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Animal models of traumatic brain injury. A critical evaluation.

William T. O'Connor*, Aoife Smyth[1] and Michael D. Gilchrist[2, 3]

Graduate Entry Medical School, University of Limerick. Limerick Ireland. [1]Applied Neurotherapeutics Research Group, Conway Institute, University College Dublin, Dublin, Ireland [2]School of Electrical, Electronic & Mechanical Engineering, University College Dublin, Dublin, Ireland, [3]School of Human Kinetics, University of Ottawa, Ottawa, Canada.

*Corresponding author.

TEL: 353-61-233750 (Direct)

TEL: 353-186-3501107 (Cell)

FAX: 353-61- 233778 (Fax)

E-Mail: William.oconnor@ul.ie

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Abstract

Traumatic brain injury (TBI) is the main cause of death in children and young adults living in the industrialised world. Animal models of brain trauma have generated an abundant amount of data that has helped gain an insight into the events that occur during and after injury. The pathogenesis of TBI is incompletely understood, in large part because patients often present with a complexity of lesions of varying severity and regional distribution. Thus, no single animal model is entirely successful in reproducing the complete spectrum of pathological changes observed after TBI. Brain injuries are broadly divided into two groups; focal and diffuse. Focal injuries are characterised by contusions (*i.e.* damage at the site of the blow) and lacerations, often accompanied by hematoma. In contrast, diffuse injuries involve brain swelling, ischemic brain damage and diffuse axonal injury (DAI) observed in the direct vicinity and also remote from the site of impact. Animal models are necessary to fully elucidate these acute and chronic changes that occur after TBI and to establish new therapeutic strategies and extend the pharmacological approach towards more effective treatment for head-injured patients. In this regard, animal models have contributed substantially to our understanding of the mechanisms of TBI in humans. In this review six established animal models of head trauma are evaluated in this study, namely, fluid percussion, rigid indentation, inertial acceleration, impact acceleration, weight-drop and dynamic cortical deformation. The validity of animal models, including how animal models constitute theories about brain injury, is also addressed.

Key words: impact • focal injury • diffuse injury • direct brain deformation • inertial acceleration

Glossary

ASDH	Acute Subdural Hematoma
CCI	Controlled Cortical Impact
DAI	Diffuse Axonal Injury
TBI	Traumatic Brain Injury

1. Introduction

Traumatic brain injury (TBI) is the main cause of death in children and young adults living in the industrialized world. Current estimates suggest that in the U.S. between 2.5 million and 6.5 million individuals are living with the consequences of TBI, much of it caused by motor vehicle accidents. The pathogenesis of TBI is incompletely understood, in large part because patients often present with a complexity of lesions of varying severity and regional distribution. Brain injuries are broadly divided into two groups; focal and diffuse. Focal injuries are characterized by contusions (*i.e.* damage at the site of the blow) and lacerations, often accompanied by hematoma. In contrast, diffuse injuries involve brain swelling, ischemic brain damage and diffuse axonal injury (DAI) observed in the direct vicinity and also remote from the site of impact. Research conducted on animal models of brain trauma over the past decades have generated an abundant amount of data that has helped gain an insight into the events that occur during and after injury. In this review we focus on the main models that cause TBI by applying mechanical energy to the head, skull or dura of the animal.

No single animal model is entirely successful in reproducing the complete spectrum of pathological changes observed after TBI and further research is necessary to fully elucidate the acute and chronic changes that occur after TBI. These studies will be directed at clarifying and validating the present concepts, establishing new therapeutic

strategies and extending the pharmacological approach towards a more effective treatment for head-injured patients. The *in vivo* animal model however, remains necessary to prove new concepts and make clinical trials successful and safe.

1.1. Ethical and Theoretical Considerations

Ethically responsible use of experimental animals should be of the utmost importance in the development of animal models of TBI. The research scientist must explain how the results may benefit human clinical practice. As few animals as possible should be used and special attention should be paid to minimizing pain or discomfort. It is clear that animals that endure pain or distress may provide erroneous data, particularly where subtle changes in neurotransmitter release are studied.

1.2. What do Animal Models Tell Us?

Although it may be impossible to model the entire complex symptomatic spectrum of TBI in an animal, selected symptoms may be mimicked and have some validity. It is helpful if an animal model of TBI be discussed in terms of its face, construct, aetiological and construct validity. These terms are now discussed.

A. ***Face validity*** refers to the phenomenological similarity between the behavior exhibited by the animal and the specific conditions of the human condition. However it is unrealistic to expect similar behaviors in rodents and humans and the aim is to search for relevant equivalents based upon the brain regions assumed to be involved.

B. ***Construct validity*** refers to similarity in underlying mechanisms even though the precise expression of behaviors may be different between experimental animals and humans.

C. ***Aetiological validity*** is an extension of construct validity and refers to the degree of similarity of aetiology between the changes seen in the experimental animals and those observed in the human. TBI is complex and animal models can be used to test hypotheses about aetiology.

D. ***Predictive validity and reliability*** refer respectively to *(a)* the predictive value that observations made in animals will have for the human condition *(b)* to the accuracy with which both the experimental and clinical observations are made. Both predictive validity and reliability are important for assay models such as those used in the development of new therapeutics. Behavioral TBI models should at minimum have predictive validity and be reliable.

2. Traumatic Brain Injury (TBI)

Head injuries can be generally grouped into scalp, skull fracture, neck and brain injuries. In clinical practice there is often a combination or an overlap of these injury groups (Viano, 1988). However, for the purposes of this study only brain injuries will be considered. To distinguish from the general term of head injury, traumatic brain injury (TBI) is defined as any damage affecting brain function resulting from non-penetrating loading of the contact and non-contact type. Neuropathologic classification has categorised two main stages in the development of brain damage after injury to the head:

A. Primary damage is due to mechanical factors (*i.e.* impact) and occurs immediately at the moment of injury. It takes the form of surface contusions (*i.e.* bruising where the pia is intact), laceration (*i.e.* where the pia is torn), diffuse axonal injury (DAI) and intra-cranial haemorrhage. Primary injury is essentially an irreversible event that warrants preventative measures *i.e.* wearing of protective helmets, seatbelts *etc.*

B. Secondary injury is delayed and is produced by complicating processes that are initiated at the moment of impact but do not present clinically for a period of hours to days after impact. Secondary injury includes damage due to ischemia, swelling (oedema) and alterations in neuronal and glial function. This delayed pathophysiological cascade is now believed to result from a combination of pathological factors including monumental rises in neurotransmitter release, notably the excitatory amino acid neurotransmitter, glutamate, which is associated with excitotoxicity (Lucas and Newhouse, 1957; Olney, 1969). Apnoea (*i.e.* respiratory failure) and hypoxia are common features of secondary injury.

This review addresses the issue of both primary and secondary injury arising from a mild or severe TBI. Findings from computerised tomography, proton emission tomography and magnetic resonance imaging studies have led to an alternative classification of brain injury relating the extent of tissue disruption and the distance from the impact (McIntosh *et al.,* 1996; Teasdale *et al.,* 1992). These are termed focal or diffuse injury and are now discussed.

2.1. Focal Injury

Focal intracranial injury is described by localised tissue damage. In severe cases, if the injury is sufficiently large it can result in coma due to brain shift, herniation and brain stem compression (Krantz and Lowenhielm, 1986). The main types of focal injury are contusions, lacerations, intracranial haematomas and raised intracranial pressure. These are now discussed in more detail.

Several types of brain contusion can occur, depending on the location and degree of impact (Bostrom and Helander, 1986). Cortical contusion is described by haemorrhages in the cerebral cortex often coupled with focal subarachnoid haemorrhaging. Sub-cortical contusions result from temporal or occipital impacts and are explained by the trajectory of the coup ('ipsilateral to impact') and contrecoup ('contralateral to impact') due to rebounding of the skull within the cranial vault. Intracranial haematomas result from rupturing of the vascular tissues, which leads to haemorrhaging in the brain and in the surrounding meninges. As a result, blood becomes trapped between other tissues, disturbing normal neurological function. Extradural haematomas occur on or above the dura mater and are due to rupture of the meningeal arteries. Subdural haematomas are clinically the most lethal focal lesion and can be of arterial or venous origin. This type of haematoma results from primary damage to blood vessels on the cortical surface.

Acute subdural hematomas (ASDH's) arise from three sources and these are; (a**)** direct laceration of the cortical arteries and veins due to penetrating injuries that lacerate the brain *e.g.* a gunshot, (b) closed head injury which results in large contusions causing bleeding into adjacent subdural space *e.g.* a blow to the head and (c) tearing of the parasagittal veins that bridge the subdural space *e.g.* due to a rapid deceleration.

Although impact to the head is the most common cause of clinical ASDH, it is the acceleration induced by the impact, and not the head contact itself that causes this type of lesion. In fact, the purest form of ASDH without head impact often results from the violent shaking of infants.

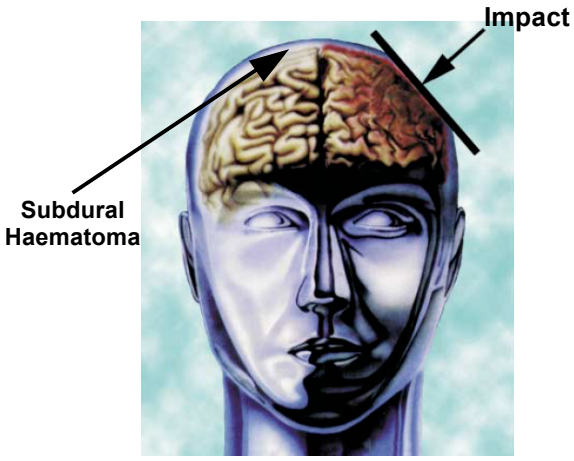


Figure 1: An idealised representation demonstrating a focal brain injury resulting from an impact. A subdural haematoma is formed as a result of vascular disruption. *Adapted from Smith and Meaney, (2000).*

2.2. Diffuse Injury

Diffuse injury results from the bulk mechanical effects associated with axonal, neural, microvascular and brain swelling injury. This type of injury is thought to result from tissue distortion and shearing caused by inertial forces that are present at the moment of injury. The most common of these are ischemic brain injury, diffuse axonal injury (DAI) and diffuse brain swelling. These changes are usually observed peripheral to the vicinity of the impact but are also observed remote to the impact site (Laurer *et al.,* 2000).

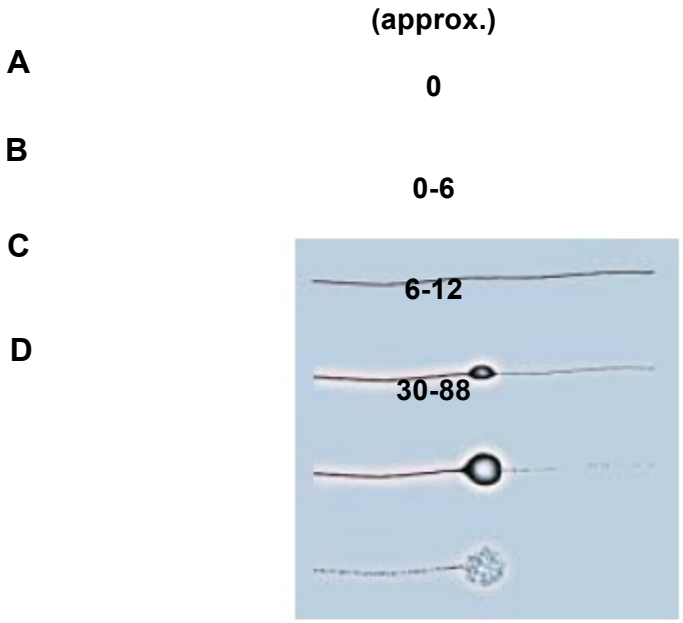


Figure 2: Illustration demonstrating the evolution of axonal bulbs and disconnection of axons following traumatic brain injury (TBI). Axon pathology has been shown to develop over the course of hours to days following injury and has even been observed for months. (**A**) Axon before TBI. (**B)** Within seconds of TBI, localised mechanical damage in the axon results in swelling in one discrete region of the axon and this can last for hours. (**C**) From days to weeks thereafter, further swelling and cytoskeletal disarray occurs and the axon disconnects immediately distal to the swollen region. (**D**) Ultimately, the entire axon undergoes degeneration. *Adapted from Smith and Meaney (2000).*

DAI is associated with widespread injury whereby shearing of the axonal tissue has occurred. Recent biomechanical studies by Smith and Meaney (2000) conclude that the susceptibility of the axons to mechanical injury appears to be due to both their viscoelastic properties and their highly organised structure in the white matter tracts. Although axons are supple under normal conditions, they behave in a brittle manner when exposed to rapid deformations associated with TBI. Accordingly, rapid stretch of axons can damage the axonal cytoskeleton resulting in a loss of elasticity and impairment of axoplasmic transport. Subsequent swelling of the axon occurs in discrete bulb formations or in elongated variscosities that accumulate in organelles. Ultimately swollen axons may become disconnected (Povlishock, 1993) and contribute to additional neuropathologic changes in brain tissue (Fig. 2). The severity of DAI is

directly related to prolonged unconsciousness, high mortality and poor outcome in survivors.

An important difference between focal and diffuse brain injury is the source and character of post-traumatic outcome (*e.g.* coma) resulting from these two general forms of injury. Focal brain injury may include mass effects from haemorrhagic contusion and/or haematoma which can induce herniation and brainstem compression. Accordingly, a resultant coma may not be immediate but may develop as a result of secondary injury. In the case of DAI, non-impact rotational acceleration can induce an immediate and prolonged post-traumatic unconsciousness in the absence of mass lesions.

3. Animal Models of Traumatic Brain Injury

Animal models of TBI play an important role in the process of evaluating and understanding the complex physiologic, behavioural and histopathologic changes associated with TBI. Since human TBI is very much a heterogeneous disease, no single animal model of TBI can mimic the whole spectrum of findings observed in human TBI. Rather, the concurrent use of several distinct yet complementary models (*e.g. in vivo* microdialysis in the rat combined with finite element modelling) is necessary to characterise the features observed upon clinical and post-mortem examination of TBI in patients and to develop novel diagnostic and therapeutic strategies for the treatment of TBI.

A number of clinical and animal studies over the past decade have now established that the principal mechanism of brain damage after head injury is due to either direct contact

(*i.e.* impact) or acceleration/deceleration types of injury (Gennarelli, 1994). Lesions due to direct impact result from an object striking the head. In contrast, acceleration/deceleration brain injury results from unrestricted head movement in the instant after injury. It is generally agreed that the focal pathologies associated with an impact are more likely to be sustained as a result of a fall, whereas the diffuse pathologies are most commonly associated with acceleration/deceleration in motor vehicle accidents.

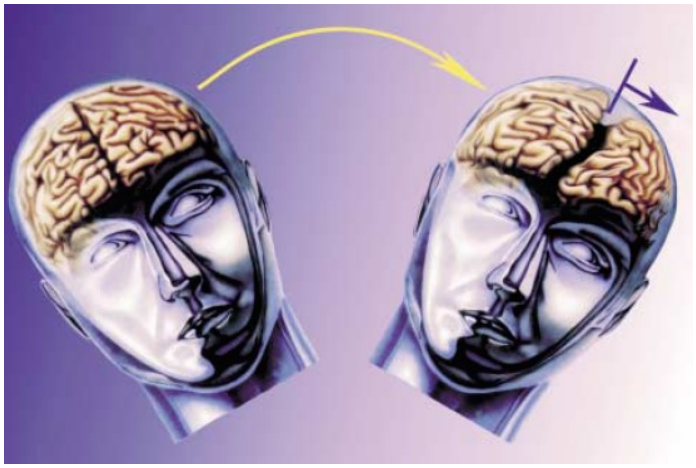
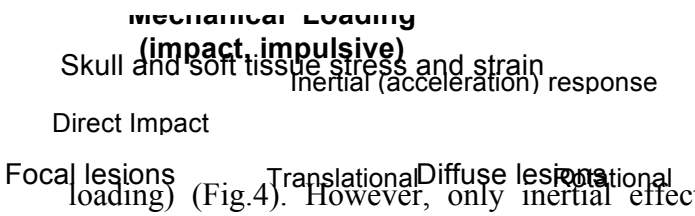


Figure 3: An idealised representation demonstrating diffuse brain injury resulting from an inertial force. Rapid rotational acceleration-deceleration of the head in the coronal plane (yellow arrow) results in deformation of the entire brain. The falx membrane along the sagittal midline acts as a barrier to lateral brain motion (blue arrow) creating high strain between the hemispheres. This overall mechanical deformation results in diffuse axonal injury (DAI) with prominent axonal pathology in midline structures. *Adapted from Smith and Meaney, (2000).*

Two mechanical phenomena constitute the most common causes of primary brain injury. These are (a) local skull distortion due to direct contact and propagation of stress waves through the brain from the point of impact (Fig.1 and Fig. 3) and (b) movement and distortion of brain material due to inertial or acceleration loading. Both of these phenomena occur when the head is struck by a rigid or padded object (*i.e.* impact



loading) (Fig.4). However, only inertial effects are present when the head moves indirectly as a result of impact to another region of the body (*i.e.* impulsive loading). In direct head impact there is a local bending of the skull, underlying tissue strain and gross movement of the brain tissue. Impulsive loading on the other had does not create local contact effects, but rather produced a non-uniform distribution of pressure and tissue strain. Both phenomena can result in significant primary tissue injury.

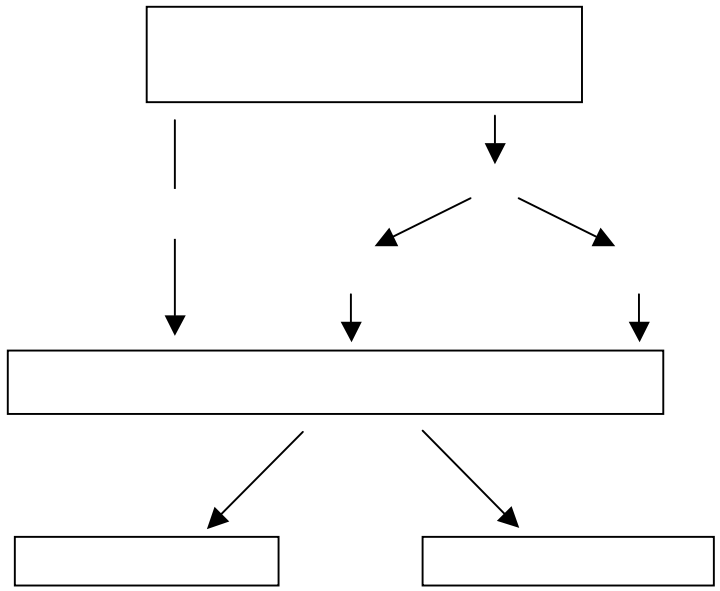


Figure 4: Mechanical loading characteristics such as the magnitude of impact force and rate of head acceleration strongly contribute to the type and severity of brain injury. Contact forces create focal lesions such as skull fracture, haematomas and cerebral contusions. Acceleration effects can cause diffuse lesions such as diffuse axonal injury (DAI) as well as numerous focal injuries.

For the purposes of clarity, experimental models of TBI, are defined under the following categories, direct brain deformation, impact acceleration and inertial acceleration and these are now discussed.

Experimental models that use gases, liquids and rigid-bodies as impacting media are divided between those which apply direct impact (invasively) to the brain (*i.e.* direct brain deformation) *via* a craniotomy and those that cause acceleration of the intracranial contents by impacting the exterior of the head itself (*i.e.* impact acceleration). Furthermore, inertial models that allow translational and/or rotational acceleration by indirect impact (*i.e.* inertial acceleration) have also been designed.

Experimental models can be graded on their behavioural, pathologic, physiologic and biochemical fidelity to that observed in human brain injury. To closely mimic the whole range of TBI observed in the clinical situation, an experimental model must also be capable of delivering variable degrees of brain trauma by adjusting the main mechanical parameters of the impact device (*e.g.* the height or mass of a free-falling weight, the depth of the traumatic impact or impact velocity, the height of the pressure impulse by adjusting the pendulum of the fluid percussion device or changes in the plane or velocity of the rotational forces). The following is a brief description of the more common TBI models currently in use.

3.1. Direct Brain Deformation

3.1.1. Controlled Cortical Impact (CCI)

The controlled cortical impact (CCI) model of TBI is an invasive impact method that was first developed for use in the ferret by Lighthall (1988) and later developed at the research laboratories of General Motors. The CCI model was adapted from similar methods employed in experimental spinal cord injury studies (Anderson, 1982). The model employs a rigid impactor to generate the mechanical energy to the intact dura with the head of the animal usually kept restrained during the delivery of the impact

Pneumatic cylinder

Piston

(Fig.5). Pressurised air acts as the source of the mechanical energy for loading to the

Piston tip

brain.

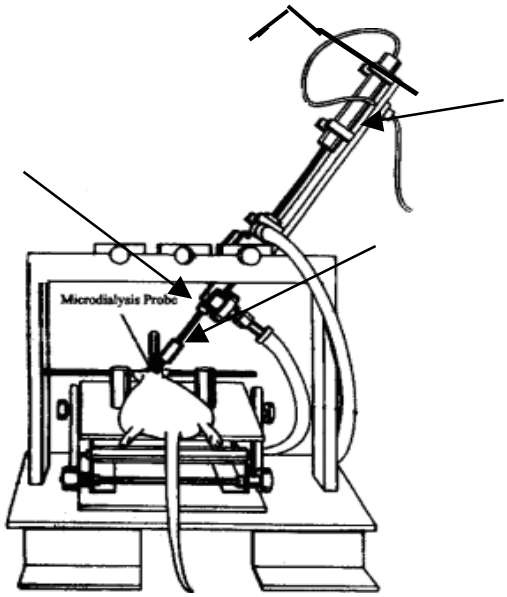
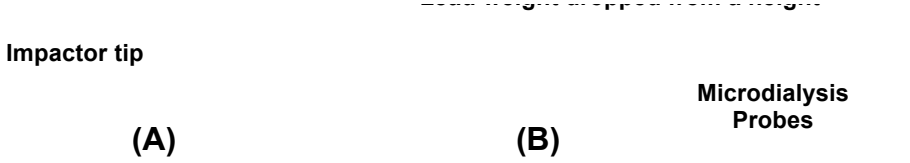


Figure 5: Schematic diagram showing the experimental setup of the controlled cortical impact (CCI) model of traumatic brain injury (TBI) with an isoflurane-anaesthetized rat *in situ*. The assembly consists of a stroke-constrained pneumatic cylinder, a piston and a piston tip, mounted on a precisely adjustable horizontal crossbar. When activated, the pressurised air drives the impactor downward at a final velocity producing focal and diffuse injuries to the intact dura. *Adapted from Cherian et al ., (1994).*

A number of key advantages with this model include the ability to control deformation parameters such as time, velocity and depth of impact (Dixon *et al.,* 1991; Baldwin *et al.,* 1996; Cherian *et al.,* 1994; Gilchrist, 2004; Colgan *et al*., 2010). Absence of risk for a rebound injury make this model superior to devices that are guided by gravity of a free-falling guided weight (Laurer *et al.,* 2000). In addition, this model can mimic the whole spectrum of focal-type damage and DAI and can be used in combination with brain microdialysis.



3.1.2. Weight Drop

Simple weight-drop methods of TBI have been used (Feeney *et al.,* 1981) to produce direct focal cortical compression *via* the exposed dura. As the name implies, the weight-drop model employs a weight that is dropped through a guiding apparatus to impact either the closed cranium, a metal plate fixed to the cranium, or most commonly, through a craniotomy directly onto the brain. This model can be successfully used in combination with microdialysis (Koizumi *et al.,* 1997) (Fig 6). However limitations of this model include variation of impact velocity by the falling impactor and the possibility of a rebound impact which together may result in the biomechanical data failing to accurately describe the resulting brain deformations.

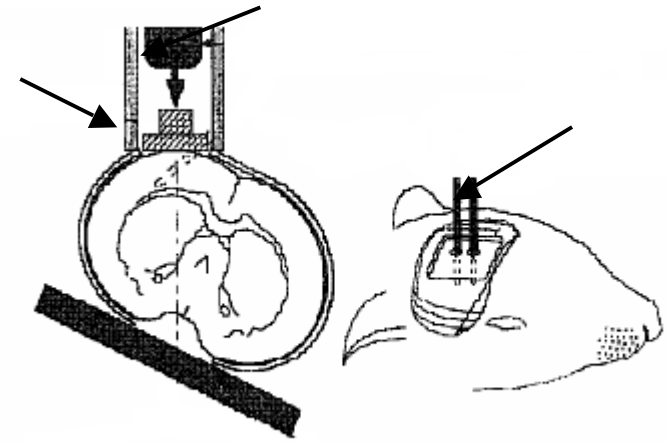


Figure 6: Schematic diagram illustrating the experimental setup of the weight-drop model of traumatic brain injury (TBI). (A) A free-falling guided weight is dropped from a pre-determined distance to deliver a TBI to the intact dura. This model can be combined with microdialysis as shown in (B). *Adapted from Koizumi et al., (1997*).

3.1.3. Vacuum Deformation

The dynamic cortical deformation model of TBI was a method developed by Shreiber *et al.,* (1999) and is based on earlier work by Murai *et al.,* (1991). This model involves rapidly deforming the exposed cerebral cortex by a transient, non-ablative vacuum pulse which causes local tensile loading of the meninges. The design of this suction apparatus consists of a syringe filled with normal saline which is primed to deliver a constant negative pressure to the exposed brain. However, two major inadequacies encountered with this method include permanent displacement of the cortex and a lack of measurement accuracy.

3.1.4. Fluid Percussion Injury

The fluid percussion injury model of TBI is currently the most commonly used and well characterised preclinical model of TBI. First reported by Lindgren and Rinder in 1965 for use in the rabbit, this model involves exposing the skull and performing a trephination by the impact of a rapid fluid bolus which strikes the intact dural surface and then moves in the epidural space concentrically from the injection area leading to diffuse loading to the brain. The trephination site can be placed centrally in the midline (Dixon *et al.,* 1987; McIntosh *et al.,* 1987) or laterally (McIntosh *et al.,* 1989). The height of the pendulum determines the force of the fluid pressure pulse that is transmitted through a saline filled reservoir and variations of this height allow reproducible modifications of injury severity (Fig. 7).

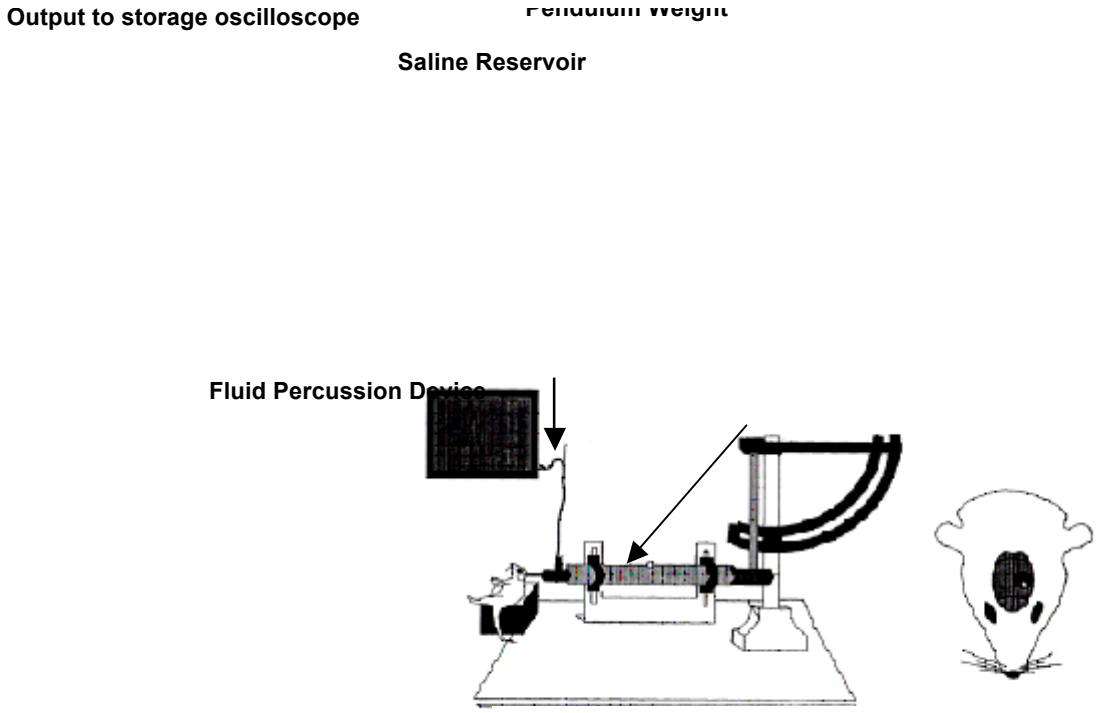


Figure 7: The fluid percussion model of traumatic brain injury (TBI). *Adapted from Lippert-Grunner et al., (2006).*

The main advantages of the fluid percussion model are similar to that described for the CCI model in that it induces graded levels of brain injury and produces axonal injuries and contusions, as well as impaired neurologic motor function and cognitive deficits (Dixon *et al.,* 1987; McIntosh et al., 1987; Yaghmai and Povlishock, 1992). It has also been modified and widely applied (Sullivan *et al.,* 1976; Povlishock *et al.,* 1983; Dixon *et al.,* 1987; McIntosh *et al.,* 1989; Yamaki *et al.,* (1994) to other animal species including the rat, dog, rabbit, cat and swine and has been used in combination with microdialysis in the rat (Faden *et al.,* 1989; Busto *et al.,* 1987; Kawamata *et al.,* 1995; Katayama *et al.,* 1990).

However, several disadvantages are associated with this model. Pressure characteristics from injection of the fluid pulse are not directly related to a mechanical impact to the brain, so a comparison of the tissue injury produced by the fluid percussion model to that observed in the clinical setting is difficult. In addition, the mechanism of tissue

injury associated with fluid percussion is not similar to those observed in clinical TBI. Also, fluid flow characteristics (*i.e.* direction, displacement and velocity) are dependent on brain geometry and the species employed, so accurate analytical and biomechanical analyses of the resultant injury are difficult to achieve suggesting that this method is not well suited for detailed biomechanical analysis.

3.2. Inertial Acceleration

A high percentage of patients suffer from vehicle accident-related TBI that is not associated with a direct impact to the head but with rotational forces leading to diffuse brain injury. Thus, both unrestrained (Ommaya and Hirsch, 1971; Ommaya *et al.,* 1973) and restrained head acceleration models have been developed with primates as the animal of choice due to their gyrencephalic brain structure and relatively large brain mass compared to body weight. A head acceleration device termed HAD-II (Ommaya and Gennarelli, 1974) was designed by biomechanical engineers at Pennsylvania State University, which allowed translational and rotational acceleration in the squirrel monkey. Subsequently, Gennarelli *et al.,* (1981) developed the Penn I system for use with the rhesus monkey and most recently, the model has been used to induce inertial acceleration in the miniature pig (Ross *et al.,* 1994; Smith *et al.,* 1997). In this model, an anaesthetised pig is positioned prone on the injury device, the head tightly fixed, and inertial loading is produced through a biphasic centroidal rotation of 110° in a 20ms time period. At present, this is the only accepted preclinical model that is known to produce widely distributed traumatic axonal pathology in the deep white matter at the root of the gyri and at the junction of white and gray matter.

However, there are many limitations with this model including the fact that it depends on the size and geometry of the skull and brain for its success (Lighthall, 1988; Lighthall *et al.,* 1989). In addition, only one research centre had performed a small number of histological and radiological investigations to elucidate the post-traumatic sequellae after inertial loading to the brain. Furthermore, high costs and technical demands may also be limiting factors.

3.3. Other Models

Many other less conventional models of TBI have been employed experimentally in animals. These include lead-tipped darts (Parkinson *et al.,* 1978), bolts (Beckman and Bean, 1969), pendulum devices (Bakay *et al.,* 1989) and padded darts fired from pistols (West *et al.,* 1982).

4. Microdialysis Methodology in Animal Models

Many of the microdialysis studies mentioned in this review address the role of the excitatory and inhibitory amino acid neurotransmitters in TBI. In this respect glutamate and GABA receive the most attention. In this case, release is much more difficult to measure and interpret since these amino acids also play important roles in general cell metabolism, in addition to serving as a neurotransmitter. Connectivity between brain regions employing dual probe dialysis is being addressed and is helping our understanding of nerve pathways and circuits (Frantz et al., 2002; O'Connor 1998, 2001). Microdialysis allows access to the area of the brain most vulnerable to TBI in the human namely the frontal lobe (Boon and de Montfort, 2002) and a subregion of this namely the prefrontal cortex is located at the anterior part of the frontal lobes, rostral to the motor and premotor regions where it plays a key role in executive

function, locomotion, learning and cognition (Tzschentke, 2001). Methodology is an important factor in explaining discrepancies between studies and apparently conflicting results in the TBI models may reflect the different models employed.

4.1. The Microdialysis Technique

Microdialysis is a technique used to monitor the chemistry of the extracellular space in living tissue. The microdialysis probe (Fig.8) is designed to mimic a blood capillary and by keeping this metaphor in mind, it is easy to conceive of the many ways in which this technique may be used. When a physiological salt solution (*i.e.* the perfusion medium or perfusate) is slowly pumped through the microdialysis probe, the perfusate equilibrates across the dialysis membrane with the surrounding fluid in the extracellular tissue. Thus, after a period of time, the perfusate will contain a representative proportion of those molecules found in the extracellular fluid. Instead of inserting an analytical device directly into the tissue (*e.g.* a biosensor), the dialysate sample is extracted and later analysed and the levels of low molecular weight molecules can be accurately determined.

4.2. The Microdialysis Probe

The microdialysis probe used in this study is constructed as a concentric tube where the perfusion fluid enters through an inner tube, flows to its distal end and exits the tube and enters the space between the inner tube and the outer dialysis membrane. The direction of flow is now reversed and the fluid moves toward the proximal end of the

probe. This is where dialysis takes place *i.e.* the diffusion of molecules between the extracellular fluid and the perfusion fluid. It is important to note that there is an exchange of molecules in both directions across the dialysis membrane. The difference in concentration across the dialysis membrane governs the direction of the gradient. In this way, an endogenous compound, such as a neurotransmitter, can be collected at the same time as an exogenous compound, such as a receptor ligand, is perfused into the tissue. Furthermore, experimental studies indicate that microdialysis causes minimal damage to the blood-brain barrier and it has been used following TBI in humans (Bullock *et al.,* 1998; Tolias *et al.,* 2002; Zauner *et al.,* 1996) and in a variety of animal models such as CCI (Palmer *et al.,* 1993 (a, b); Rose *et al.,* 2002; Stover *et al.,* 2004), fluid percussion (Faden *et al.,* 1989) and weight-drop (Koizumi *et al.,* 1997; Nilsson *et al.,* 1990). Thus, microdialysis is an excellent technique to study physiological, TBI-induced and pharmacologically-manipulated neurotransmission in the intact brain.

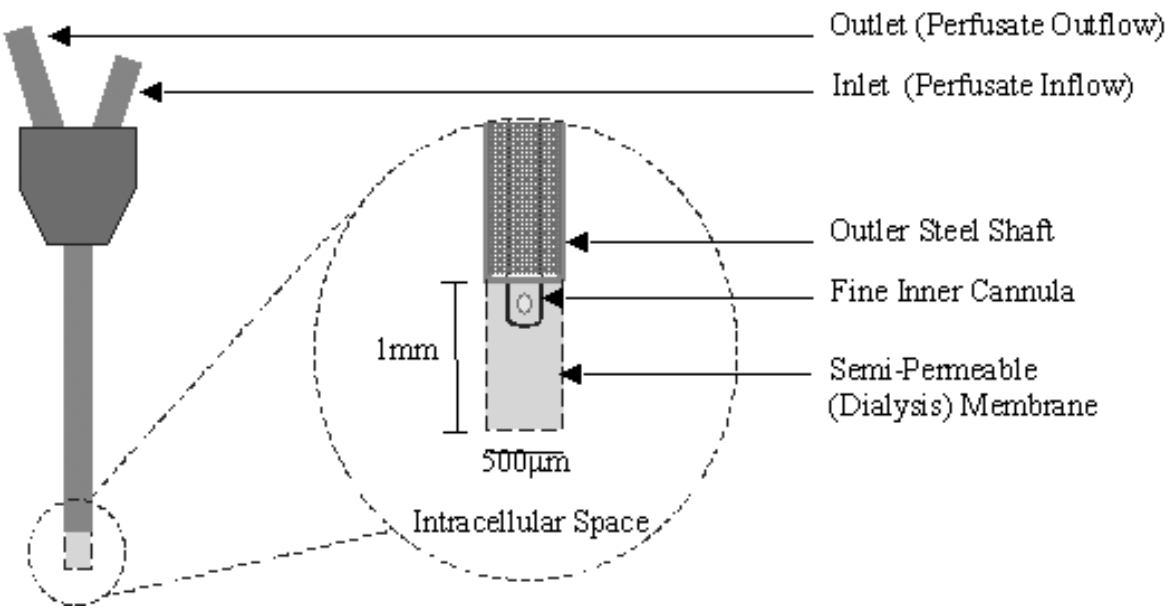


Figure 8: Schematic representation of a microdialysis probe showing the inlet cannula where perfusate enters the probe, the outlet where dialysate exits the probe and the semi-permeable dialysis membrane (1mm length and 500µm outer diameter). Solutes

cross the dialysis membrane from and to the intracellular space. *Adapted from O'Shea et al., (2008).*

4.3. Glutamate and GABA

On the basis of their functional actions in the central nervous system amino acid neurotransmitters have been divided into two general categories namely excitatory amino acid transmitters (*e.g.* glutamate and aspartate) which act to depolarise neuronal membranes and inhibitory amino acid transmitters (*e.g.* GABA and glycine) which act to hyperpolarise neuronal membranes.

A number of studies in rats have shown that experimental TBI is associated with an immediate and profound increase in extracellular EAA concentrations which are related to the severity of impact (Faden *et al.,* 1989; Katayama *et al.,* 1990; Nilsson *et al.,* 1990; Palmer *et al.,* 1993). However, major discrepancies have been noted in these studies with respect to the degree and duration of neurotransmitter release. In human studies, Baker *et al.,* (1993) reported that CSF glutamate is elevated from 4.9-17μM to 14-474μM following TBI for up to 3 days post-impact, while Palmer *et al.,* (1994) reported prolonged (up to 4 days) 2-8-fold increases in CSF glutamate and aspartate concentrations after TBI. These findings support the concept that TBI is associated with an increase in extracellular EAAs that actively destroy neurons and thus may contribute to secondary injury.

Nilsson *et al.,* (1990) reported that following weight-drop injury in the rat, dialysate GABA levels are increased from an undetectable level to 0.6-1.2μM at the site of impact in the cortex in the first 10min following impact and this normalised within 20-30min after TBI. Palmer *et al.,* (1994) found that in head-injured humans, the

concentration of CSF GABA was 56- to 317-fold higher than in non-impacted controls. It has been proposed that this elevated extracellular GABA may be neuroprotective and ameliorate excitotoxicity (Nilsson *et al.,* 1990).

RELATIVE UTILITY OF MODELS FOR DUPLICATING HUMAN TRAUMATIC BRAIN INJURY CONDITIONS

Model	Concussion	Contusion	Axonal Injury	ASDH	Skull Fracture	Suitability for Microdialysis
Weight Drop	+++	+	+	-	+++	Yes (Koizumi *et al.,* 1997)
Fluid Percussion	+++	+	+	-	-	Yes (Katayama *et al.,* 1989)
Controlled Cortical Impact (CCI)	+++	++	++	-	-	Yes (Dixon *et al.,* 1995)
Dynamic Cortical Deformation	-	-	-	-	-	-

5. Concluding Remarks and Outlook

A major requirement in choosing a model of TBI is to develop a system that will provide a high-level of useful and accurate impact data. In this regard, it is also imperative that an impact be applied in a repeatable, precise and quantifiable manner.

Inertial	+++	6	+++	++	-	-
Impact Acceleration	+++	+	++	-	±	-

Table 1: Relative utility of models for duplicating human traumatic brain injury conditions. ASDH=acute subdural hematoma; ICH=intracerebral hematoma. – does not duplicate the condition; ± inconsistent; + duplicates to some degree; ++ greater fidelity; +++ greatest fidelity. *Adapted from Gennarelli, (1994).*

Unprotected direct impact (*i.e.* when impact is delivered directly to the skull) in the rat results in either no change, or dramatic changes, due to the extremely steep injury tolerance curve of the rat skull. The occurrence of skull fracture from impact is not well correlated with injury in the rat model (Lighthall *et al.,* 1989) and direct cranial impact methods have a high degree of variability in the response such that even a slight change in the impact parameters may change the injury outcome from minor to fatal (Nilsson *et al.,* 1978). The relative utility of models for duplicating human TBI conditions is shown in Table 1.

The translational value of animal models of TBI depends in large part on the degree to which they reproduce patterns similar to those experienced in the human. The use of animal models also allows for a better understanding of the neurobiological mechanisms underlying therapy including the prediction of novel and better treatments for brain injury. At present, there is a major unmet need for drugs to treat the cognitive deficits in brain injury. In this regard, the study of neurotransmitter interactions within and between brain regions can facilitate the development of novel compounds targeted to treat those cognitive deficits not limited to a single pharmacological class. It is hoped that we are edging closer to a stage where we can predict drug efficacy in brain injured patients (against all classes of symptoms) from the efficacy seen in animal models. This in turn should greatly facilitate the discovery of improved drug treatments for TBI.

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