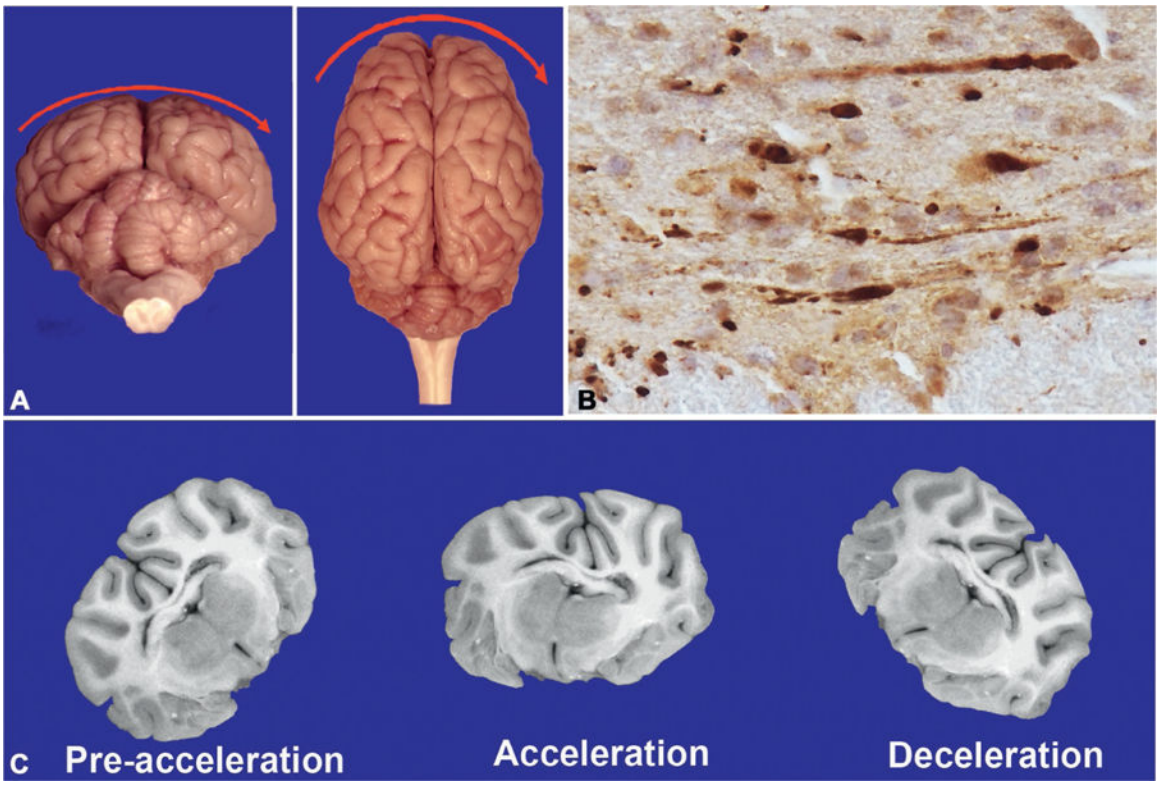

Fig. 8.5.

A model of rotational acceleration in swine. The HYGE device is capable of inducing head rotation in multiple planes (**A**) to induce clinically relevant axonal pathology. Specifically, APP immunoreactivity reveals tortuous varicose axons in addition to swollen disconnected axonal terminals (also referred to as axonal bulbs or retraction balls) indistinguishable from diffuse axonal injury in humans (**B**). The brain is rapidly deformed due to the forces caused by rapid acceleration/deceleration. The computer-generated graphic shows a visual representation of rapid rotation in the coronal plane (**C**).