·综述·

创伤性颅脑损伤动物模型研究概况

鲁菁[1]，屈媛媛[1]，邵玉莹[1]，郭述豪[1]，冯楚文[2,3]，孙维伯[4]，李彬彬[1]，孙冬玮[5]，杨添淞[2,3,6]

作者单位
1. 黑龙江中医药大学研究生学院 哈尔滨 150040
2. 黑龙江中医药大学 哈尔滨 150040
3. 黑龙江中医药大学附属第一医院 哈尔滨 150040
4. 哈尔滨医科大学第一临床医学院 哈尔滨 150040
5. 深圳市宝安区中心医院 广东 深圳 518101
6. 黑龙江省中医药信息学重点实验室 哈尔滨 150040

基金项目
深圳市基础研究专项（No. 20210319094926010）
收稿日期
2023-04-13

通讯作者
杨添淞
yangtiansong2006@163.com

摘要 创伤性颅脑损伤（TBI）是世界上青年人致残、致死的主要原因，动物模型作为TBI损伤机制的研究载体，对研究TBI发生发展和具体损伤机制具有重要作用。由于TBI病理机制复杂，目前关于TBI动物模型的建造方案较多，大多从损伤病因及损伤性质进行区别，但尚无统一的TBI模型制备标准，且仍处于不断开发、补充和完善中。本文总结了国内外TBI模型常用的实验动物，并根据局灶性损伤、弥漫性损伤和混合性损伤三种TBI不同损伤性质对常见TBI的造模方法进行综述，以期为TBI的基础研究和临床治疗提供思路和帮助。

关键词 创伤性颅脑损伤；动物模型；综述

中图分类号 R741；R651.1+5 **文献标识码** A **DOI** 10.16780/j.cnki.sjssgncj.20230273

本文引用格式：鲁菁, 屈媛媛, 邵玉莹, 郭述豪, 冯楚文, 孙维伯, 李彬彬, 孙冬玮, 杨添淞. 创伤性颅脑损伤动物模型研究概况[J]. 神经损伤与功能重建, 2023, 18(9): 534-538, 542.

A General Review of Animal Models of Traumatic Brain Injury *LU Jing[1], QU Yuanyuan[1], SHAO Yuying[1], GUO Shuhao[1], FENG Chuwen[2,3], SUN Weibo[4], LI Binbin[1], SUN Dongwei[5], YANG Tiansong[2,3,6]. 1. Graduate School of Heilongjiang University of Chinese Medicine, Harbin 150040, China; 2. Heilongjiang University of Traditional Chinese Medicine, Harbin 150040, China; 3. The First Affiliated Hospital of Heilongjiang University of Traditional Chinese Medicine, Harbin 150040, China; 4. The First Clinical Medical College of Harbin Medical University, Harbin 150040, China; 5. Shenzhen Baoan District Central Hospital, Guangdong 518101, China; 6. Key Laboratory of Informatics of Traditional Chinese Medicine of Heilongjiang Province, Harbin 150040, China*

Abstract Traumatic craniocerebral injury (TBI) is the main cause of disability and death among young individuals worldwide. Animal models are important tools for studying the underlying mechanism of TBI injury and play an important role in studying the occurrence and development of TBI and its specific injury process. Due to the complicated pathological mechanisms of TBI, there are currently various protocols for establishing TBI animal models, mostly based on the cause and nature of injury. However, there is no unified standard for the preparation of TBI model, and the field is still evolving, with ongoing development, supplementation and improvement. This paper summarizes the experimental animals commonly used for TBI worldwide, and, reviews the commonly used modeling methods of TBI based on the different injury characteristics: focal injury, diffuse injury and mixed injury. This review will provide insights and assistance for basic research and clinical treatment of TBI.

Keywords traumatic brain injury; animal models; review

创伤性颅脑损伤（traumatic brain injury，TBI）又叫脑外伤，是一种头部受到外界急剧暴力产生的脑部损伤[1]，常表现为一系列的自主神经功能紊乱、认知障碍、意识障碍等临床症状[2]。近年来，交通事故和跌倒成为TBI主要的致病原因，全球TBI发生率呈持续上升趋势[3]，TBI的总死亡率高达20%～30%，中、重度TBI永久伤残率更是分别达到60%和100%[4]。世界卫生组织统计表示，发展中国家的TBI发生率较高，且男性发病率高于女性[5]，TBI已逐渐成为严重危害人类健康和导致全球经济损失的重大疾病之一。

TBI损伤机制复杂，由于医学伦理学和道德层面的约束，动物模型是研究TBI不可缺少的工具，为研究TBI损伤的机制和治疗提供了最佳选择。目前存在的TBI动物模型都各有特点，根据TBI损伤性质的不同可将TBI模型分为局灶性损伤模型、弥漫性损伤模型和混合性损伤模型[6]。本文综述了国内外常用于TBI造模的8种实验动物，并根据上述TBI损伤性质对常见TBI动物模型的造模原理和建立方案予以归纳总结，以期为研究TBI损伤机制和治疗方案提供参考。

1 TBI的临床特点

TBI是神经外科常见的中枢神经损伤性疾病之一，多由交通事故、战争、跌倒和体育活动引起，病情复杂，继发损伤严重。临床常导致脑水肿、颅内出血、低氧血症和低血压等疾病，表现为头痛头晕、恶心呕吐、意识障碍、认知功能障碍及其他中枢神经系统损伤性症状或体征[7]。TBI最主要的特征为机械力的即时损伤与后续病理生理过程中的继发性损伤，机械力直接导致神经元或弥漫性轴索损伤、挫伤、撕裂伤和血管破裂，继发性损伤主要由神经炎

症、代谢障碍、神经元死亡、血脑屏障破坏等介导[8]。因此，即时损伤被认为是无法治愈，而迟发性继发性损伤虽然破坏性更强，但也为干预提供了窗口，目前针对TBI的治疗方法主要是手术治疗和支持性治疗，支持性治疗主要包括高压氧、神经刺激、干细胞疗法、音乐疗法等[9-13]。

2 TBI模型常用的实验动物

TBI的研究得到发展有赖于动物模型在分子、细胞和生物体水平上的损伤复制，早期TBI模型主要使用猫、狗、猪等非灵长类动物，随后啮齿类动物进入研究者视角，并成为主流[14]。不同种类实验动物模型的开发使其在实验中各自发挥独特的作用，减少动物差异值的探讨，使研究结果更加可靠，见表1。

3 常见的TBI动物模型

3.1 局灶性脑损伤模型

局灶性脑损伤是指头部受到打击、车祸或猝然的暴力袭击造成脑组织局部损伤[6]，其动物模型主要包括Feeney's落体打击模型、控制性皮质撞击（controlled cortical impact，CCI）模型等。

3.1.1 Feeney's落体打击模型 1981年Feeney改进了由Allne建立的落体打击模型，开发了大鼠脑皮质挫伤模型。该造模方法需开窗后落体打击作用于硬脑膜，造成免疫细胞浸润、血脑屏障破坏、神经元死亡、细胞凋亡等TBI相关病理改变[40]。采用Feeney's法制备的脑外伤模型大鼠会出现大面积脑组织损伤和蛛网膜下腔出血，脑皮质中IL-6、IL-1β、IL-10、TNF-α等促炎因子表达增多，脑含水量增多，与TBI损伤机理高度重叠[41]。刘若尘等[42]在左侧颅骨冠状缝后6 mm、矢状缝左侧旁开4 mm处进行开窗，从35 cm高处垂直下落砝码打击直径5 mm的窗口，造成左脑顶叶挫裂伤、出血血肿、神经元凋亡坏死等中度TBI症状。20 cm高下坠30 g重物打击位于矢状缝右侧5 mm、冠状缝后2 mm处直径1 mm的颅骨窗口也可造成中度TBI，使大鼠出现神经功能缺损、右侧顶叶皮质神经元自噬等病理改变[43]。Feeney's法可通过调整重物坠落的高度和坠落物的重量调节颅脑损伤的严重程度，具有可控性好、可重复性高的优点。

3.1.2 CCI模型 CCI模型是通过气动或电磁冲击装置，驱动刚性撞击头，撞击硬脑膜，造成脑皮质损伤模拟TBI[44]。造模时，可以选择单侧或双侧颅骨开窗打击，通过调节打击深度、停留时间和打击速率可以复制出不同程度的脑损伤[45]。有研究表示，CCI后脑损伤的严重程度与皮质变形时间和打击速度呈正相关，打击后脑组织损伤常表现为打击侧皮质挫伤、出血和血脑屏障破坏等[46]。

Hegdekar等[47]使用凸起尖端直径为3.5 mm的撞击头，以打击速度6 m/s，打击深度2 mm的CCI仪器参数撞击小鼠左顶骨中央骨窗诱导中度TBI，使小鼠出现认知功能障碍的行为学改变以及脑皮质挫伤、海马神经元细胞损失增加等。朱海燕等[48]将CCI参数设置为尖端直径3 mm，速度4.5 m/s，打击深度1.2 mm，停留时间20 ms，撞击右侧顶颞部硬脑膜，小鼠损伤区域出现血液灌注

表1 TBI常用实验动物特点及应用

实验动物	分类	特点	应用
大鼠	小型啮齿目哺乳动物	最常用的实验动物之一，反应灵敏，价格便宜，较小鼠采血量大，易于实验操作	用于探讨TBI对血脑屏障功能障碍[15]及慢性认知和脑血管功能的影响[16]等
小鼠	小型啮齿目哺乳动物	最常用的实验动物之一，体型小，易于控制，饲养简单，繁殖快	用于研究药物治疗TBI的机制[17,18]及TBI后突触丧失和认知障碍的新型小胶质介导机制等[19]
兔	小型兔形目哺乳动物	性格温顺，容易饲养管理，价格便宜，神经系统发达。	用于评估TBI及其预后的影响因素[20-22]
雪貂	小型食肉目哺乳动物	含有与人类似的白质、沟回和位于腹侧位置的海马等脑组织结构的小型回脑哺乳动物，可较好地复制出人脑损伤[23]	用于研究TBI后脑结构和机制变化[24,25]
猪	大型偶蹄目哺乳动物	拥有与人相似的白灰质比例、相对较大的脑质量、脑回卷积，可作为临床前研究的中间动物，但成本较高，遗传和机制调节较困难[26]	作为验证TBI药物疗效的中间动物[27]及对典型小动物模型TBI机制的补充[28]
羊	大型偶蹄目哺乳动物	性格温顺，大脑与人类具有高度结构同源性，拥有类人的脊柱长度、椎管宽度、脑脊液体积以及神经肌肉接头形态，是模拟TBI等神经系统疾病的绝佳候选者[29]	用于评估TBI所需新型仪器[30]及深入了解TBI机制等[31,32]
果蝇	小型双翅目昆虫	具有一系列遗传和生物学方法的模型系统，可用于快速揭示与作为神经系统疾病基础的异质性TBI相关的纵向病理生理过程[33]	可参与调查TBI后死亡率[34]及基因表达[35]的影响因素等
斑马鱼	小型鲤形目硬骨鱼	是神经科学研究中流行的新型模式生物，与哺乳动物具有高度的遗传同源性和细胞信号通路，神经再生功能十分活跃，既适合模拟TBI的临床症状及其致病机制，也适用于研究TBI相关的分子病理学[36]	可研究TBI后网络神经修复和再生的机制[37,38]及药物疗效[39]

量减少，神经炎症与神经元凋亡等TBI病理改变。另一研究者用5 mm直径的尖端，以4 m/s的速率打击2.8 mm深度，使大鼠脑皮质损伤而不伤及海马诱导中度TBI，大鼠神经功能缺陷评分、脑含水量及脑指数均明显升高，海马区出现神经元丢失及损伤[49]。

CCI造模法参数设置灵活，随着更精准的CCI仪器研发创造，操作简单、可重复性高、稳定性强等优点使CCI造模方法在基础研究中使用率越来越高。

3.2 弥漫性脑损伤模型

弥漫性脑损伤与加速或减速的冲击波有关，主要由交通事故时头部不受限制的运动或炸弹引起的冲击波传播造成[6]，其特征包括神经血管损伤、弥漫性轴索损伤（diffuse axonal injury，DAI）等[50]。动物模型主要有爆炸冲击波创伤模型（blast-mediated traumatic brain injury，bTBI）、Marmarou落体打击模型和工程旋转加速度的闭头冲击模型（Closed Head Impact Model of Engineered Rotational Acceleration，CHIMERA）。

3.2.1 爆炸冲击波创伤模型 爆炸冲击波诱导的TBI脑损伤是一种由非穿透性超音速爆炸波载荷脉冲造成的纯粹的弥漫性损伤[6]，多见于战争中的军人和战地人民。实验室常通过压缩空气或现场引爆炸药引起的冲击波和气压波致实验动物出现皮质弥漫性充血、出血、脑水肿等TBI病理特征[51,52]。

在对爆炸波引起颅脑损伤机理的数值模拟研究中，通过建立三维数值模型，发展出爆炸冲击波-头部流固耦合模型，从压力分布、脑组织压力、颅骨变形等方面研究了爆炸波使脑组织受压损伤的演化过程，证实爆炸冲击波可造成TBI[53]。将小鼠腹侧面向爆炸源检测单次和重复爆炸暴露（每天1次，连续4 d）诱导小鼠轻度TBI（脑震荡性TBI），使其空间记忆受损，海马体、内侧前额叶皮质及基底外侧杏仁核出现髓鞘和轴突损伤[54]。Murugan等[55]将小鼠放置在冲击管中距冲击波点2.8 m，出口3.05 m的位置处，接受峰值为180 kPa超压的冲击波诱导中度TBI，激活的小胶质细胞与单核细胞在bTBI小鼠模型全脑中均有浸润，从前额皮质到小脑均受到爆炸暴露的影响，并伴有认知功能障碍。

bTBI可复刻战争中军人和战斗人民的主要致病因素，转化程度高，目前由于实验设备、操作安全性和受众人群等诸多原因，国内对于该类造模方法尚未普及，国外研究相对较多。

3.2.2 Marmarou落体打击模型 Marmarou落体打击模型首创于1994年，是一种在矢状缝、前囟和人字缝之间暴露颅骨，并放置金属片，再对金属片进行落体打击，造成动物分级脑损伤的撞击加速度模型，且该模型不导致大规模高血压激增或过度脑干损伤[56]。Marmarou落体打击模型可概括人类TBI的许多关键诊断病理生理学特征，如癫痫发作、硬脑膜/脑内血肿、血脑屏障破坏、神经炎症、脑水肿、感觉运动障碍及认知功能障碍等[57]。

Marmarou法可诱导大鼠产生弥漫性脑损伤，Amiresmaili等[58]将300 g重物从2 m高处砸向麻醉大鼠头骨3 mm厚、直径10 mm的钢板，TBI大鼠兽医昏迷量表评分升高，并出现脑水肿、血脑屏障破坏等病理改变。Bagri等[59]用250 g圆柱形金属重物撞击大鼠前囟和后囟之间的金属盘诱导脑损伤后，大鼠运动能力、学习记忆能力下降，损伤皮质神经化学递质失衡、生化异常等。有研究者增加重物重量至450 g并缩短下降高度至1 m打击大鼠头顶部直径10 mm、厚3 mm的钢盘进行TBI造模，大鼠出现前肢脱皮屈曲畸形、呼吸变浅、角膜和疼痛反射消失则为造模成功，病理表现为脑干中血清葡萄糖显著下降，能量代谢障碍，少突胶质细胞死亡及脱髓鞘致轴突变性等DAI相关改变[60]。

Marmarou落体打击模型能可靠地模拟头部撞击引起的闭合性头部损伤，在脑白质中产生DAI，且不伴有大脑局灶性挫伤和颅骨骨折，具有可重复可扩展的优点。

3.2.3 工程旋转加速度的闭头冲击模型 CHIMERA是一种较新颖的非手术冲击加速度TBI模型，目前已用于大鼠、小鼠和雪貂造模，该造模方法是通过调节气压调节阀控制金属活塞的释放和速度，使其以理想的速度撞击动物头部背表面[61]。CHIMERA诱导的动物模型具有典型的白质胶质增生和轴索损伤为特征的DAI，常表现出剧烈的急性神经功能损伤、炎症因子水平上升、血脑屏障破坏、血浆总tau和神经丝轻链水平升高及微结构血管异常等TBI常见病理变化[62]。

给予50 g不锈钢活塞2.5 J的冲击功打击小鼠头部下方的3D打印聚乳酸，进行闭头冲击造模，造模后小鼠血浆神经胶质纤维酸性蛋白快速升高[63]。Desai等[64]使用相同的方法以0.55 J的能量对小鼠进行重复闭式头部撞击造模（每天1次，连续3 d），小鼠TBI后视觉功能缺陷，空间学习、记忆能力下降，出现神经胶质细胞活化、轴突损伤等TBI病理改变。将小鼠30°角仰卧位固定于CHIMERA动物床上，以0.6 J、4.9 m/s撞击小鼠头部背侧，单次和重复CHIMERA诱导小鼠TBI后出现脑膜损伤，磁共振成像显示脑膜和大脑动态对比增强，视束和上丘的星形胶质细胞数量增加[65]。

由于CHIMERA模型结合了接触性脑震荡与加速/减速和旋转损伤等多个方面，无论单次还是重复都能可靠地模拟TBI的弥漫性轴索损伤，目前该造模方法的使用率逐渐上升[66]。

3.3 混合性脑损伤模型

混合性脑损伤是由跌倒和竞技运动损害为主引起的头部损伤类型[6]，动物模型主要是侧向液体冲击模型（lateral fluid percussion injury，LFPI）。

液体冲击模型（fluid percussion injury，FPI）是由摆锤打击液体容器的传感活塞，使容器里的生理盐水快速注入颅腔，对硬脑膜施加液体压力脉冲，导致脑组织变形和移位，从而造成挫伤、硬膜下血肿和出血、弥漫性皮质下神经元损伤等[67]。根据颅骨开窗位置不同，FPI模型又分为正中液压模型（midline fluid percussion injury，MFPI）和LFPI，MFPI诱导弥漫性TBI，LFPI则诱导同侧大脑半球的局灶性皮质损伤和对侧大脑半球的弥漫性损伤[68]。

Newell等[69]在造模前一天在幼年小鼠前囟和后囟之间、侧颅骨边缘和矢状缝之间区域进行开窗，并固定和封闭Luer-Lock接口，TBI造模时以1.1～1.3个大气压使摆锤角度在9.8°～11°之间变化，当小鼠进入深度麻醉后，释放钟摆，使生理盐水通过20英寸、直径3 mm的静脉内管从Luer-Lock接口处对小鼠硬脑膜

产生短暂的流体脉冲，造成局灶性组织损伤、弥漫性轴索损伤、神经炎症、神经功能缺陷和学习障碍等。高脂饮食饲养8周后的大鼠通过1.6个大气压或2.4个大气压在25 ms内冲击位于右侧颅骨距前囟4 mm、矢状缝3 mm的液压冲击装置模拟TBI后，大鼠神经功能损伤，出现脑梗死、大脑皮质神经元凋亡和神经炎症等[70]。秦娜等[71]以(3±0.2)个大气压峰值冲击压力通过大鼠冠状缝后5 mm、矢状缝左侧3 mm处的连接管对大鼠硬脑膜进行液压冲击，造模后大鼠出现明显脑挫裂伤、脑膜损伤、皮质神经元坏死和凋亡等混合性脑损伤病理特征。

LFPI模型表现出混合性TBI的标志性临床特征，可精确控制和测量压力大小，可重复性高，但由于其对重度TBI短暂性呼吸暂停症状的模拟，该模型死亡率较其他造模方法高。

4 小结

TBI的发生常常并非单一，而是多种损伤类型并存，现有的TBI动物模型可根据不同击打方式、损伤性质等模拟出人类TBI的受伤过程和病理改变，不同实验动物也在模拟TBI中拥有自己独特的优势，各TBI动物模型在TBI机制、病理变化、治疗干预等基础研究中广泛应用，但目前尚未存在国际公认的TBI造模方法。由于实验动物与人类之间存在物种差异，损伤后的变化并不一致，造模成功的标准、不同实验动物的物种和个体差异、造模仪器参数的调整等，也都使得TBI模型存在不能客观化、定量化、标准化的问题。因此，提高各造模方法的可重复性和稳定性是增加研究可靠性的方案之一。结合TBI临床症状、病理改变等使TBI模型的评价标准多元化、步骤标准规范化，制备出理想的与临床实际TBI机制及损伤分级类似的动物模型仍是未来需要努力的方向。

参考文献

[1] 李妍, 齐曼曼, 缴宝杰, 等. IL-18结合蛋白在创伤性颅脑损伤大鼠认知功能障碍中的作用及其机制[J]. 解放军医学杂志, 2023, 48: 776-783. DOI: 10.11855/j.issn.0577-7402.1618.2023.0103.
[2] 朱虹全, 鲁君, 周铱然, 等. RSNA2022中枢神经影像学[J]. 放射学实践, 2023, 38: 2-10. DOI: 10.13609/j.cnki.1000-0313.2023.01.001.
[3] Mateu NC. Traumatic brain injury in Denmark 2008-2012[J]. Scand J Public Health, 2020, 48: 331-337. DOI: 10.1177/1403494819852826.
[4] Vella MA, Crandall ML, Patel MB. Acute Management of Traumatic Brain Injury[J]. Surg Clin North Am, 2017, 97: 1015-1030. DOI: 10.1016/j.suc.2017.06.003.
[5] GBD 2016 Neurology Collaborators. Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016[J]. Lancet Neurol, 2019, 18: 459-480. DOI: 10.1016/S1474-4422(18)30499-X.
[6] Ma X, Aravind A, Pfister BJ, et al. Animal Models of Traumatic Brain Injury and Assessment of Injury Severity[J]. Mol Neurobiol, 2019, 56: 5332-5345.DOI: 10.1007/s12035-018-1454-5.
[7] Michinaga S, Koyama Y. Pathophysiological Responses and Roles of Astrocytes in Traumatic Brain Injury[J]. Int J Mol Sci, 2021, 22: 6418. DOI: 10.3390/ijms22126418.
[8] Zhou Y, Shao A, Yao Y, et al. Dual roles of astrocytes in plasticity and reconstruction after traumatic brain injury[J]. Cell Commun Signal, 2020, 18: 62. DOI: 10.1186/s12964-020-00549-2.
[9] Asehnoune K, Taccone FS, Singer M. High oxygen level in traumatic brain injury patients. Never ending story?[J]. Intensive Care Med, 2022, 48: 1772-1774. DOI: 10.1007/s00134-022-06903-x.
[10] Nardone R, Sebastianelli L, Versace V, et al. Repetitive transcranial magnetic stimulation in traumatic brain injury: Evidence from animal and human studies[J]. Brain Res Bull, 2020, 159: 44-52. DOI: 10.1016/j.brainresbull.2020.03.016.
[11] Tiefenbach J, Chan HH, Machado AG, et al. Neurostimulation for Functional Recovery After Traumatic Brain Injury: Current Evidence and Future Directions for Invasive Surgical Approaches[J]. Neurosurgery, 2022, 91: 823-830. DOI: 10.1227/neu.0000000000002134.
[12] Lu Y, Zhou X, Cheng J, et al. Early Intensified Rehabilitation Training with Hyperbaric Oxygen Therapy Improves Functional Disorders and Prognosis of Patients with Traumatic Brain Injury[J]. Adv Wound Care (New Rochelle), 2021, 10: 663-670. DOI: 10.1089/wound.2018.0876.
[13] Siponkoski ST, Martinez-Molina N, Kuusela L, et al. Music Therapy Enhances Executive Functions and Prefrontal Structural Neuroplasticity after Traumatic Brain Injury: Evidence from a Randomized Controlled Trial[J]. J Neurotrauma, 2020, 37: 618-634. DOI: 10.1089/neu.2019.6413.
[14] Ackermans NL, Varghese M, Wicinski B, et al. Unconventional animal models for traumatic brain injury and chronic traumatic encephalopathy[J]. J Neurosci Res, 2021, 99: 2463-2477. DOI: 10.1002/jnr.24920.
[15] Guo P, Jin Z, Wang J, et al. Irisin Rescues Blood-Brain Barrier Permeability following Traumatic Brain Injury and Contributes to the Neuroprotection of Exercise in Traumatic Brain Injury[J]. Oxid Med Cell Longev, 2021, 2021: 1118981. DOI: 10.1155/2021/1118981.
[16] Griffiths DR, Law LM, Young C, et al. Chronic Cognitive and

表2 TBI常见造模方法概述

模型名称	损伤性质	开窗与否	撞击部位	撞击物	主要损伤部位	优点	缺点
Feeney's落体打击模型	局灶性脑损伤	开窗	硬脑膜	重物	大脑皮质	可控性好，可重复性高，便宜	死亡率高、容易二次损伤
控制性皮质撞击模型	/	开窗	硬脑膜	刚性撞击头	大脑皮质	操作简单、稳定性强	损伤类型局限
爆炸冲击波创伤模型	弥漫性脑损伤	不开窗	身体/头部	爆炸波/气压波	轴索	转化程度高	受众人群局限，操作安全性较低
Marmarou落体打击模型	/	不开窗	颅骨表面的金属片	重物	轴索	可重复性好，可扩展	可控性较差，容易二次损伤
工程旋转加速度的闭头冲击模型	/	不开窗	头部下方的3D打印聚乳酸	金属活塞	轴索	稳定性高、转化程度较高	使用率较低，模型本身研究不足
液体冲击模型	混合型脑损伤	开窗	硬脑膜	生理盐水	大脑皮质与轴索	精确度、可重复性高	死亡率极高

Cerebrovascular Function after Mild Traumatic Brain Injury in Rats[J]. J Neurotrauma, 2022, 39: 1429-1441. DOI: 10.1089/neu.2022.0015.
[17] Wang H, Zhou XM, Wu LY, et al. Aucubin alleviates oxidative stress and inflammation via Nrf2-mediated signaling activity in experimental traumatic brain injury[J]. J Neuroinflammation, 2020, 17: 188. DOI: 10.1186/s12974-020-01863-9.
[18] Zhang XS, Lu Y, Li W, et al. Astaxanthin ameliorates oxidative stress and neuronal apoptosis via SIRT1/NRF2/Prx2/ASK1/p38 after traumatic brain injury in mice[J]. Br J Pharmacol, 2021, 178: 1114-1132. DOI: 10.1111/bph.15346.
[19] Krukowski K, Nolan A, Becker M, et al. Novel microglia-mediated mechanisms underlying synaptic loss and cognitive impairment after traumatic brain injury[J]. Brain Behav Immun, 2021, 98: 122-135. DOI: 10.1016/j.bbi.2021.08.210.
[20] Liu KL, Yu XJ, Sun TZ, et al. Effects of seawater immersion on open traumatic brain injury in rabbit model[J]. Brain Res, 2020, 1743: 146903. DOI: 10.1016/j.brainres.2020.146903.
[21] 潘晓飞, 曹鑫意, 张崇辉, 等. 控制减压技术影响兔重型颅脑损伤后NDRG2表达机制[J]. 安徽医科大学学报, 2021, 56: 1824-1828. DOI: 10.19405/j.cnki.issn1000-1492.2021.11.029
[22] Martinez-Gonzalez E, Garcia-Olmo D, Mayordomo-Aranda E, et al. Does hemofiltration protect the brain after head trauma? An experimental study in rabbits[J]. Intensive Care Med Exp, 2020, 8: 66. DOI: 10.1186/s40635-020-00357-5.
[23] Schwerin SC, Hutchinson EB, Radomski KL, et al. Establishing the ferret as a gyrencephalic animal model of traumatic brain injury: Optimization of controlled cortical impact procedures[J]. J Neurosci Methods, 2017, 285: 82-96. DOI: 10.1016/j.jneumeth.2017.05.010.
[24] Schwerin SC, Chatterjee M, Hutchinson EB, et al. Expression of GFAP and Tau Following Blast Exposure in the Cerebral Cortex of Ferrets [J]. J Neuropathol Exp Neurol, 2021, 80: 112-128. DOI: 10.1093/jnen/nlaa157.
[25] Hutchinson EB, Romero-Lozano A, Johnson HR, et al. Translationally Relevant Magnetic Resonance Imaging Markers in a Ferret Model of Closed Head Injury[J]. Front Neurosci, 2021, 15: 779533. DOI: 10.3389/fnins.2021.779533.
[26] Grovola MR, von Reyn C, Loane DJ, et al. Understanding microglial responses in large animal models of traumatic brain injury: an underutilized resource for preclinical and translational research[J]. J Neuroinflammation, 2023, 20: 67. DOI: 10.1186/s12974-023-02730-z.
[27] Wang J, Shi Y, Cao S, et al. Polynitroxylated PEGylated hemoglobin protects pig brain neocortical gray and white matter after traumatic brain injury and hemorrhagic shock[J]. Front Med Technol, 2023, 5: 1074643. DOI: 10.3389/fmedt.2023.1074643.
[28] Kinder HA, Baker EW, West FD. The pig as a preclinical traumatic brain injury model: current models, functional outcome measures, and translational detection strategies[J]. Neural Regen Res, 2019, 14: 413-424. DOI: 10.4103/1673-5374.245334.
[29] Murray SJ, Mitchell NL. The Translational Benefits of Sheep as Large Animal Models of Human Neurological Disorders[J]. Front Vet Sci, 2022, 9: 831838. DOI: 10.3389/fvets.2022.831838.
[30] Dixon B, Turner R, Christou C. Assessment of a Non-Invasive Brain Oximeter in a Sheep Model of Acute Brain Injury[J]. 2019, 12: 479-487. DOI: 10.2147/MDER.S235804.
[31] Townsend JM, Kiyotake EA, Easley J, et al. Comparison of a Thiolated Demineralized Bone Matrix Hydrogel to a Clinical Product Control for Regeneration of Large Sheep Cranial Defects[J]. Materialia (Oxf), 2023, 27: 101690. DOI: 10.1016/j.mtla.2023.101690.
[32] Converse MI, Monson KL. Biaxial softening of isolated cerebral arteries following axial overstretch[J]. J Mech Behav Biomed Mater, 2021, 118: 104447. DOI: 10.1016/j.jmbbm.2021.104447.
[33] Buhlman LM, Krishna G, Jones TB, et al. Drosophila as a model to explore secondary injury cascades after traumatic brain injury[J]. Biomed Pharmacother, 2021, 142: 112079. DOI: 10.1016/j.biopha.2021.112079.
[34] Blommer J, Fischer MC, Olszewski AR, et al. Ketogenic diet reduces early mortality following traumatic brain injury in Drosophila via the PPARgamma ortholog Eip75B[J]. PLoS One, 2021, 16: e0258873. DOI: 10.1371/journal.pone.0258873.
[35] Shah EJ, Huttemann M, Sanderson TH, et al. Inhibiting Mitochondrial Cytochrome c Oxidase Downregulates Gene Transcription After Traumatic Brain Injury in Drosophila[J]. Front Physiol, 2021,12: 628777. DOI: 10.3389/fphys.2021.628777.
[36] Tikhonova MA, Maslov NA, Bashirzade AA, et al. A Novel Laser-Based Zebrafish Model for Studying Traumatic Brain Injury and Its Molecular Targets[J]. Pharmaceutics, 2022, 14: 1751. DOI: 10.3390/pharmaceutics14081751.
[37] Zambusi A, Novoselc KT, Hutten S, et al. TDP-43 condensates and lipid droplets regulate the reactivity of microglia and regeneration after traumatic brain injury[J]. Nat Neurosci, 2022, 25: 1608-1625. DOI: 10.1038/s41593-022-01199-y.
[38] Li Z, Xiao J, Xu X, et al. M-CSF, IL-6, and TGF-beta promote generation of a new subset of tissue repair macrophage for traumatic brain injury recovery[J]. Sci Adv, 2021, 7: eabb6260. DOI: 10.1126/sciadv.abb6260.
[39] Chaoul V, Awad M, Harb F, et al. Saffron Extract Attenuates Anxiogenic Effect and Improves Cognitive Behavior in an Adult Zebrafish Model of Traumatic Brain Injury[J]. Int J Mol Sci, 2022, 23: 11600. DOI: 10.3390/ijms231911600.
[40] Navarrete C, Garcia-Martin A, Correa-Saez A, et al. A cannabidiol aminoquinone derivative activates the PP2A/B55alpha/HIF pathway and shows protective effects in a murine model of traumatic brain injury[J]. J Neuroinflammation, 2022, 19: 177. DOI: 10.1186/s12974-022-02540-9.
[41] 林树楷, 刘仲海, 刘珍, 等. m6A RNA甲基化修饰在颅脑损伤模型大鼠坏死性凋亡中的作用[J]. 中国组织工程研究, 2023, 27: 3167-3172. DOI: 10.12307/2023.187.
[42] 刘若尘, 吴涛, 王瑞辉, 等. 电针对创伤性颅脑损伤大鼠神经功能及损伤区脑组织p-JNK和Beclin-1表达的影响[J]. 针刺研究, 2023, 48: 475-480. DOI: 10.13702/j.1000-0607.20230089
[43] Zhao S, Wang S, Cao L, et al. Acupuncture promotes nerve repair through the benign regulation of mTOR-mediated neuronal autophagy in traumatic brain injury rats[J]. CNS Neurosci Ther, 2023, 29: 458-470. DOI: 10.1111/cns.14018.
[44] Qiu S, Jiang W, Alam MS, et al. Viscoelastic characterization of injured brain tissue after controlled cortical impact (CCI) using a mouse model[J]. J Neurosci Methods, 2020, 330: 108463. DOI: 10.1016/j.jneumeth.2019.108463.
[45] Ramirez S, Mukherjee A, Sepulveda S, et al. Modeling Traumatic Brain Injury in Human Cerebral Organoids[J]. Cells, 2021, 10: 2683. DOI: 10.3390/cells10102683.
[46] Wu N, Cheng CJ, Zhong JJ, et al. Essential role of MALAT1 in reducing traumatic brain injury[J]. Neural Regen Res, 2022, 17: 1776-1784. DOI: 10.4103/1673-5374.332156.
[47] Hegdekar N, Sarkar C, Bustos S, et al. Inhibition of autophagy in microglia and macrophages exacerbates innate immune responses and worsens brain injury outcomes[J]. Autophagy, 2023, 19: 2026-2044. DOI: 10.1080/15548627.2023.2167689.
[48] 朱海燕, 赵晓晶, 宋晶晶, 等. 紫草素通过抑制氧化应激和神经炎症在脑外伤后发挥神经保护作用[J]. 南京医科大学学报(自然科学版), 2022, 42: 1055-1064. DOI: 10.7655/NYDXBNS20220802.
[49] 罗飞, 张明辉, 陈立珂, 等. 迷迭香酸抑制NLRP3炎性小体的活化对创伤性颅脑损伤大鼠脑组织损伤和海马区神经元凋亡的影响[J]. 免疫学杂志, 2021, 37: 568-574. DOI: 10.13431/j.cnki.immunol.j.20210078.
[50] Siedhoff HR, Chen S, Song H, et al. Perspectives on Primary Blast Injury of the Brain: Translational Insights Into Non-inertial Low-Intensity Blast Injury[J]. Front Neurol, 2021, 12: 818169. DOI: 10.3389/fneur.2021.818169.
[51] Li Y, Lv W, Cheng G, et al. Effect of Early Normobaric Hyperoxia on Blast-Induced Traumatic Brain Injury in Rats[J]. Neurochem Res, 2020, 45: 2723-2731. DOI: 10.1007/s11064-020-03123-x.
[52] Clark AT, Abrahamson EE, Harper MM, et al. Chronic effects of blast injury on the microvasculature in a transgenic mouse model of Alzheimer's disease related Abeta amyloidosis[J]. Fluids Barriers CNS, 2022, 19: 5. DOI: 10.1186/s12987-021-00301-z.
[53] 栗志杰, 由小川, 柳占立, 等. 爆炸冲击波作用下颅脑损伤机理的数

（下转第542页）

electrophysiological biomarkers of diabetic neuropathy and painful diabetic neuropathy[J]. Clin Ther, 2021, 43: 1441-1456.
[12] Lefaucheur JP. Clinical neurophysiology of pain[J]. Handb Clin Neurol, 2019, 161: 121-148.
[13] Ünlütürk Z, Öztekin SNS, Alkan H, et al. Which scale is more useful to detect diabetic neuropathic pain?: a cross-sectional study[J]. BMC Endocr Disord, 2022, 22: 56.
[14] Vas P. Laser doppler imager flare (LDIflare) small fibre function[D]. Wolverhampton: University of Warwick, 2017.
[15] Sharma S, Vas P, Rayman G. Small fiber neuropathy in diabetes polyneuropathy: is it time to change[J]? J Diabetes Sci Technol, 2022, 16: 321-331.
[16] Bondugulapati LR, Narayen N. Corneal confocal microscopy: potential usage in the context of diabetes mellitus[J]. Practical Diabetes, 2021, 38: 20-22.
[17] Jin Y, Wang W, Chen W, et al. Corneal confocal microscopy: a useful tool for diagnosis of small fiber neuropathy in type 2 diabetes[J]. J Diabetes Investig, 2021, 12: 2183-2189.
[18] Kim SH, Park TS, Jin HY. Metformin preserves peripheral nerve damage with comparable effects to alpha lipoic acid in streptozotocin/high-fat diet induced diabetic rats[J]. Diabetes Metab J, 2020, 44: 842-853.
[19] Hagedorn JM, Engle AM, George TK, et al. An overview of painful diabetic peripheral neuropathy: diagnosis and treatment advancements[J]. Diabetes Res Clin Pract, 2022, 188: 109928.
[20] Alam U, Sloan G, Tesfaye S. Treating pain in diabetic neuropathy: current and developmental drugs[J]. Drugs, 2020, 80: 363-384.
[21] Tesfaye S, Sloan G, Petrie J, et al. Comparison of amitriptyline supplemented with pregabalin, pregabalin supplemented with amitriptyline, and duloxetine supplemented with pregabalin for the treatment of diabetic peripheral neuropathic pain (OPTION-DM): a multicentre, double-blind, randomised crossover trial[J]. Lancet, 2022, 400: 680-690.
[22] Putz Z, Tordai D, Hajdú N, et al. Vitamin D in the prevention and treatment of diabetic neuropathy[J]. Clin Ther, 2022, 44: 813-823.
[23] Alam U, Petropoulos IN, Ponirakis G, et al. Vitamin D deficiency is associated with painful diabetic neuropathy[J]. Diabetes/Metab Res Rev, 2021, 37: e3361.
[24] Qureshi Z, Ali MN, Khalid M. An insight into potential pharmacotherapeutic agents for painful diabetic neuropathy[J]. J Diabetes Res, 2022, 2022: 9989272.
[25] Hesselink JMK, Kopsky DJ. Topical phenytoin cream in small fiber neuropathic pain: fast onset of perceptible pain relief[J]. Int J Pain Relief, 2017, 1: 15-19.
[26] Lumpatki SB, Kavitha KV, Manohar MV, et al. Approach to painful diabetic peripheral neuropathy[J]. Chron Diabetes Res Pract, 2022, 1: 99-113.
[27] Liampas A, Rekatsina M, Vadalouca A, et al. Non-pharmacological management of painful peripheral neuropathies: a systematic review[J]. Adv Ther, 2020, 37: 4096-4106.
[28] 姜静雯, 黄淑玉, 廖世波, 等. 凝血功能与2型糖尿病周围神经病变的相关性研究[J]. 神经损伤与功能重建, 2022, 17: 791-793.

（本文编辑：雷琪）

（上接第538页）

值模拟研究[J]. 爆炸与冲击, 2020, 40: 100-111. DOI: 10.11883/bzycj-2018-0348
[54] Nonaka M, Taylor WW, Bukalo O, et al. Behavioral and Myelin-Related Abnormalities after Blast-Induced Mild Traumatic Brain Injury in Mice [J]. J Neurotrauma, 2021, 38: 1551-1571. DOI: 10.1089/neu.2020.7254.
[55] Murugan M, Ravula A, Gandhi A, et al. Chemokine signaling mediated monocyte infiltration affects anxiety-like behavior following blast injury[J]. Brain Behav Immun, 2020, 88: 340-352. DOI: 10.1016/j.bbi.2020.03.029.
[56] Marmarou A, Foda MA, van den Brink W, et al. A new model of diffuse brain injury in rats. Part I: Pathophysiology and biomechanics[J]. J Neurosurg, 1994, 80: 291-300. DOI: 10.3171/jns.1994.80.2.0291.
[57] Hentig J, Cloghessy K, Lahne M, et al. Zebrafish Blunt-Force TBI Induces Heterogenous Injury Pathologies That Mimic Human TBI and Responds with Sonic Hedgehog-Dependent Cell Proliferation across the Neuroaxis[J]. Biomedicines, 2021, 9: 861. DOI: 10.3390/biomedicines9080861.
[58] Amiresmaili S, Shahrokhi N, Khaksari M, et al. The Hepatoprotective mechanisms of 17beta-estradiol after traumatic brain injury in male rats: Classical and non-classical estrogen receptors[J]. Ecotoxicol Environ Saf, 2021, 213: 111987. DOI: 10.1016/j.ecoenv.2021.111987.
[59] Bagri K, Deshmukh R. Vinpocetine restores cognitive and motor functions in Traumatic brain injury challenged rats[J]. Inflammopharmacology, 2022, 30: 2243-2259. DOI: 10.1007/s10787-022-01059-y.
[60] Mu J, Wang T, Li M, et al. Ketogenic diet protects myelin and axons in diffuse axonal injury[J]. Nutr Neurosci, 2022, 25: 1534-1547. DOI: 10.1080/1028415X.2021.1875300.
[61] McNamara EH, Grillakis AA, Tucker LB, et al. The closed-head impact model of engineered rotational acceleration (CHIMERA) as an application for traumatic brain injury pre-clinical research: A status report [J]. Exp Neurol, 2020, 333: 113409. DOI: 10.1016/j.expneurol.2020.113409.
[62] Bashir A, Abebe ZA, McInnes KA, et al. Increased severity of the CHIMERA model induces acute vascular injury, sub-acute deficits in memory recall, and chronic white matter gliosis[J]. Exp Neurol, 2020, 324: 113116. DOI: 10.1016/j.expneurol.2019.113116.
[63] Button EB, Cheng WH, Barron C, et al. Development of a novel, sensitive translational immunoassay to detect plasma glial fibrillary acidic protein (GFAP) after murine traumatic brain injury[J]. Alzheimers Res Ther, 2021, 13: 58. DOI: 10.1186/s13195-021-00793-9.
[64] Desai A, Chen H, Kevala K, et al. Higher n-3 Polyunsaturated Fatty Acid Diet Improves Long-Term Neuropathological and Functional Outcome after Repeated Mild Traumatic Brain Injury[J]. J Neurotrauma, 2021, 38: 2622-2632. DOI: 10.1089/neu.2021.0096.
[65] McNamara EH, Knutsen A, Korotcov A, et al. Meningeal and Visual Pathway Magnetic Resonance Imaging Analysis after Single and Repetitive Closed-Head Impact Model of Engineered Rotational Acceleration (CHIMERA)-Induced Disruption in Male and Female Mice [J]. J Neurotrauma, 2022, 39: 784-799. DOI: 10.1089/neu.2021.0494.
[66] Tucker LB, Fu AH, McCabe JT. Hippocampal-Dependent Cognitive Dysfunction following Repeated Diffuse Rotational Brain Injury in Male and Female Mice[J]. J Neurotrauma, 2021, 38: 1585-1606. DOI: 10.1089/neu.2021.0025.
[67] Aleem M, Goswami N, Kumar M, et al. Low-pressure fluid percussion minimally adds to the sham craniectomy-induced neurobehavioral changes: Implication for experimental traumatic brain injury model[J]. Exp Neurol, 2020, 329: 113290. DOI: 10.1016/j.expneurol.2020.113290.
[68] Witcher KG, Dziabis JE, Bray CE, et al. Comparison between midline and lateral fluid percussion injury in mice reveals prolonged but divergent cortical neuroinflammation[J]. Brain Res, 2020, 1746: 146987. DOI: 10.1016/j.brainres.2020.146987.
[69] Newell EA, Todd BP, Luo Z, et al. A Mouse Model for Juvenile, Lateral Fluid Percussion Brain Injury Reveals Sex-Dependent Differences in Neuroinflammation and Functional Recovery[J]. J Neurotrauma, 2020, 37: 635-646. DOI: 10.1089/neu.2019.6675.
[70] Kuo JR, Lim SW, Zheng HX, et al. Triglyceride is a Good Biomarker of Increased Injury Severity on a High Fat Diet Rat After Traumatic Brain Injury[J]. Neurochem Res, 2020, 45: 1536-1550. DOI: 10.1007/s11064-020-03018-x.
[71] 秦娜, 黄林, 董瑞, 等. 虎杖苷减轻大鼠创伤性颅脑损伤后的肠损伤：基于激活Sirt1介导的SOD2和HMGB1去乙酰化抑制氧化应激和炎症反应[J]. 南方医科大学学报, 2022, 42: 93-100. DOI: 10.12122/j.issn.1673-4254.2022.01.11.

（本文编辑：王晶）