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CHAPTER 326 – Animal Models of Traumatic Brain Injury

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Traumatic brain injury (TBI) is a complex condition that is well recognized to consist of a spectrum of insults involving a number of mechanisms of injury, degrees of severity, and types of pathology. This is readily apparent when comparing cranial computed tomographic scans of patients with severe TBI, in whom contusion, diffuse axonal injury (DAI), and subdural, subarachnoid, or parenchymal hemorrhages, as well as other pathologic findings, can be seen in various combinations.[1] A number of additional factors can affect the clinical outcome of patients with TBI, such as secondary insults, gender, age, genetic polymorphisms, drug use, and others.[2] It is thus logical that a menu of experimental models is needed both to study these pathologies and to successfully translate new therapies to clinical care. Several well-characterized experimental animal models of TBI have been developed and are the focus of this chapter (Fig. 326-1). We discuss these models, the relevant outcomes in experimental TBI, the covariates that have been incorporated into models to mimic the clinical condition, and confounding factors that affect the animal models, such as anesthetics and strain differences.

Experimental Models

Controlled Cortical Impact

Experimental TBI induced with a pneumatic impactor was first introduced for use in laboratory ferrets by Lighthall and colleagues [3,4] and subsequently adapted for rats by Dixon and associates[5] in an attempt to better control the biomechanical parameters of brain injury. Unlike the fluid percussion (FP) injury device, which disperses a stream of solution intracranially that cannot be readily quantified, the controlled cortical impact (CCI) model of experimental TBI takes advantage of biomechanical events contributing to injury (Fig. 326-2A and D). These events can be analyzed by establishing a quantifiable relationship between measurable engineering parameters, such as force, velocity, and tissue deformation, and the magnitude of tissue damage or functional impairment (or both). These controlled mechanical variables enable accurate, reliable, and independent control of the deformation parameters over a wide range of contact velocities.
The CCI injury device typically consists of a small-bore (1.975 cm), double-acting stroke-constrained pneumatic cylinder with a 5.0-cm stroke. The cylinder is rigidly mounted on a crossbar in either an angled (perpendicular to the dura surface) or vertical position. The lower rod end has an impact tip attached that varies in geometry (rounded or flat edge) and diameter (5 to 6 mm for rat CCI), and the upper rod end is attached to a velocity-measuring sensor system. The impactor tip is pneumatically driven at a predetermined velocity, depth, and duration of tissue deformation. In rats, a depth of penetration of this device of 2.6 to 2.8 mm with a velocity of 4.0 m/sec and a dwell time of 50 to 150 msec consistently produces an injury of moderate severity. However, the exact injury parameters depend on the particular laboratory. The velocity of the impacting shaft is controlled by varying the gas pressure. Other CCI devices have recently been developed that use electromagnetic actuators to drive the impactor tip in an effort to provide greater control of the impact parameters.[6-8]

Rat Controlled Cortical Impact Model

The rat CCI model also produces morphologic and cerebrovascular injury responses that resemble certain aspects of human TBI. Commonly observed are graded histologic and axonal derangements,[3-5,9,10] as well as disruption of the blood-brain barrier (BBB),[11,12] subdural and intraparenchymal hematoma, edema, inflammation, and alterations in cerebral blood flow (CBF).[12] Similarly, the CCI model also produces neurobehavioral and cognitive impairments similar to those observed in human patients. In contrast to other TBI models, the CCI device induces a significantly pronounced cortical contusion.

Rat CCI produces graded morphologic and functional responses that can be used to monitor injury severity and evaluate therapies. Lesion volumes produced by CCI are calculated by measuring tissue loss in serial coronal sections stained with hematoxylin and eosin. Hippocampal neuronal loss/survival is measured semiquantitatively by counting healthy-appearing neurons or by using unbiased stereologic methods.[13] Recent studies of CCI with the de Olmos amino-cupric-silver staining method have indicated that CCI can induce neurodegeneration in regions distant from the site of impact in rats.[14] A variety of tests are used to evaluate neurological and cognitive function after CCI. Gross vestibulomotor function is assessed in the rat with a beam-balancing task. Finer components of vestibulomotor function and coordination are assessed with a beam-walking task.[15-18] Cognitive function in rodents after CCI has primarily been assessed with the Morris water maze test.[19-24] Conditioned fear response can also be used to assess cognitive function after TBI.[25]

Mouse Controlled Cortical Impact Model

With the development of mutant strains of mice, including both gene knockout and transgenic lines, a version of the CCI model in mice has logically followed. Smith and colleagues characterized this model in the C57BL6 mouse—the background commonly used to produce relevant mutant strains.[26] The depth of deformation was scaled down to 1.0 to 1.2 mm based on the cortical thickness of the mouse versus rat, and for a given impact velocity, an insult of similar severity to that commonly seen in rats was produced. Outcome testing is similar to that used in rats except that neurologic status can also be measured in mice with a “grip test” adapted from Hall.[27] CCI is unquestionably the most common model used to produce experimental TBI in mice, and because mice are steadily becoming the most popular species, the mouse CCI model is taking on greater importance in the field.

Pig Controlled Cortical Impact Model

In general, large-animal models of TBI are justified for complex physiologic and biomechanical studies that require large brain
mass. By increasing the size of the impact tip and depth of impact, the CCI model has easily been scaled up to larger animals such as the pig. Using a direct focal impact method, Duhaime and associates demonstrated in piglets of different ages a vulnerability to mechanical trauma that increased progressively during maturation.[28] CCI produced in swine with a pneumatic impactor has been shown to result in clinically relevant pathophysiology such as edema, cell death, white matter damage, and cerebrovascular dysregulation.[29,30] Pig CCI models may be the most useful TBI model to mimic the neurological intensive care unit environment.

**Primate Controlled Cortical Impact Model**

Recently, the CCI technique has been applied to monkeys.[31] Impact applied to the right frontal cortex produced edema (as assessed by magnetic resonance imaging [MRI]) and histopathologic changes, including necrotic cell death, axonal spheroids, astrocytosis, and accumulation of macrophages. The monkey CCI model may prove valuable for preclinical safety studies to facilitate the translation of experimental neurotherapeutics to humans.

**Fluid Percussion**

First described by Lindgren and Rinder in a rabbit model of TBI,[32] the FP device has since been used in several other animal species, including cats,[33,34] rats,[35-37] pigs,[38-40] and mice.[41] The FP device (see Fig. 326-2B and E) consists of a Plexiglas cylinder filled with physiologic saline and enclosed at one end by a male Luer-Lock fitting that is subsequently paired with a female fitting. Injury is produced when a metal pendulum strikes the piston of the injury device from a predetermined height and causes rapid injection of saline into the closed cranium. The resulting pressure pulse induces a brief increase in intracranial pressure (ICP) with associated displacement and deformation of neural tissue. The severity of injury is regulated by varying the height of the pendulum, which corresponds to variations in extracranial pressure pulses expressed in atmospheres. Increased magnitudes of tissue deformation are associated with increased brain injury.

**Rat Midline Fluid Percussion**

Midline FP in rats is produced by placing the injury screw along the central sagittal suture midway between the bregma and lambda. Midline FP has been used to induce concussive injuries[38] and can produce cognitive deficits in the absence of overt hippocampal cell death.[42] Although the lateral FP model has been popular for studying neuronal cell death mechanisms, there is a recent resurgence of interest in midline FP because of the increased interest in diffuse brain injury associated with sports concussions and blast-induced TBI.

**Rat Lateral Fluid Percussion**

Lateral FP in rats is produced by placing the injury screw over the parietal cortex midway between the bregma and lambda. Lateral FP is advantageous for producing hippocampal cell death and cortical contusions.[43] Furthermore, lateral FP injury in the rat has been shown to produce vascular and BBB disruption,[44] reductions in CBF,[45] cerebral edema, tissue shearing,[46] and intraparenchymal hemorrhage, all of which contribute to the formation of a focal lesion in the injured cortex.[47-53]

**Pig Fluid Percussion**

The immature pig FP model is useful for studying CBF, pial artery diameter, and cerebral oxygenation.[54] Moreover, rapid increases in ICP have been observed in piglets after FP-induced TBI.[38] Midline FP can result in a reproducible secondary increase in ICP accompanied by patterns of diffuse brain damage in immature and juvenile piglets.[55] FP injury in pigs has also been used in combination with secondary insults (see later).

**Closed Head Injury Models**

Closed head injury models are thought to produce injury by transmitting mechanical forces through the skull to the brain. There are three main variations of closed head injury models. The first is a focal impact applied to the intact skull. Hall and coworkers produced concussive injury in mice by dropping a 50-g weight 18 cm onto the intact skull.[57] The Shohomi laboratory has characterized and applied a closed head impact model in both rats[58] and mice[59] that produces edema, functional deficits, and significant hippocampal neuronal cell death. For weight drop models, the height and mass of the falling weight are adjusted according to the desired severity of injury, with further distances and increased weight producing more injury than less distant and lighter weights.

The second type of closed head model is the Marmarou impact acceleration model (see Fig. 326-2C and F). In this model, a weight is attached to a string, and when the predetermined height above the cranium is obtained, the weight is released through a guide tube and subsequently strikes a cemented disk (“helmet”) on the skull to prevent skull fracture.[60] During impact the rat's head is rapidly accelerated downward into a foam pad, which facilitates relatively slower head deceleration. Impact acceleration produces a diffuse injury without noticeable contusions or hippocampal cell loss.[60] Brainstem injury or DAI (or both)[61] and elevations in ICP have also been observed after closed head impact acceleration injury.[62]

Finally, the group at the University of Pennsylvania developed and described a closed head rotation model originally characterized in monkeys[63] and successfully adapted to swine. DAI and transient posttraumatic unconsciousness have been shown to be produced in miniature swine by rapid acceleration and deceleration of the head in the coronal plane, without impact.[64] Recently, this model has been further applied to immature piglets and found to produce a range of clinically relevant functional deficits that correlate with neuropathologic axonal damage.[65]
Complex Models of Traumatic Brain Injury—Secondary Insults, Polytrauma, and Blast Injury

It is well recognized that TBI is often complicated by secondary insults such as hypoxemia, hemorrhagic shock, or polytrauma.[66] The injured brain is highly vulnerable to these insults because autoregulatory mechanisms are often compromised early after the injury and metabolic demands are generally high in the early postinjury period.[67] Thus, secondary insults can have devastating consequences. A number of modifications of established models have been developed to mimic the pathophysiology of these various insults.

Traumatic Brain Injury Plus Hypoxemia

Ishige and colleagues incorporated secondary hypoxemia into a lateral FP injury model in rats.[68] A period of hypoxemia (PaO₂ of 40 mm Hg for 30 minutes, beginning immediately after the insult) that alone had no consequences in rats dramatically exacerbated the pathology as determined by numerous outcome criteria, including electrophysiology, function, blood flow, edema, and histology. Subsequently, Clark and associates characterized an analogous model of combined CCI plus hypoxemia in rats—again using 30 minutes of hypoxemia at a level similar to previous studies.[69] Marked exacerbation of DNA damage and neuronal death was seen in the hippocampus underlying the contusion. This model has been used to study the effect of various neuroprotective therapies.[70,71] In the work of Clark and colleagues, monitoring of arterial blood pressure revealed that hypotension commonly develops after approximately 20 minutes of hypoxemia[69]; thus, it is likely that the models using hypoxemia are actually models of combined hypoxemia and hypotension.

Traumatic Brain Injury Plus Hemorrhage

Hemorrhagic hypotension and hemorrhagic shock after TBI are common insults in the setting of polytrauma and have taken on greater significance in combat casualty care with the recent surge in blast-induced TBI from the improvised explosive devices (IEDs) used in terrorist attacks.[72] TBI greatly enhances vulnerability of the organism to the hypotensive effects of hemorrhage, and blood loss that would otherwise be well tolerated can lead to shock.[73,74] In addition, hemorrhage produces anemia and may result in extracerebral organ injury, thus further increasing secondary brain damage, mortality, or both. Much of the work incorporating this combined insult has focused on evaluation of the effect of various resuscitation strategies on survival and intracranial dynamics in large-animal models of FP injury such cats[75] and pigs.[76] In these studies, volume-controlled hemorrhage was generally induced and followed after various durations of shock by resuscitation with fluids such as crystalloids, hypertonic saline, colloids, or pressors, and resuscitation of hemorrhagic shock with standard crystalloid solutions after TBI was found to markedly exacerbate brain swelling and ICP. This earlier work has been followed by numerous studies, such as studies involving CCI plus hemorrhagic shock in pigs to evaluate the effect of resuscitation with hemoglobin solutions[77] on cerebral hemodynamics, MRI outcomes, and brain tissue PO₂. Studies of TBI plus hemorrhagic shock are less common in rodent models. Matsushita and coworkers examined the effect of moderate hypotension (mean arterial blood pressure [MAP] of 60 mm Hg for 30 minutes) induced by hemorrhage in rats after lateral FP and reported reduced CBF and an increase in the contusion area,[78] whereas Schütz and coauthors reported that hemorrhagic hypotension (MAP of 50 to 60 mm Hg for 30 minutes) failed to worsen the histologic damage but increased the functional deficits.[79] More recently, Dennis and colleagues reported the first model of combined TBI and hemorrhagic shock in mice and demonstrated that 90 minutes but not 60 minutes of hemorrhagic shock to a MAP of 30 to 40 mm Hg immediately after CCI exacerbated hippocampal neuronal death assessed 7 days after the combined insult.[80] In that model, as in many large-animal models of TBI plus hemorrhage, a protocol that included insult, “prehospital,” and “hospital” phases was incorporated to maximize its clinical relevance (Fig. 326-3). Rodent models of combined TBI and hemorrhagic shock have only begun to be used to explore the effects of novel therapies.

FIGURE 326-3 Schematic of a typical experimental protocol addressing combined traumatic brain injury (TBI) and a secondary insult—in this example, hemorrhagic shock. Frequently, these protocols are designed to provide a clinically realistic scenario that includes an insult phase, a prehospital phase (mimicking
Traumatic Brain Injury Plus Polytrauma

Given the recent interest in blast injury and polytrauma, a number of new models of experimental TBI accompanied by extracerebral trauma have been developed, including models such as combined blunt trauma to the head, chest, and femur in pigs, among others.[81] Most of the studies in these polytrauma models have focused on the hemodynamic effects of resuscitation fluids rather than on neuroprotection. In this regard, a key fact is that extracerebral trauma leads to cytokine production, which can further exacerbate the brain injury. This hypothesis was recently directly supported by Utagawa and associates, who reported that systemic administration of interleukin-1β at doses that did not produce hypotension exacerbated the histologic damage and functional deficits in rats after lateral FP injury.[82]

Blast-Induced Traumatic Brain Injury

Because blast-induced injuries have been the leading cause of TBI in Operation Iraqi Freedom, this form of TBI has taken on tremendous importance in experimental TBI research.[83,84] Blast injuries result from blast overpressure waves and a variety of other forces as a consequence of the detonation of explosive materials—most commonly IEDs. The recent use of body armor in the U.S. military has protected the highly vulnerable lung and gut from blast forces and shifted the site of primary damage in exposed soldiers to the limbs and brain. Recent studies have begun to model blast-induced TBI in rats, mice, and pigs. There are a number of potentially unique facets of blast-induced TBI, including pronounced acute cerebral swelling, vasospasm, and hemorrhage—particularly with severe insults.[85] Penetrating injury from shrapnel and burns can also accompany a severe blast.[86] Similarly, a retrograde pulse of venous or cerebrospinal fluid pressure into the brain from a blast has also been suggested to mediate vascular injury.[87] Cernak and coauthors provided some of the earliest reports on the effect of blast in rodent models with the use of blast overpressure waves produced by a shock tube and highlighted an important role for oxidative stress.[88] More recently, seminal work by Long and associates reported that body armor could markedly reduce mortality from blast overpressure injury in rats, again in a shock tube, and that rats protected by body armor and exposed to blast overpressure injury exhibited marked axonal injury as an important neuropathologic feature.[89] Work in large-animal models of explosive blast and studies of therapies have only begun to be explored.
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