



REVIEW

Open Access

Experimental traumatic brain injury

Christiane Albert-Weissenberger^{1*}, Anna-Leena Sirén²

Abstract

Traumatic brain injury, a leading cause of death and disability, is a result of an outside force causing mechanical disruption of brain tissue and delayed pathogenic events which collectively exacerbate the injury. These pathogenic injury processes are poorly understood and accordingly no effective neuroprotective treatment is available so far. Experimental models are essential for further clarification of the highly complex pathology of traumatic brain injury towards the development of novel treatments. Among the rodent models of traumatic brain injury the most commonly used are the weight-drop, the fluid percussion, and the cortical contusion injury models. As the entire spectrum of events that might occur in traumatic brain injury cannot be covered by one single rodent model, the design and choice of a specific model represents a major challenge for neuroscientists. This review summarizes and evaluates the strengths and weaknesses of the currently available rodent models for traumatic brain injury.

Traumatic brain injury (TBI) is a result of an outside force causing immediate mechanical disruption of brain tissue and delayed pathogenic events which collectively mediate widespread neurodegeneration (reviewed by [1]). It is a heterogeneous disorder that can vary in the type of brain injury, distribution of brain damage and mechanisms of damage (Table 1). The primary damage of brain tissue can be diffuse or focal whereby the circumstances of injury determine the relative degree to which diffuse and focal trauma develops. Primary injury caused by direct impact to the head is considered to be largely focal, and results in cortical contusion, vascular injury and hemorrhages accompanied by ischemia. In contrast, diffuse brain injury characterized by diffuse axonal injury is caused by acceleration/deceleration forces. Depending upon the nature of primary injury, various cell responses are triggered that can exacerbate the injury. To date, these secondary injury processes are poorly understood.

TBI remains a leading cause of death and disability in the industrialized countries [2,3] and represents a growing health problem also in the developing countries [4-7]; therefore even a modest outcome improvement could have major public health implications. As the immediate cell death resulting from the initial impact on the brain tissue is irreversible, treatments focus on interruption or inhibition of the secondary injury cascades expanding this primary injury. Nonetheless, no

effective neuroprotective treatment is available so far [8-11]. The use of animal models is essential for better understanding of the secondary injury processes and for the development on novel therapies. Although large animal models may be necessary to investigate specific aspects of TBI, rodents (mice and rats) have emerged as the most commonly used species (for a review see [12]), since they are easily available to many researchers, normative data for a wide range of physiological and behavioral variables in rodents are well documented and transgenic technologies allow the generation of rodent lines with specific genetic alterations. A number of mouse and rat models have been developed to induce brain trauma. Of these the most commonly used are weight-drop injury, fluid percussion injury (FPI), and cortical contusion injury (CCI). However, the entire spectrum of events that might occur in TBI cannot be covered by one single rodent model. Therefore, this review evaluates the strengths and weaknesses of the currently available rodent models for TBI (Table 2).

Weight-drop models

The weight-drop models use the gravitational forces of a free falling weight to produce a largely focal [13-15] or diffuse [16-19] brain injury. The impact of the free falling weight is delivered to the exposed skull in rat [14] and mouse [20] or the intact dura in rat [21,22]. When the impact is delivered to the exposed skull, generally soft tips, e.g. silicon-covered [15] reduce the risk of skull fractures. For inducing focal brain injury, the animals

* Correspondence: Albert_C2@klinik.uni-wuerzburg.de

¹University of Würzburg, Department of Neurology, Würzburg, Germany
Full list of author information is available at the end of the article

Table 1 Leading clinical causes and types of TBI in the United States 2002 - 2006 [2]

Cause	Percentage of		Physical mechanism	Primary brain injury
	TBI	TBI-related deaths		
Falls	35.2%	18.9%	impact resulting in the acceleration of the head and brain [125,126]	closed head injury
Road traffic accidents	17.3%	31.8%	impact and acceleration of the head and brain [125,127]	closed head injury
Struck by/against events	16.5%	0.7%	impact resulting in the acceleration of the head and brain [125,126]	closed head injury

are placed on non-flexible platforms in order to minimize dissipation of energy [13-15]. In contrast, crucial for inducing a diffuse brain injury is an impact widely distributed over the skull and the use of flexible platforms allowing the head to accelerate, e.g. foam-type platforms [16,17,19] or platforms with elastic springs [18]. The severity of head trauma can be varied by using different weights and/or heights of the weight-drop. The high mortality rate due to apnea can be reduced by early respiratory support and the usage of animals with a certain age and weight [16,17].

Feeney's weight-drop model

Typically this rat model in which an impact is delivered to the intact dura [21,22] results in a cortical contusion

with hemorrhage [23] and damage of the blood-brain barrier [24,25]. Inflammatory processes lead to activation of microglia and astrocytes, activation of the complement system and invasion of neutrophils and macrophages [22,23,25-31]. Delayed microcirculatory disturbances and cortical spreading depression [32] have also been reported in this model. The pattern of post-traumatic cell death depends on the severity of impact [33]. Although the primary injury is largely focal, diffusely distributed axonal injury has been observed in the neuropil of the cortical lesion [23].

Shohami's weight-drop model

Shapira et al. and Chen et al., later introduced a model for closed-head injury using a weight-drop impact to

Table 2 Experimental rodent models of closed-head injury

Model	Species	Injury	Strengths	Weaknesses
Weight-drop models				
Feeney's weight-drop	rat [22]	predominantly focal	injury mechanism and inflicted injury is close to human TBI	high mortality rate due to apnea and skull fractures
Shohami's weight-drop	rat [14], mouse [15]	predominantly focal	severity of injury can be adjusted	not highly reproducible
Marmarou's weight-drop	rat [16,17], mouse [43]	predominantly diffuse	well characterized neuroscoring immediately after injury allows randomization	
FP models				
MFP	rat [46,47]	mixed	severity of injury can be adjusted	requires craniotomy that may compensate for ICP increases
LFP	rat [48], mouse [49]	mixed	inflicted injury is highly reproducible within one laboratory	no immediate post-injury neuroscoring possible inflicted injury is variable between laboratories high mortality rate due to apnea
CCI	rat [72], mouse [73]	predominantly focal	severity of injury can be adjusted inflicted injury is highly reproducible	requires craniotomy no immediate post-injury neuroscoring
Cryogenic brain lesion	rat [92], mouse [93]	focal	severity of injury can be adjusted inflicted injury is highly reproducible and easily quantifiable	mimics only conditionally human TBI

one side of the unprotected skull in rat [14] and mouse [15,20], respectively. The injury severity in this model is dependent on the mass and falling height of the weight used. Thus, heavier weights and/or increased falling height produces an ipsilateral cortical brain contusion and blood-brain barrier disruption followed by brain edema, activation of the complement system, cell death evolving over time from the contusion site and invasion of inflammatory cells [13,15,23,34-37]. A modified model using lighter weights and/or shorter fall heights resulted in a concussive-like brain injury, bilateral cell loss, short duration of brain edema and long-lasting cognitive deficits [23]. Moreover, bilateral diffuse brain damage, cell death (bilateral and beneath the impact site), and inflammatory responses were reported [38-41]. In general mild weight-drop injuries are associated with a diffuse injury pattern whereas more severe weight-drop injuries produce a focal contusion. A disadvantage of the weight-drop model is the high variability of the injury severity. A major advantage of this model is that it can be quickly performed under gas-anesthesia and thus allows neurological scoring immediately after injury [15,20]. Thus clinically relevant randomization of animals into the various treatment groups is possible.

Marmarou's weight-drop model (Impact acceleration model)

To model "whole head" motion resulting in a diffuse brain injury, Marmarou et al. [16,17] allows the head to accelerate at impact. Depending on the severity of injury, the induced brain injury results in hemorrhages, neuronal cell death, astrogliosis, diffuse axonal injury, and cytotoxic brain edema [17,23,26,42,43]. This impact acceleration model using a weight-drop is a useful model for investigating diffuse brain injuries ranging from mild to severe.

Taken together, weight-drop models provide a straightforward way to assess brain injuries close to the clinical conditions ranging from focal to diffuse brain injuries.

Fluid percussion injury models

Fluid percussion injury (FPI) models produce brain injury by rapidly injecting fluid volumes onto the intact dural surface through a craniotomy. The craniotomy is made either centrally (CFP, MFP), over the sagittal suture midway between bregma and lambda, or laterally (LFP), over the parietal cortex. Graded levels of injury severity can be achieved by adjusting the force of the fluid pressure pulse. Like in various other TBI models, a high mortality rate due to apnea is evident [44,45].

The central (CFP) and lateral (LFP) fluid percussion injury models were adapted to rats in 1987 [46,47] and in 1989 [48,49], respectively. These models produce a

mixed type of brain injury. Traumatic pathology includes cortical contusion, hemorrhage and a cytotoxic and/or vasogenic brain edema either typically bilateral for CFP injury or ipsilateral for LFP injury [23,26,50]. The delayed progression of brain damage is accompanied by astrogliosis, diffuse axonal injury, inflammatory events, cortical spreading depression and neurodegeneration [23,26,45,50-61]. Regardless of injury location, FPI leads to cognitive dysfunction [23,51,55,61,62] and thus it can be a useful model for posttraumatic dementia. Furthermore, FPI delivered laterally is an appropriate model for posttraumatic epilepsy [63].

The FPI model in the rat has been the most widely used model for TBI. Nevertheless, for both CFP and LFP variability's in injury parameters between laboratories are evident. For instance, initial studies using LFP detected an ipsilateral brain injury [64] whereas some later studies detected a widespread, bilateral brain injury [65-67]. One crucial factor determining the outcome severity in this model seems to be the positioning of the craniotomy as already a small shift in the craniotomy site is associated with marked differences in neurological outcome, lesion location and size [68,69]. Thus, establishing a FPI model necessitates extensive methodological fine-tuning to obtain a standardized outcome in respect to its severity and pathophysiology. Once the FPI model is established, the induced brain trauma seems to be highly reproducible.

To enable the use of transgenic mice, Carbonell et al. [49] adapted the FPI model to the mouse. Similar to the rat, the inflicted injury in mice leads to cognitive dysfunction, microglial activation and neuronal and axonal damage [23,49,51,63,70,71].

Controlled cortical impact injury model

Controlled cortical impact (CCI) models utilize a pneumatic pistol to deform laterally the exposed dura and provide controlled impact and quantifiable biomechanical parameters. This model was adapted to rat in 1991 [72] and to mouse in 1995 [73] and produces graded, reproducible brain injury.

Dependent on the severity of injury, CCI results in an ipsilateral injury with cortical contusion, hemorrhage and blood-brain barrier disruption [74]. Neuronal cell death and degeneration, astrogliosis, microglial activation, inflammatory events, axonal damage, cognitive deficits, excitotoxicity and cortical spreading depressions are reported to ensue [23,26,30,73,75-82]. Particularly with regard to brain edema, CCI is an important model as it presumably causes a cytotoxic and a vasogenic brain edema [23,26,83-89] and thus it reflects the clinical situation of posttraumatic brain edema formation. The predominantly focal brain injury caused by CCI makes this model to a useful tool for studying the

pathophysiology of the secondary processes induced by focal brain injury. Interestingly, CCI in rodents is associated with posttraumatic seizure activity similar to the injury-induced epilepsy in humans [90,91]. Thus this model is particularly suitable to study pathomechanisms of posttraumatic epilepsy.

Cryogenic injury model

The method of cryogenic injury in rodents [92,93] leads to a focal brain lesion. The brain injury in this model is generally produced by applying a cold rod to the exposed dura in rats (e.g. on the parietal cortex using a copper cylinder filled with a mixture of acetone and dry ice (-78°C) [94]) or skull in mice (e.g. on the parietal cortex using a copper cylinder filled with liquid nitrogen (-183°C) [95]). In some studies, a dry ice pellet was directly applied to the skull of the rat or mouse [96,97]. Different injury severities can be achieved by varying the contact time to the exposed cortex [98].

In rodents, cortical cryogenic injury results in a focal brain lesion and breakdown of the blood-brain barrier [94,95]. The primary lesion is surrounded by a penumbral zone where secondary processes lead to an extension of lesion size accompanied by neuronal cell death and cytotoxic and vasogenic edema [98,99]. These secondary processes also include activation of astrocytes and inflammation [95,96,100-103]. Moreover, it was reported recently that a discrete cryogenic lesion to the parietal cortex of juvenile mice causes delayed global neurodegeneration [104]. Due to epileptic activities surrounding the focal lesion, this method is also used for mimicking certain aspects of epilepsy [105-107].

The cryogenic brain lesion model is particularly suited for investigating TBI-associated blood-brain barrier leakage and vasogenic brain edema. However, this focal trauma model lacks the contrecoup and diffuse axonal injuries that typically complicate human head injuries [1]. Thus the cryogenic brain lesion model only conditionally mimics the clinical situation. Although various other models reflect more realistically the pathophysiological characteristic of TBI, the cryogenic brain lesion model has one major advantage: The lesions caused by the cryogenic injury model are clearly circumscribed and highly reproducible in size, location and pathophysiological processes of the secondary lesion expansion at the cortical impact site. The high reproducibility of the cortical lesion is particularly useful to screen the impact of pharmacological treatments or gene knockout on secondary lesion development after focal brain injury.

Other models

Models to induce diffuse brain injury

In addition to the original Marmarou's weight-drop model, various other impact acceleration models that

induce diffuse brain injuries have been described in the literature. As an example, in one model the rat is placed on its back while the head is accelerated upward by a piston [108]. The severity of injury depends on the impact velocity of the piston. In another study, rats were subjected to impact acceleration head injury, using a pneumatic impact targeted to a steel disc centered onto their skull. The animal's head was supported by a soft pad to decelerate the head after the impact [109]. To induce moderate head concussion without focal injury, a pendulum can be used that stroke on the skull midline of rats [110].

Models to induce focal brain injury

In an attempt to create a model of focal cerebral contusion without diffuse brain injury, Shreiber et al. (1999) generated cerebral contusions and associated evolving damage by a transient non-ablative vacuum pulse applied to the exposed cerebral cortex [111]. Other models designed to generate focal cortical injury inject fluids leading to an inflammatory response and a progressive cavitation [112], apply a mechanical suction force through the intact dura [113] or apply a stab wound [114]. Each of these models result in clearly circumscribed focal lesions and thus, similar to the cryogenic injury model, they might be helpful in studies evaluating putative treatments by monitoring the focal lesion size.

Models to mimic blast-induced neurotrauma

In recent years, exposure to blast is becoming more frequent foremost in military populations. Brain injuries due to blast are caused by particles propelled by blast-force, acceleration and deceleration forces and/or the blast wave itself [115]. The non-impact blast injury exhibits an interesting pathophysiology characterized by diffuse cerebral brain edema, extreme hyperemia and a delayed vasospasm [115]. To investigate blast-induced neurotrauma different models have been established. As an example, to mimic a non-impact blast-induced neurotrauma, rodents were fixed and exposed to blast waves caused by detonation of explosive [116] or compressed air [117]. Recently the pathobiology of TBI caused by blast and the animal models for non-impact blast injury have been recently reviewed by Cernak and Noble-Haeusslein [115].

Combined and modified injury models

If no convenient model is available to address specific research topics, the modification of already existing animal models might be useful. As an example human TBI is often induced by angular (a combination of linear and rotational) accelerations, e.g. TBI caused by car accidents. This clinical scenario was mimicked in rats by instantly rotating the animal to reproduce rotational

acceleration after it had sustained the impact that produced linear acceleration using the Marmarou's weight drop model [118]. Another example is the Maryland model, in which Kilbourne et al. mimicked a frontal impact by modifying the impact-acceleration model of Marmarou [119]. To simulate concussions in National Football League players, a rat model was developed in which a pneumatic pressure in the style of CCI models is used to impact laterally the helmet-protected head [120]. Clinical TBI is frequently accompanied by complications such as hypoxic episodes and sepsis. In order to mimic those clinical situations, they can be integrated in the study design (hypoxia [121,122] and sepsis [123]).

Cell culture models

Cell culture is currently the most promising alternative to animal research. The use of cell culture models simulating TBI might be useful for certain research goals, such as high throughput drug screenings or the assessment of the effect of trauma on individual cell types. The current available cell culture models include models using disruption of various cell cultures by laceration, compression, acceleration or stretch injury (reviewed by [124]).

Outlook

Initially, the rodent models for TBI were designed to mimic closely the clinical sequelae of human TBI. In this respect, the most straightforward rodent models are the weight-drop models by Marmarou and Shohami as they closely mimic the real life TBI. The inflicted injuries are predominantly diffuse or focal in nature, respectively. Similarly the FPI model and CCI model mimic various injury processes associated with human TBI. Probably due to the excellent reproducibility of induced brain trauma, FPI and CCI are the most widely used rodent models for TBI. However, even small modifications in the experimental design often lead to differences in primary injury and hence to differences in pathobiological processes leading to secondary injury. Considering the heterogeneity of human TBI, scientific hypothesis should be tested in multiple rodent models resulting in distinct types of injury. Thus, models solely mimicking focal or diffuse injury are needed.

In conclusion, there are numerous rodent models of TBI available, widely varying in their ability to model pathomechanisms associated with human TBI. They provide the experimental backbone for investigating TBI pathomechanisms and for the initial testing of neuroprotective compounds.

Acknowledgements

This work received financial support from the Wilhelm Sander Foundation (Munich, Germany).

Author details

¹University of Würzburg, Department of Neurology, Würzburg, Germany.

²University of Würzburg, Department of Neurosurgery, Würzburg, Germany.

Authors' contributions

CAW drafted the manuscript. ALS corrected and wrote the final manuscript. Both authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Received: 20 May 2010 Accepted: 13 August 2010

Published: 13 August 2010

References

1. Gaetz M: **The neurophysiology of brain injury.** *Clin Neurophysiol* 2004, **115**:4-18.
2. Division of Injury Response, National Center for Injury Prevention and Control Centers for Disease Control and Prevention, U.S. Department of Health and Human Services: **Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations, and Deaths, 2002-2006.** Atlanta 2010.
3. Maegele M, Engel D, Bouillon B, Lefering R, Fach H, Raum M, Buchheister B, Schaefer U, Klug N, Neugebauer E: **Incidence and outcome of traumatic brain injury in an urban area in Western Europe over 10 years.** *Eur Surg Res* 2007, **39**:372-379.
4. Mock C, Josphura M, Goosen J, Lormand JD, Maier R: **Strengthening trauma systems globally: the Essential Trauma Care Project.** *J Trauma* 2005, **59**:1243-1246.
5. Yattoo G, Tabish A: **The profile of head injuries and traumatic brain injury deaths in Kashmir.** *J Trauma Manag Outcomes* 2008, **2**:5.
6. Chiu WT, Huang SJ, Tsai SH, Lin JW, Tsai MD, Lin TJ, Huang WC: **The impact of time, legislation, and geography on the epidemiology of traumatic brain injury.** *J Clin Neurosci* 2007, **14**:930-935.
7. Martins ET, Linhares MN, Sousa DS, Schroeder HK, Meinerz J, Rigo LA, Bertotti MM, Gullo J, Hohl A, Dal-Pizzol F, Walz R: **Mortality in severe traumatic brain injury: a multivariate analysis of 748 Brazilian patients from Florianopolis City.** *J Trauma* 2009, **67**:85-90.
8. Xiong Y, Mahmood A, Chopp M: **Emerging treatments for traumatic brain injury.** *Expert Opin Emerg Drugs* 2009, **14**:67-84.
9. Doppenberg EM, Choi SC, Bullock R: **Clinical trials in traumatic brain injury: lessons for the future.** *J Neurosurg Anesthesiol* 2004, **16**:87-94.
10. Maas AI: **Neuroprotective agents in traumatic brain injury.** *Expert Opin Investig Drugs* 2001, **10**:753-767.
11. Faden AI: **Neuroprotection and traumatic brain injury: theoretical option or realistic proposition.** *Curr Opin Neurol* 2002, **15**:707-712.
12. Statler KD, Jenkins LW, Dixon CE, Clark RS, Marion DW, Kochanek PM: **The simple model versus the super model: translating experimental traumatic brain injury research to the bedside.** *J Neurotrauma* 2001, **18**:1195-1206.
13. Shohami E, Shapira Y, Cotev S: **Experimental closed head injury in rats: prostaglandin production in a noninjured zone.** *Neurosurgery* 1988, **22**:859-863.
14. Shapira Y, Shohami E, Sidi A, Soffer D, Freeman S, Cotev S: **Experimental closed head injury in rats: mechanical, pathophysiological, and neurologic properties.** *Crit Care Med* 1988, **16**:258-265.
15. Flierl MA, Stahel PF, Beauchamp KM, Morgan SJ, Smith WR, Shohami E: **Mouse closed head injury model induced by a weight-drop device.** *Nat Protoc* 2009, **4**:1328-1337.
16. Foda MA, Marmarou A: **A new model of diffuse brain injury in rats. Part II: Morphological characterization.** *J Neurosurg* 1994, **80**:301-313.
17. Marmarou A, Foda MA, van den Brink W, Campbell J, Kita H, Demetriadou K: **A new model of diffuse brain injury in rats. Part I: Pathophysiology and biomechanics.** *J Neurosurg* 1994, **80**:291-300.
18. Blaha M, Schwab J, Vajnerova O, Bednar M, Vajner L, Michal T: **Intracranial pressure and experimental model of diffuse brain injury in rats.** *J Korean Neurosurg Soc* 2010, **47**:7-10.
19. Adelson PD, Robichaud P, Hamilton RL, Kochanek PM: **A model of diffuse traumatic brain injury in the immature rat.** *J Neurosurg* 1996, **85**:877-884.

20. Chen Y, Constantini S, Trembovler V, Weinstock M, Shohami E: **An experimental model of closed head injury in mice: pathophysiology, histopathology, and cognitive deficits.** *J Neurotrauma* 1996, **13**:557-568.
21. Dail WG, Feeney DM, Murray HM, Linn RT, Boyeson MG: **Responses to cortical injury: II. Widespread depression of the activity of an enzyme in cortex remote from a focal injury.** *Brain Res* 1981, **211**:79-89.
22. Feeney DM, Boyeson MG, Linn RT, Murray HM, Dail WG: **Responses to cortical injury: I. Methodology and local effects of contusions in the rat.** *Brain Res* 1981, **211**:67-77.
23. Morales DM, Marklund N, Lebold D, Thompson HJ, Pitkanen A, Maxwell WL, Longhi L, Laurer H, Maegele M, Neugebauer E, Graham DJ, Stocchetti N, McIntosh TK: **Experimental models of traumatic brain injury: do we really need to build a better mousetrap?** *Neuroscience* 2005, **136**:971-989.
24. Mikawa S, Kinouchi H, Kamii H, Gobbelt GT, Chen SF, Carlson E, Epstein CJ, Chan PH: **Attenuation of acute and chronic damage following traumatic brain injury in copper, zinc-superoxide dismutase transgenic mice.** *J Neurosurg* 1996, **85**:885-891.
25. Bellander BM, von Holst H, Fredman P, Svensson M: **Activation of the complement cascade and increase of clusterin in the brain following a cortical contusion in the adult rat.** *J Neurosurg* 1996, **85**:468-475.
26. Cernak I: **Animal models of head trauma.** *NeuroRx* 2005, **2**:410-422.
27. Isaksson J, Hillered L, Olsson Y: **Cognitive and histopathological outcome after weight-drop brain injury in the rat: influence of systemic administration of monoclonal antibodies to ICAM-1.** *Acta Neuropathol* 2001, **102**:246-256.
28. Allen GV, Gerami D, Esser MJ: **Conditioning effects of repetitive mild neurotrauma on motor function in an animal model of focal brain injury.** *Neuroscience* 2000, **99**:93-105.
29. Uhl MW, Biagas KV, Grundl PD, Barmada MA, Schiding JK, Nemoto EM, Kochanek PM: **Effects of neutropenia on edema, histology, and cerebral blood flow after traumatic brain injury in rats.** *J Neurotrauma* 1994, **11**:303-315.
30. DeKosky ST, Goss JR, Miller PD, Styren SD, Kochanek PM, Marion D: **Upregulation of nerve growth factor following cortical trauma.** *Exp Neurol* 1994, **130**:173-177.
31. Holmin S, Schalling M, Hojeberg B, Nordqvist AC, Skeftruna AK, Mathiesen T: **Delayed cytokine expression in rat brain following experimental contusion.** *J Neurosurg* 1997, **86**:493-504.
32. Nilsson P, Gazelius B, Carlsson H, Hillered L: **Continuous measurement of changes in regional cerebral blood flow following cortical compression contusion trauma in the rat.** *J Neurotrauma* 1996, **13**:201-207.
33. Lindh C, Wennersten A, Arnberg F, Holmin S, Mathiesen T: **Differences in cell death between high and low energy brain injury in adult rats.** *Acta Neurochir (Wien)* 2008, **150**:1269-1275.
34. Umschwief G, Shein NA, Alexandrovich AG, Trembovler V, Horowitz M, Shohami E: **Heat acclimation provides sustained improvement in functional recovery and attenuates apoptosis after traumatic brain injury.** *J Cereb Blood Flow Metab* 2010, **30**:616-627.
35. Shohami E, Novikov M, Horowitz M: **Long term exposure to heat reduces edema formation after closed head injury in the rat.** *Acta Neurochir Suppl (Wien)* 1994, **60**:443-445.
36. Leinase I, Rozanski M, Harhausen D, Thurman JM, Schmidt OI, Hossini AM, Taha ME, Rittirsch D, Ward PA, Holers VM, Ertel W, Stahel PF: **Inhibition of the alternative complement activation pathway in traumatic brain injury by a monoclonal anti-factor B antibody: a randomized placebo-controlled study in mice.** *J Neuroinflammation* 2007, **4**:13.
37. Leinase I, Holers VM, Thurman JM, Harhausen D, Schmidt OI, Pietzcker M, Taha ME, Rittirsch D, Huber-Lang M, Smith WR, Ward PA, Stahel PF: **Reduced neuronal cell death after experimental brain injury in mice lacking a functional alternative pathway of complement activation.** *BMC Neurosci* 2006, **7**:55.
38. Tweedie D, Millan A, Holloway HW, Li Y, Harvey BK, Shen H, Pistell PJ, Lahiri DK, Hoffer BJ, Wang Y, Pick CG, Greig NH: **Apoptotic and behavioral sequelae of mild brain trauma in mice.** *J Neurosci Res* 2007, **85**:805-815.
39. Zohar O, Schreiber S, Getslev V, Schwartz JP, Mullins PG, Pick CG: **Closed-head minimal traumatic brain injury produces long-term cognitive deficits in mice.** *Neuroscience* 2003, **118**:949-955.
40. Tashlykov V, Katz Y, Gazit V, Zohar O, Schreiber S, Pick CG: **Apoptotic changes in the cortex and hippocampus following minimal brain trauma in mice.** *Brain Res* 2007, **1130**:197-205.
41. Israelsson C, Wang Y, Kylberg A, Pick CG, Hoffer B, Ebendal T: **Closed head injury in a mouse model results in molecular changes indicating inflammatory responses.** *J Neurotrauma* 2009, **26**:1307-1314.
42. Ding JY, Kreipke CW, Speirs SL, Schafer P, Schafer S, Rafols JA: **Hypoxia-inducible factor-1alpha signaling in aquaporin upregulation after traumatic brain injury.** *Neurosci Lett* 2009, **453**:68-72.
43. Nawashiro H, Messing A, Azzam N, Brenner M: **Mice lacking GFAP are hypersensitive to traumatic cerebrospinal injury.** *Neuroreport* 1998, **9**:1691-1696.
44. Levesseur JE, Patterson JL Jr, Ghatak NR, Kontos HA, Choi SC: **Combined effect of respirator-induced ventilation and superoxide dismutase in experimental brain injury.** *J Neurosurg* 1989, **71**:573-577.
45. Yamaki T, Murakami N, Iwamoto Y, Sakakibara T, Kobori N, Ueda S, Kikuchi T, Uwahodo Y: **Evaluation of learning and memory dysfunction and histological findings in rats with chronic stage contusion and diffuse axonal injury.** *Brain Res* 1997, **752**:151-160.
46. McIntosh TK, Noble L, Andrews B, Faden AL: **Traumatic brain injury in the rat: characterization of a midline fluid-percussion model.** *Cent Nerv Syst Trauma* 1987, **4**:119-134.
47. Dixon CE, Lyeth BG, Povlishock JT, Findling RL, Hamm RJ, Marmarou A, Young HF, Hayes RL: **A fluid percussion model of experimental brain injury in the rat.** *J Neurosurg* 1987, **67**:110-119.
48. McIntosh TK, Vink R, Noble L, Yamakami I, Fernyak S, Soares H, Faden AL: **Traumatic brain injury in the rat: characterization of a lateral fluid-percussion model.** *Neuroscience* 1989, **28**:233-244.
49. Carbonell WS, Maris DO, McCall T, Grady MS: **Adaptation of the fluid percussion injury model to the mouse.** *J Neurotrauma* 1998, **15**:217-229.
50. Yamaki T, Murakami N, Iwamoto Y, Yoshino E, Nakagawa Y, Ueda S, Horikawa J, Tsujii T: **A modified fluid percussion device.** *J Neurotrauma* 1994, **11**:613-622.
51. Thompson HJ, Lifshitz J, Marklund N, Grady MS, Graham DI, Hovda DA, McIntosh TK: **Lateral fluid percussion brain injury: a 15-year review and evaluation.** *J Neurotrauma* 2005, **22**:42-75.
52. Keeling KL, Hicks RR, Mahesh J, Billings BB, Kotwal GJ: **Local neutrophil influx following lateral fluid-percussion brain injury in rats is associated with accumulation of complement activation fragments of the third component (C3) of the complement system.** *J Neuroimmunol* 2000, **105**:20-30.
53. Kelley BJ, Lifshitz J, Povlishock JT: **Neuroinflammatory responses after experimental diffuse traumatic brain injury.** *J Neuropathol Exp Neurol* 2007, **66**:989-1001.
54. Rogatsky GG, Sonn J, Kamenir Y, Zarchin N, Mayevsky A: **Relationship between intracranial pressure and cortical spreading depression following fluid percussion brain injury in rats.** *J Neurotrauma* 2003, **20**:1315-1325.
55. Yamaki T, Murakami N, Iwamoto Y, Sakakibara T, Kobori N, Ueda S, Uwahodo Y, Kikuchi T: **Cognitive dysfunction and histological findings in rats with chronic-stage contusion and diffuse axonal injury.** *Brain Res Brain Res Protoc* 1998, **3**:100-106.
56. McGinn MJ, Kelley BJ, Akinyi L, Oli MW, Liu MC, Hayes RL, Wang KK, Povlishock JT: **Biochemical, structural, and biomarker evidence for calpain-mediated cytoskeletal change after diffuse brain injury uncomplicated by contusion.** *J Neuropathol Exp Neurol* 2009, **68**:241-249.
57. Hall KD, Lifshitz J: **Diffuse traumatic brain injury initially attenuates and later expands activation of the rat somatosensory whisker circuit concomitant with neuroplastic responses.** *Brain Res* 2010, **1323**:161-173.
58. McNamara KC, Lisembee AM, Lifshitz J: **The Whisker Nuisance Task Identifies a Late Onset, Persistent Sensory Sensitivity in Diffuse Brain-Injured Rats.** *J Neurotrauma* 2010, **27**:695-706.
59. Myer DJ, Gurkoff GG, Lee SM, Hovda DA, Sofroniew MV: **Essential protective roles of reactive astrocytes in traumatic brain injury.** *Brain* 2006, **129**:2761-2772.
60. Murakami N, Yamaki T, Iwamoto Y, Sakakibara T, Kobori N, Fushiki S, Ueda S: **Experimental brain injury induces expression of amyloid precursor protein, which may be related to neuronal loss in the hippocampus.** *J Neurotrauma* 1998, **15**:993-1003.
61. Hoshino S, Tamaoka A, Takahashi M, Kobayashi S, Furukawa T, Oaki Y, Mori O, Matsuno S, Shoji S, Inomata M, Teramoto A: **Emergence of immunoreactivities for phosphorylated tau and amyloid-beta protein in chronic stage of fluid percussion injury in rat brain.** *Neuroreport* 1998, **9**:1879-1883.

62. Miyazaki S, Katayama Y, Lyeth BG, Jenkins LW, DeWitt DS, Goldberg SJ, Newlon PG, Hayes RL: **Enduring suppression of hippocampal long-term potentiation following traumatic brain injury in rat.** *Brain Res* 1992, **585**:335-339.
63. Pitkanen A, Immonen RJ, Grohn OH, Kharatishvili I: **From traumatic brain injury to posttraumatic epilepsy: what animal models tell us about the process and treatment options.** *Epilepsia* 2009, **50**(Suppl 2):21-29.
64. Smith DH, Okiyama K, Thomas MJ, Claussen B, McIntosh TK: **Evaluation of memory dysfunction following experimental brain injury using the Morris water maze.** *J Neurotrauma* 1991, **8**:259-269.
65. Soares HD, Thomas M, Cloherty K, McIntosh TK: **Development of prolonged focal cerebral edema and regional cation changes following experimental brain injury in the rat.** *J Neurochem* 1992, **58**:1845-1852.
66. Pierce JE, Trojanowski JQ, Graham DI, Smith DH, McIntosh TK: **Immunohistochemical characterization of alterations in the distribution of amyloid precursor proteins and beta-amyloid peptide after experimental brain injury in the rat.** *J Neurosci* 1996, **16**:1083-1090.
67. Smith DH, Lowenstein DH, Gennarelli TA, McIntosh TK: **Persistent memory dysfunction is associated with bilateral hippocampal damage following experimental brain injury.** *Neurosci Lett* 1994, **168**:151-154.
68. Vink R, Mullins PG, Temple MD, Bao W, Faden AI: **Small shifts in craniotomy position in the lateral fluid percussion injury model are associated with differential lesion development.** *J Neurotrauma* 2001, **18**:839-847.
69. Floyd CL, Golden KM, Black RT, Hamm RJ, Lyeth BG: **Craniectomy position affects morris water maze performance and hippocampal cell loss after parasagittal fluid percussion.** *J Neurotrauma* 2002, **19**:303-316.
70. Carbonell WS, Grady MS: **Regional and temporal characterization of neuronal, glial, and axonal response after traumatic brain injury in the mouse.** *Acta Neuropathol* 1999, **98**:396-406.
71. Spain A, Daumas S, Lifshitz J, Rhodes J, Andrews PJ, Horsburgh K, Fowler JH: **Mild Fluid Percussion Injury in Mice Produces Evolving Selective Axonal Pathology and Cognitive Deficits Relevant to Human Brain Injury.** *J Neurotrauma* 2010.
72. Dixon CE, Clifton GL, Lighthall JW, Yaghami AA, Hayes RL: **A controlled cortical impact model of traumatic brain injury in the rat.** *J Neurosci Methods* 1991, **39**:253-262.
73. Smith DH, Soares HD, Pierce JS, Perlman KG, Saatman KE, Meaney DF, Dixon CE, McIntosh TK: **A model of parasagittal controlled cortical impact in the mouse: cognitive and histopathologic effects.** *J Neurotrauma* 1995, **12**:169-178.
74. Dhillon HS, Donaldson D, Dempsey RJ, Prasad MR: **Regional levels of free fatty acids and Evans blue extravasation after experimental brain injury.** *J Neurotrauma* 1994, **11**:405-415.
75. Griesbach GS, Sutton RL, Hovda DA, Ying Z, Gomez-Pinilla F: **Controlled contusion injury alters molecular systems associated with cognitive performance.** *J Neurosci Res* 2009, **87**:795-805.
76. Adelson PD, Whalen MJ, Kochanek PM, Robichaud P, Carlos TM: **Blood brain barrier permeability and acute inflammation in two models of traumatic brain injury in the immature rat: a preliminary report.** *Acta Neurochir Suppl* 1998, **71**:104-106.
77. von Baumgarten L, Trabold R, Thal S, Back T, Plesnila N: **Role of cortical spreading depressions for secondary brain damage after traumatic brain injury in mice.** *J Cereb Blood Flow Metab* 2008, **28**:1353-1360.
78. Hall ED, Bryant YD, Cho W, Sullivan PG: **Evolution of post-traumatic neurodegeneration after controlled cortical impact traumatic brain injury in mice and rats as assessed by the de Olmos silver and fluorojade staining methods.** *J Neurotrauma* 2008, **25**:235-247.
79. Chen SF, Hsu CW, Huang WH, Wang JY: **Post-injury baicalein improves histological and functional outcomes and reduces inflammatory cytokines after experimental traumatic brain injury.** *Br J Pharmacol* 2008, **155**:1279-1296.
80. Sandhir R, Onyszchuk G, Berman NE: **Exacerbated glial response in the aged mouse hippocampus following controlled cortical impact injury.** *Exp Neurol* 2008, **213**:372-380.
81. Igarashi T, Potts MB, Noble-Haueslein LJ: **Injury severity determines Purkinje cell loss and microglial activation in the cerebellum after cortical contusion injury.** *Exp Neurol* 2007, **203**:258-268.
82. Koshinaga M, Katayama Y, Fukushima M, Oshima H, Suma T, Takahata T: **Rapid and widespread microglial activation induced by traumatic brain injury in rat brain slices.** *J Neurotrauma* 2000, **17**:185-192.
83. Elliott MB, Jallo JJ, Tuma RF: **An investigation of cerebral edema and injury volume assessments for controlled cortical impact injury.** *J Neurosci Methods* 2008, **168**:320-324.
84. Schuhmann MU, Mokhtarzadeh M, Stichtenoth DO, Skardelly M, Klinge PM, Gutzki FM, Samii M, Brinker T: **Temporal profiles of cerebrospinal fluid leukotrienes, brain edema and inflammatory response following experimental brain injury.** *Neurosci Res* 2003, **25**:481-491.
85. Kiening KL, van Landeghem FK, Schreiber S, Thomale UW, von Deimling A, Unterberg AW, Stover JF: **Decreased hemispheric Aquaporin-4 is linked to evolving brain edema following controlled cortical impact injury in rats.** *Neurosci Lett* 2002, **324**:105-108.
86. Baskaya MK, Rao AM, Dogan A, Donaldson D, Dempsey RJ: **The biphasic opening of the blood-brain barrier in the cortex and hippocampus after traumatic brain injury in rats.** *Neurosci Lett* 1997, **226**:33-36.
87. Baskaya MK, Dogan A, Temiz C, Dempsey RJ: **Application of 2,3,5-triphenyltetrazolium chloride staining to evaluate injury volume after controlled cortical impact brain injury: role of brain edema in evolution of injury volume.** *J Neurotrauma* 2000, **17**:93-99.
88. Stroop R, Thomale UW, Pauser S, Bernarding J, Vollmann W, Wolf KJ, Lanksch WR, Unterberg AW: **Magnetic resonance imaging studies with cluster algorithm for characterization of brain edema after controlled cortical impact injury (CCII).** *Acta Neurochir Suppl* 1998, **71**:303-305.
89. Unterberg AW, Stroop R, Thomale UW, Kiening KL, Pauser S, Vollmann W: **Characterisation of brain edema following "controlled cortical impact injury" in rats.** *Acta Neurochir Suppl* 1997, **70**:106-108.
90. Statler KD, Scheerlinck P, Pouliot W, Hamilton M, White HS, Dudek FE: **A potential model of pediatric posttraumatic epilepsy.** *Epilepsy Res* 2009, **86**:221-223.
91. Hunt RF, Scheff SW, Smith BN: **Posttraumatic epilepsy after controlled cortical impact injury in mice.** *Exp Neurol* 2009, **215**:243-252.
92. Pappius HM: **Local cerebral glucose utilization in thermally traumatized rat brain.** *Ann Neurol* 1981, **9**:484-491.
93. Tengvar C, Olsson Y: **Uptake of macromolecules into neurons from a focal vasogenic cerebral edema and subsequent axonal spread to other brain regions. A preliminary study in the mouse with horseradish peroxidase as a tracer.** *Acta Neuropathol* 1982, **57**:233-235.
94. Rakos G, Kis Z, Nagy D, Lur G, Farkas T, Hortobagyi T, Vecsei L, Toldi J: **Evans Blue fluorescence permits the rapid visualization of non-intact cells in the perilesional rim of cold-injured rat brain.** *Acta Neurobiol Exp (Wars)* 2007, **67**:149-154.
95. Raslan F, Schwarz T, Meuth SG, Austinat M, Bader M, Renne T, Roosen K, Stoll G, Siren AL, Kleinschnitz C: **Inhibition of bradykinin receptor B1 protects mice from focal brain injury by reducing blood-brain barrier leakage and inflammation.** *J Cereb Blood Flow Metab* 2010, **30**:1477-1486.
96. Pifarre P, Prado J, Giral M, Molinero A, Hidalgo J, Garcia A: **Cyclic GMP phosphodiesterase inhibition alters the glial inflammatory response, reduces oxidative stress and cell death and increases angiogenesis following focal brain injury.** *J Neurochem* 2010, **112**:807-817.
97. Giral M, Penkowa M, Lago N, Molinero A, Hidalgo J: **Metallothionein-1+2 protect the CNS after a focal brain injury.** *Exp Neurol* 2002, **173**:114-128.
98. Eriskat J, Furst M, Stoffel M, Baethmann A: **Correlation of lesion volume and brain swelling from a focal brain trauma.** *Acta Neurochir Suppl* 2003, **86**:265-266.
99. Stoffel M, Blau C, Reinl H, Breidt J, Gersonde K, Baethmann A, Plesnila N: **Identification of brain tissue necrosis by MRI: validation by histomorphometry.** *J Neurotrauma* 2004, **21**:733-740.
100. Bordey A, Hablitz JJ, Sontheimer H: **Reactive astrocytes show enhanced inwardly rectifying K+ currents in situ.** *Neuroreport* 2000, **11**:3151-3155.
101. Penkowa M, Giral M, Lago N, Camats J, Carrasco J, Hernandez J, Molinero A, Campbell IL, Hidalgo J: **Astrocyte-targeted expression of IL-6 protects the CNS against a focal brain injury.** *Exp Neurol* 2003, **181**:130-148.
102. Penkowa M, Giral M, Carrasco J, Hadberg H, Hidalgo J: **Impaired inflammatory response and increased oxidative stress and neurodegeneration after brain injury in interleukin-6-deficient mice.** *Glia* 2000, **32**:271-285.
103. Quintana A, Giral M, Rojas S, Penkowa M, Campbell IL, Hidalgo J, Molinero A: **Differential role of tumor necrosis factor receptors in mouse brain inflammatory responses in cryolesion brain injury.** *J Neurosci Res* 2005, **82**:701-716.

104. Siren AL, Radyushkin K, Boretius S, Kammer D, Riechers CC, Natt O, Sargin D, Watanabe T, Sperling S, Michaelis T, Price J, Meyer B, Frahm J, Ehrenreich H: **Global brain atrophy after unilateral parietal lesion and its prevention by erythropoietin.** *Brain* 2006, **129**:480-489.
105. Lewin E: **The production of epileptogenic cortical foci in experimental animals by freezing.** *Purpura* New York: Raven Press; Purpura DP, Perry JK, Tower DB, Woodbury DM, Walter R 1972.
106. Coutinho-Netto J, Boyar MM, Abdul-Ghani AS, Bradford HF: **In vivo inhibition of incorporation of [U-14C]glucose into proteins in experimental focal epilepsy.** *Epilepsia* 1982, **23**:383-389.
107. Redecker C, Luhmann HJ, Hagemann G, Fritschy JM, Witte OW: **Differential downregulation of GABAA receptor subunits in widespread brain regions in the freeze-lesion model of focal cortical malformations.** *J Neurosci* 2000, **20**:5045-5053.
108. Nilsson B, Ponten U: **Experimental head injury in the rat. Part 2: Regional brain energy metabolism in concussive trauma.** *J Neurosurg* 1977, **47**:252-261.
109. Maruichi K, Kuroda S, Chiba Y, Hokari M, Shichinohe H, Hida K, Iwasaki Y: **Graded model of diffuse axonal injury for studying head injury-induced cognitive dysfunction in rats.** *Neuropathology* 2009, **29**:132-139.
110. Goldman H, Hodgson V, Morehead M, Hazlett J, Murphy S: **Cerebrovascular changes in a rat model of moderate closed-head injury.** *J Neurotrauma* 1991, **8**:129-144.
111. Shreiber DJ, Bain AC, Ross DT, Smith DH, Gennarelli TA, McIntosh TK, Meaney DF: **Experimental investigation of cerebral contusion: histopathological and immunohistochemical evaluation of dynamic cortical deformation.** *J Neuropathol Exp Neurol* 1999, **58**:153-164.
112. Fitch MT, Doller C, Combs CK, Landreth GE, Silver J: **Cellular and molecular mechanisms of glial scarring and progressive cavitation: in vivo and in vitro analysis of inflammation-induced secondary injury after CNS trauma.** *J Neurosci* 1999, **19**:8182-8198.
113. Mathew P, Bullock R, Graham DJ, Maxwell WL, Teasdale GM, McCulloch J: **A new experimental model of contusion in the rat. Histopathological analysis and temporal patterns of cerebral blood flow disturbances.** *J Neurosurg* 1996, **85**:860-870.
114. Mori S: **Uptake of (3 H)thymidine by corpus callosum cells in rats following a stab wound of the brain.** *Brain Res* 1972, **46**:177-186.
115. Cernak I, Noble-Haeusslein LJ: **Traumatic brain injury: an overview of pathobiology with emphasis on military populations.** *J Cereb Blood Flow Metab* 2010, **30**:255-266.
116. Richmond DR, Damon EG, Bowen IG, Fletcher ER, White CS: **Air-blast studies with eight species of mammals.** *Techn Progr Rep DASA 1854. Fission Prod Inhal Proj* 1967, 1-44.
117. Cernak I, Savic J, Malicevic Z, Zunic G, Radosevic P, Ivanovic I, Davidovic L: **Involvement of the central nervous system in the general response to pulmonary blast injury.** *J Trauma* 1996, **40**:100-104.
118. Wang HC, Duan ZX, Wu FF, Xie L, Zhang H, Ma YB: **A New Rat Model for Diffuse Axonal Injury Using a Combination of Linear Acceleration and Angular Acceleration.** *J Neurotrauma* 2010, **27**:707-719.
119. Kilbourne M, Kuehn R, Tosun C, Caridi J, Keledjian K, Bochicchio G, Scalea T, Gerzanich V, Simard JM: **Novel model of frontal impact closed head injury in the rat.** *J Neurotrauma* 2009, **26**:2233-2243.
120. Viano DC, Hamberger A, Bolouri H, Saljo A: **Concussion in professional football: animal model of brain injury-part 15.** *Neurosurgery* 2009, **64**:1162-1173.
121. Ishige N, Pitts LH, Berry I, Carlson SG, Nishimura MC, Moseley ME, Weinstein PR: **The effect of hypoxia on traumatic head injury in rats: alterations in neurologic function, brain edema, and cerebral blood flow.** *J Cereb Blood Flow Metab* 1987, **7**:759-767.
122. Tanno H, Nockels RP, Pitts LH, Noble LJ: **Breakdown of the blood-brain barrier after fluid percussion brain injury in the rat: Part 2: Effect of hypoxia on permeability to plasma proteins.** *J Neurotrauma* 1992, **9**:335-347.
123. Venturi L, Miranda M, Selmi V, Vitali L, Tani A, Margheri M, De Gaudio AR, Ademri C: **Systemic sepsis exacerbates mild post-traumatic brain injury in the rat.** *J Neurotrauma* 2009, **26**:1547-1556.
124. Morrison AL, Saatman KE, Meaney DF, McIntosh TK: **In vitro central nervous system models of mechanically induced trauma: a review.** *J Neurotrauma* 1998, **15**:911-928.
125. Morrison AL, King TM, Korell MA, Smialek JE, Troncoso JC: **Acceleration-deceleration injuries to the brain in blunt force trauma.** *Am J Forensic Med Pathol* 1998, **19**:109-112.
126. Yanagida Y, Fujiwara S, Mizoi Y: **Differences in the intracranial pressure caused by a 'blow' and/or a 'fall'-an experimental study using physical models of the head and neck.** *Forensic Sci Int* 1989, **41**:135-145.
127. McLean AJ: **Brain injury without head impact?** *J Neurotrauma* 1995, **12**:621-625.

doi:10.1186/2040-7378-2-16

Cite this article as: Albert-Weissenberger and Sirén: Experimental traumatic brain injury. *Experimental & Translational Stroke Medicine* 2010 2:16.

Submit your next manuscript to BioMed Central and take full advantage of:

- Convenient online submission
- Thorough peer review
- No space constraints or color figure charges
- Immediate publication on acceptance
- Inclusion in PubMed, CAS, Scopus and Google Scholar
- Research which is freely available for redistribution

Submit your manuscript at
www.biomedcentral.com/submit

