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谵妄动物模型和评价方法研究进展

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【摘要】 谵妄是以意识模糊、思维混乱和注意力集中困难为特征的急性脑功能障碍综合征,主要影响 ICU 和老年住院患者。其不仅治疗成本高昂,还可能导致严重并发症及死亡率增加。由于其病因复杂、病理机制不明,临床对谵妄的药物治疗很大程度是无效的。而构建动物模型是理解谵妄疾病机制、筛选新药和研究干预措施的有力工具。本文通过回顾国内外近年来谵妄动物模型相关的实验研究,从动物选择、模型构建方法、模型评价三个方面总结谵妄动物模型构建及评价方法的最新进展,为基于谵妄动物模型开展的实验研究提供参考。

【关键词】 谵妄;动物模型;评价方法;造模方法;研究进展
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Research progress in animal models of delirium and their evaluation methods

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【Abstract】 Delirium is an acute brain dysfunction syndrome characterized by confusion and difficulty concentrating, which mainly affects intensive care unit patients and elderly inpatients. Treatment is expensive and may also lead to increased risks of serious complications and death. The complex etiology and unknown pathological mechanisms of delirium mean that clinical drug treatment is largely ineffective. Animal models therefore provide a powerful tool to help understand the mechanism of delirium, screen new drugs, and study potential intervention measures. We review experimental research related to delirium animal models worldwide, and summarize the latest progress in the construction and evaluation of these models from the aspects of animal selection, model construction method , and model evaluation, to provide a reference for further experimental research based on delirium animal models.

【Keywords】 delirium; animal models; evaluation methods; modeling method; research progress
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谵妄是一种急性脑功能障碍综合征,表现为突然出现的意识模糊、思维混乱和注意力无法集中,是 ICU 和老年住院患者死亡的常见原因[1-3]。谵妄的发生与高龄、药物、感染、手术、麻醉及睡眠障碍等均密切相关,但迄今为止其具体的病理机制尚不清楚[4-5]。据统计,高达 50%的老年人和约 35%的 ICU 患者会受到谵妄的影响[6-7]。一旦发生谵妄,不仅治疗成本高昂、住院时间延长,还可能导致患者出现严重并发症、长期认知障碍、生活质量下降及发病率和死亡率增加[8-9]。此外,临床对谵妄的药物治疗在很大程度上是无效的,这表明对其病理生理学的了解不足[10]。因此,阐明导致谵妄的机制途径和确定合理的治疗干预靶点具有重要的临床价值。

构建动物模型对理解谵妄疾病机制、筛选新药和研究干预措施具有重要意义。本文通过总结近年来关于谵妄动物实验模型的构建及评价方法,旨在为谵妄发病机制研究的基础科研实验提供有价值的参考。

1 实验动物选择

1.1 啮齿类动物

目前,谵妄动物模型主要以啮齿类动物为主。因其遗传信息、免疫系统及认知能力均与人类相似且成本较低[11-12]。常用物种包括 C57BL/6 小鼠、SD 大鼠、Wistar 大鼠和 Fischer-344 大鼠。其中 C57BL/6 小鼠因遗传背景稳定、学习与记忆能力强且基因易于操控性使其成为该领域的首选模型动物。且维护成本较大鼠低,进一步增加了其在谵妄研究中的普及性[13-14]。而相较于小鼠,大鼠的认知功能和脑部结构更加复杂,体型较大,使它们更适合于需要复杂神经结构研究或进行手术模拟谵妄的实验[15]。其中,SD 大鼠突出特点是性格温顺,行为表现稳定,Wistar 被证明具有较高焦虑水平,而 Fischer-344 大鼠成长较快,寿命短[16-18]。此外,啮齿类动物的年龄也是构建谵妄模型时的一个重要考虑因素。鉴于高龄是谵妄最显著的风险因素之一,许多研究使用老年小鼠或大鼠来模拟并研究谵妄[11]。

1.2 斑马鱼

最近有研究表明,斑马鱼可能成为谵妄研究领域的新模式生物[19]。斑马鱼除具有与人类高度相似的遗传和生理同源性外,在各类行为学测试中也表现出稳定的行为特征,且对多种谵妄风险药物具有较高的敏感性,因此在筛选谵妄相关药物研究中具有重要潜力。野生型(wild type, WT)斑马鱼较常用于神经行为科学研究,并已被应用于谵妄动物模型中。实验室常用的 WT 型斑马鱼可细分为多个品系,包括 AB 斑马鱼、Tübingen long(TL)斑马鱼和 wild indian karyotype(WIK)斑马鱼。其中,AB 斑马鱼遗传背景稳定,在多个行为学参数上显示出高度一致性,使其成为可靠的行为学研究模型,为许多实验的首选品系[20]。TL 斑马鱼在行为测试中展现出与 AB 斑马鱼相似的重复性和稳定性,同时,它们显示出较强的群体凝聚力和探索行为,故成为研究社交和探索性行为的理想选择[21]。WIK 斑马鱼则在特定的行为测试,如新型水箱测试中,表现出较高的焦虑水平,使其研究与焦虑相关的行为测试研究时更有价值[22]。

2 谵妄动物实验模型

2.1 啮齿类动物实验模型

2.1.1 药物诱导模型

药源性谵妄是临床常见现象,具有谵妄风险的药物类型包括抗胆碱能类、苯二氮䓬类及阿片类等[23-24],其中抗胆碱能类药物已被证实是谵妄的高风险药物[25]。同样在啮齿类动物模型研究中,腹腔注射东莨菪碱(Scopolamine, Scop)或阿托品是建立此类模型最常用的方法。以下是对几种利用谵妄风险药物构建动物模型的介绍和总结。

(1)抗胆碱能类药物,中枢胆碱能系统参与调节人与动物的记忆、注意力及认知功能[26]。Scop 和阿托品是非选择性 M 型胆碱能受体拮抗剂,可通过拮抗神经递质乙酰胆碱受体损害记忆性能[27]。在临床研究中,出现谵妄的患者血清中抗胆碱能药物水平较高,而认知功能保持完整的患者血清中水平较低,这表明其可能是谵妄的致病因子[28]。在啮齿类动物模型中腹腔注射 Scop 可使记忆、认知功能受损及焦虑增加,引发多动型谵妄样表型[29]。有研究显示,中等剂量的 Scop(3.0 mg/kg)能在 30 min 内导致大脑默认模式网络(default mode network, DMN)功能连接中断,表现出谵妄样特征[30-31]。其他实验则采用了 1.8 mg/kg 或 2.0 mg/kg 剂量,或一次性腹腔注射高剂量(15 mg/kg)的 Scop 来构建啮齿类动物谵妄模型[29,32-35]。阿托品在构建谵妄动物模型中也显示出与 Scop 相似的效果,会损害刺

激敏感性、感觉辨别能力、视觉及行为模式,并诱发谵妄样状态[36-39]。最近将阿托品纳入谵妄动物模型的报告显示,静脉注射较高剂量阿托品(范围为 13.5 ~ 55 mg/kg)可引起大鼠的谵妄样症状,其中 13.5 mg/kg 或 27.5 mg/kg 的剂量似乎是更合理的选择[40-41]。

(2)苯二氮䓬类药物,属于 γ-氨基丁酸(gamma aminobutyric acid, GABA)受体激动剂。GABA 是中枢神经系统(central nervous system, CNS)内主要的抑制性神经递质,该类药物可通过影响 GABA 对 CNS 产生抑制作用。临床上苯二氮䓬类药物主要用于治疗惊恐障碍和广泛性焦虑障碍,但连续输注会增加危重成人谵妄的风险[42-43]。其机制可能与睡眠中断导致昼夜节律紊乱相关[44-45]。在动物模型中,腹腔注射 10 mg/kg 咪达唑仑可致小鼠出现认知障碍、活动降低及严重记忆缺陷的谵妄样表型[46-48]。

(3)阿片类药物,可通过降低乙酰胆碱及增加多巴胺和谷氨酸活性引起患者谵妄[49]。氯胺酮作为一种 N-甲基-D-天门冬胺酸(N-methyl-d-aspartate, NMDA)受体拮抗剂,属于阿片类麻醉剂。以往研究证实麻醉与手术可导致小鼠出现时间依赖性和年龄依赖性的谵妄,但麻醉剂本身对小鼠谵妄样行为的影响尚未评估[50]。REN 等[51]使用氯胺酮(ketamine, KET)构建谵妄动物模型。结果表明单次静脉注射 40 mg/kg KET 诱导了小鼠的谵妄样状态,其机制可能与干扰细胞内 TAU 蛋白的运输有关,为理解阿片类药物引起的谵妄提供了新的生物学机制。通过对这些药物诱发的动物谵妄模型的研究,可以深入理解药源性谵妄的发病机制,并为开发有效的预防和治疗策略提供科学依据。

2.1.2　麻醉/手术模型

麻醉和手术是术后谵妄(postoperative delirium, POD)的风险因素。目前为止 POD 的确切发病机制仍不清楚,但通过模拟人类 POD 的动物实验为此提供了重要见解。以下是目前用于建立啮齿类动物 POD 模型的方法概述:

(1)腹部手术,异氟醚麻醉下的剖腹术是建立 POD 模型的成熟方法。作从剑突至耻骨联合近端切口并穿透腹膜腔,将小肠从腹腔外移,轻柔摩擦小肠 0.5 ~ 1.5 min 后再放回腹腔,缝合切口,即可完剖腹手术[52-56]。也可三次循环夹闭肠系膜上动脉(superior mesenteric artery, SAM)10 min 或夹闭 SAM 20 min 基础上联合剖腹术来构建 POD 模型[34,57]。

(2)胫骨骨折术,是另一种建立此类模型常用术式之一。将小鼠左/右后肢内侧皮肤切开,暴露中上段胫骨并折断胫骨中段,将无菌钢针插入胫骨髓腔至胫骨平台水平即可完成[58-61]。

(3)心脏手术,由于 POD 是心脏大手术后普遍并发症[62]。故 JIA 等[63]将小鼠 4 ~ 5 肋间侧切,暴露左心室,结扎左前降支 45 min 后松解,为其进行心肌缺血再灌注手术,成功构建了心脏术后 POD 模型。

(4)导尿术,有报道称住院患者使用留置导尿管与发生谵妄之间存在显著关联[64]。为此,JIANG 等[65]进行了深入研究。他们通过为小鼠施行导尿术(urinary catheterization, UC)并将导尿管留置 24 h,结果发现 UC 可通过降低脑葡萄糖和能量,导致小鼠出现类似谵妄的行为。

(5)足部切口术,术后疼痛与患者发生谵妄有关[66]。使用刀片穿透足底皮肤和筋膜,从足跟近端 2 mm 处向脚趾方向做 0.5 ~ 0.8 cm 的纵向切口,分离肌肉,抬高跖肌腱并在其上做约 0.2 cm 的纵行切口,成功建立因足切口疼痛引起的 POD 小鼠模型[67]。

(6)胸部创伤术,当身体发生严重创伤后,谵妄发生率可高达 59%[68]。通过使用可以压缩空气的冲击波发生器,将其喷嘴指向动物的胸部后打开高速阀门,对小鼠形成以胸部为中心的单次爆炸波,可建立外周创伤后谵妄动物模型[69]。

综上所述,这些研究共同揭示了麻醉下不同类型的手术操作对小鼠注意力、认知功能和行为的影响,为术后谵妄的机制研究提供了有价值的实验模型

2.1.3　感染诱导模型

外周炎症是谵妄公认诱因,但尚未明确了解它扰乱大脑功能的确切机制。谵妄感染诱导模型即通过在小鼠或大鼠体内注射特定的感染诱导剂来模拟。其中腹腔注射脂多糖(lipopolysaccharide, LPS)是最常用的方式。在构建谵妄动物模型实验中,LPS 常用剂量范围为 0.05 ~ 0.33 mg/kg,这种低剂量 LPS 可诱导啮齿动物出现谵妄样的可逆性疾病行为[11,29,70-74]。也有研究将 LPS 剂量调整至 5 mg/kg[75]。另有研究使用微生物盲肠浆液(cecal slurry, CS)作为感染诱导剂,以 1.5 mg/g 的剂量注

射入小鼠腹腔,导致小鼠产生脓毒症,而引发谵妄样行为[76]。此外,RASHID 等[77]为雌性 C57BL/6 小鼠尿道接种了大肠杆菌而导致其出现了谵妄样行为,这进一步扩展了谵妄感染诱导模型的应用范围。总的来说,这些研究为探索外周炎症与谵妄之间的联系及其对大脑功能的影响提供了重要的实验模型。

2.1.4 昼夜节律干扰模型

昼夜节律紊乱与患者发生谵妄之间存在明显的关联,可能与睡眠-唤醒周期混乱、褪黑激素和皮质醇节律失调以及时钟基因表达改变相关[78-80]。CHEN 等[81]进行了研究,他们使用两种不同方法干扰小鼠昼夜节律。第一种方法是每 2 d 将光照时间提前 8 h 并持续 10 d 建立时差小鼠,结果显示小鼠在新物体识别试验(novel object recognition test, NORT)和 Y 迷宫自发交替试验(Y-maze spontaneous alternation test, YMT)中表现出谵妄的表型。第二种是对小鼠持续 14 d 光照,结果恒定照明同样导致了海马依赖性认知能力受损的谵妄样特征。又通过使用 Per2 缺失小鼠(昼夜节律紊乱的遗传模型)进一步证实昼夜节律与谵妄之间的密切联系。这些实验结果表明,干扰啮齿类动物昼夜节律会增加其对认知障碍的易感性,可能是一种构建谵妄模型的有效方法。

2.1.5 多因素模型

谵妄的形成不是由单一因素直接导致,而是多个因素综合作用的结果。这些因素包括但不限于老龄化、手术干预、药物使用以及环境变化。因此,一个包含多种风险因素的综合模型才能更准确地模拟人类的谵妄状态。ILLENDULA 等[82]的研究为此提供了重要的实证支持。他们将老年小鼠麻醉,为其进行腹部手术(包括轻轻揉搓左右降结肠、横结肠、肝、脾 5 min,再将腹腔内容物暴露于空气中 10 min)。术后又将小鼠置于模拟了 ICU 灯光及噪音的环境中 12 h。即在高龄、麻醉、手术及 ICU 环境的多因素背景下模拟谵妄。研究数据显示,该背景下小鼠的行为改变与临床上观察到的人类谵妄状态具有高度一致性。该模型与之前提到的诸多单一促发因素模型相比,更符合谵妄发生发展机制,有助于揭示谵妄的复杂病因,并为临床提供更加精准的治疗方案。

2.2 斑马鱼动物实验模型

斑马鱼对多种谵妄风险药物都高度敏感,包括东莨菪碱、阿托品、氯胺酮等[83-84]。尤其斑马鱼大脑显示相对较高数量的乙酰胆碱受体,可结合 M 型受体拮抗剂[85]。其 M 受体的结合特性与哺乳动物相似,表明斑马鱼是评估胆碱能行为调节和筛选谵妄相关药物潜在有用的模式生物。与啮齿类动物模型一样,抗胆碱能药物对记忆的损害作用也已在斑马鱼中得到证实[86]。VOLGIN 等[87]以斑马鱼为实验动物研究对比了东莨菪碱和阿托品对其行为的影响。该研究将不同浓度阿托品和东莨菪碱分别溶解于 500 mL 烧杯中,将斑马鱼转移至含药烧杯为其喂食药物。通过行为测试结果发现 90 mg/L 的阿托品和 120 mg/L 东莨菪碱对斑马鱼的行为影响部分重叠胆碱能药物引发的谵妄样效应(如临床谵妄表现出的躁动、焦虑和易怒)。虽然该研究未在斑马鱼身上全面捕捉到谵妄所有关键特征,但通过首次比较两种谵妄高风险药物对成年斑马鱼行为的影响,揭示了斑马鱼在谵妄研究领域的价值,也指出谵妄研究领域需要进一步跨物种实验来深化理解。

根据实验动物不同,谵妄动物模型主要分为啮齿类模型与斑马鱼模型。其中,啮齿类动物模型构建方法较为成熟,包括药物诱导、麻醉/手术诱导、感染诱导、昼夜节律干扰诱导及结合多种因素诱导。斑马鱼是近几年谵妄研究领域的新模式生物,主要通过抗胆碱能药物诱导谵妄。本文对以上每种模型的具体诱导方法及优缺点进行了总结,详见表 1。

3 谵妄动物模型评价

在动物模型中,诊断谵妄主要依赖于行为学方法,即基于对动物行为的观察来判断其是否展现出类似人类谵妄状态的特征。该诊断模式在本质上与临床判定患者谵妄的混乱评估方法(confusion assessment method, CAM)具有类似性[88]。CAM 核心包含四个临床特征:(1)急性和波动性变化;(2)注意力障碍;(3)思维紊乱;(4)意识水平的变化[89]。在临床上,当特征 1 与特征 2 同时阳性的基础上发生了特征 3 或 4 即可诊断为谵妄[90]。

3.1 啮齿类动物模型评价

在啮齿类动物模型中,CAM 原则同样适用。依据 CAM 诊断的内容:(1)急性和波动性,指与基线状态相比受到促发因素影响后行为变化的突发性以及病程严重程度的波动性,在动物模型中,可通

表 1　谵妄动物模型构建方法及优劣势分析

Table 1　Advantage and disadvantage analysis and reliability evaluation of common rodent models of delirium

实验动物 Animals	模型种类 Types	建模方法 Construction	优点 Advantage	缺点 Disadvantage	应用 Application
啮齿类动物（小鼠或大鼠） Rodents (Mice or rats)	药物诱导模型 Drug-induced model	（1）腹腔注射东莨菪碱[29, 30, 32-34]； （2）静脉注射阿托品[40-41]； （3）腹腔注射咪达唑仑[46]； （4）腹腔注射氯胺酮[51] (1) Intraperitoneal injection of scopolamine[29, 30, 32-34]； (2) Intravenous injection atropine[40-41]； (3) Intraperitoneal injection of midazolam[46]； (4) Intraperitoneal injection of ketamine[51]	（1）操作简便； （2）成模时间短； （3）可重复性高，可控性好 (1) Easy operation； (2) Short molding time； (3) High repeatability and good controllability	药物副作用或许对实验有影响 Drug side effects may have played a role in the experiment	（1）抗谵妄药物研究、东莨菪碱参与谵妄发病机制的研究； （2）抗谵妄药物研究； （3）麻醉剂诱发神经毒性机制相关研究 (1) Resist delirium drug research, scopolamine to participate in the study to the pathogenesis of delirium (2) Anti-delirium drug studies (3) Related studies on the mechanism of anesthesia-induced neurotoxicity
	麻醉/手术模型 Anesthesia/surgical model	（1）麻醉/腹部手术[34, 52-57]； （2）麻醉/胫骨骨折术[58-60]； （3）麻醉/心脏手术[63]； （4）麻醉/导尿术[65]； （5）麻醉/足部切口术[67]； （6）麻醉/胸部创伤术[69] (1) Anesthesia/abdominal surgery[34, 52-57]； (2) Anesthesia/tibial fracture surgery[58-60]； (3) Anesthesia/myocardial ischemia-reperfusion (IR) surgery[63]； (4) Anesthesia/urinary catheterization[65]； (5) Anesthesia/foot incisional pain surgery[67]； (6) Anesthesia/Thoracic trauma[69]	（1）与术后谵妄临床相关性高； （2）模拟了谵妄多因素的病理生理机制 (1) High clinical correlation with postoperative delirium； (2) Multi-factor pathophysiological mechanism of delirium was simulated	（1）可变性大，手术操作的的复杂性可能导致时间结果之间的差异； （2）技术要求高； （3）动物死亡率较高 (1) Large variability, the complexity of the surgical procedure may lead to differences between the time results.； (2) High technical requirements； (3) High animal mortality	POD 发病机制研究、POD 潜在干预靶点及治疗药物开发相关研究 mechanism of POD, POD potential targets for intervention and treatment of drug development related research
	感染诱导模型 Infection induced model	（1）腹腔注射脂多糖[29, 70-75]； （2）腹腔注射盲肠浆液[76]； （3）尿道接种大肠杆菌[77] (1) LPS was injected intraperitoneally[29, 70-75]； (2) CS was injected intraperitoneally[76]； (3) Urethra was inoculated with *Escherichia coli*[77]	（1）主针对炎症与谵妄之间的联系进行研究； （2）操作简便 (1) To study the relationship between inflammation and delirium.； (2) Easy to operate	（1）不同动物对炎症的反应可能不一致，影响结果的一致性； （2）炎症反应严重程度难以精确控制 (1) Different animals may have different responses to inflammation, which may affect the consistency of the results.； (2) Severity of inflammatory response is difficult to precisely control	抗谵妄药物研究、系统性炎症与神经炎症参与谵妄发病相关研究 Delirium drug resistance research, systemic inflammation, and nerve inflammation involved in the onset of delirium related research

续表 1

实验动物 Animals	模型种类 Types	建模方法 Construction	优点 Advantage	缺点 Disadvantage	应用 Application
啮齿类动物（小鼠或大鼠）Rodents (Mice or rats)	昼夜节律干扰模型 Circadian rhythm disturbance model	延长光照时间 10 d/持续光照 14 d [81] Extended light duration for 10 days/continuous light duration for 14 days [81]	(1) 实验条件易于控制；(2) 无需药物或手术，减少了动物的痛苦 (1) Experimental condition is easy to control; (2) There is no need for drugs or surgery, and the suffering of animals is reduced	实验周期较长 Experimental period was long	谵妄潜在干预靶点研究 Delirium non-drug therapy targets for research
	多因素模型 Multivariate model	麻醉、手术、ICU 环境联合模拟 [82] Anesthesia, surgery, and ICU environment simulation [82]	(1) 更好地模拟了谵妄的多因素本质；(2) 结合多种诱导因素，提高了模型临床适用性 (1) Better simulate the multi-factor nature of delirium; (2) Combined with a variety of inducing factors, the clinical applicability of the model is improved	(1) 实验设计复杂；(2) 多因素作用导致数据解释困难 (1) Experimental design was complicated; (2) Multiple factors lead to difficulties in data interpretation	谵妄多因素模型开发、突触功能障碍参与 POD 发病机制相关研究 Synaptic dysfunction in delirium multi-factor model development, POD pathogenesis related research
斑马鱼 Zebrafish	抗胆碱能药物诱导模型 Anticholinergic drug induction model	喂食东莨菪碱和阿托品 [87] Scopolamine and atropine were fed [87]	(1) 研究成本低；(2) 操作简便、成模时间短 (1) Research the cost is low; (2) Simple operation, short ChengMo time	斑马鱼行为评估方法不如啮齿类动物成熟和多样化 Zebrafish behavioral assessment methods are less mature and diverse than those of rodents	开发与评估谵妄跨物种模型 Development and evaluation of delirium across species model

过短时间内重复评估谵妄诱导前后的行为变化来捕捉[50,82]。(2)注意力障碍，主要指注意力不集中。谵妄动物模型研究中常用测定注意力的行为实验包括五项选择连续反应时间任务(5-choice serial reaction time task, 5-CSRTT)、注意力集转移任务(attentional set-shifting task, AST)、埋藏食物试验(buried food test, BFT)以及可以反映注意力的实验如震惊反射前脉冲抑制(pre-pulse inhibition of acoustic startle response, PPI)、YMT、旷场试验(open-field test, OFT)及新物体识别试验(novel object recognition test, NORT)。(3)思维紊乱，指思维无组织性、逻辑性及连贯性。可通过 BFT 检测。(4)意识水平的变化，指出现警惕性(高警觉性，对环境敏感、不安)、嗜睡、昏睡甚至昏迷。可在高架迷宫试验(elevated plus maze test, EPM)、OFT 及 NORT 中判断模型动物的意识水平的变化。对于人类谵妄的核心特征，目前没有单一测试能完全评估，故评估模型动物是否出现谵妄样行为时，需要采用一系列的行为测试，具体见表 2。

此外免疫学方法(包括蛋白质印迹法、实时荧光定量 PCR、酶联免疫吸附试验与免疫组化)、神经病理学检测(包括神经元标记、突触密度测量等)及脑电图(electroencephalogram, EEG)等技术也被用于啮齿类动物谵妄模型研究。这些方法主要目的是检测模型动物的谵妄潜在生物标志物，使行为学检测具有更强的表面效度。同时有助于理解特定生物标记物与谵妄之间的关联，过渡到识别与谵妄相关的因果机制，从而阐明人类谵妄的神经生理学和病理学机制。

3.2 斑马鱼动物模型评价

斑马鱼是谵妄研究领域一种潜在有效的生物模型，但目前应用尚属有限[19]。依据 VOLGIN 等[87]的研究，通过新型水箱测试(novel tank test, NTT)、明暗测试(light-dark test , LDT)及聚群测试(shoaling test, SLT)可评估斑马鱼类似于谵妄的焦虑样行为特征。上述啮齿类谵妄动物模型与斑马鱼谵妄动物模型中常用行为学评价方法，以及每种行为学方法的评价指标、优点及缺点详见表 2。

4 总结与展望

目前，谵妄动物模型主要聚焦于啮齿类动物。在对模型构建方法进行综合分析后，可以明显看

表 2　常见谵妄动物模型行为学评价方法

Table 2　Behavioral evaluation methods for common delirium animal models

简介 Introduction	实验装置 Device	评价指标 Evaluation	优点 Advantage	缺点 Disadvantage	应用 Application
五项选择连续反应时间任务[60, 91-92] 5-Choice serial reaction time task[60, 91-92]	内有 5 个照明孔和一个食物托盘的密闭暗舱 An airtight dark chamber with five lighting holes and a food tray	正确反应、准确率、遗漏百分比 Correct responses、accuracy rate、omission rate	(1)可对多认知领域测试； (2)任务难度灵活性较高； (3)对药物干预的反应敏感 (1)For more cognitive flexibility test; (2) Difficulty of the task is higher; (3) Sensitive to drug intervention	(1)训练周期长； (2)数据解释复杂，需要考虑多种行为参数； (3)需要专门的设备和软件 (1) Long training period; (2) Data to explain complex, need to consider a variety of parameters; (3) Need special equipment and software	评价持续性注意力 Evaluating sustained attention
注意力集转移任务[71, 82, 93-94] Attentional set-shifting task[71, 82, 93-94]	分为等候区和测试区的双腔室密闭立方体箱子 Two-chamber closed cube boxes divided into waiting and testing areas	挖掘次数、错误次数、错误率 Burrowing times, error number, error rate	(1)侧重于评估认知灵活性； (2)可对多认知领域测试 (1) Focus on assessing cognitive flexibility; (2) More cognitive field testing	(1)训练周期长； (2)测试过程耗时长； (3)数据解释复杂，需要考虑多种行为参数 (1) Long training period; (2) Time-consuming testing process ; (3) Complex data interpretation, which requires multiple behavioral parameters to be considered	评价持续性注意力和认知灵活性 Sustained attention and cognitive flexibility were evaluated
埋藏食物测试[52, 55, 57, 75] Buried food test[52, 55, 57, 75]	装有垫料和食物的饲养笼 A feeding cage with bedding and food	进食潜伏期 Latency of eating the food	(1)直观、快速且成本较低； (2)无需复杂设备 (1) Direct, quick and lower cost,; (2) Without complex equipment	(1)受动物饥饿状态和食物偏好的影响； (2)结果可能不够稳定，需要多次测试以确认 (1) It is affected by the hunger state and food preference of animals; (2) Results may not be stable enough to be confirmed by multiple testing	评价持续性注意力和有序思维 Sustained attention and ordered thinking were evaluated
Y 迷宫自发交替试验[51, 52, 58, 95] Y-maze spontaneous alternation test[51, 52, 58, 95]	臂间角度为 120° 呈“Y”字形的迷路箱 Labyrinth box with an interarm angle of 120° in a “Y” shape	进入新臂次数、在新臂停留时间 Entries to novel arm, time spent in novel arm	(1)无需训练； (2)操作简单，可在短时间内完成测试，快速评估空间工作记忆 (1) No training; (2) Operation is simple, it can be finished in a short time test, rapid assessment of spatial working memory	受动物活动性和探索倾向影响 It is affected by animal activity and exploration tendency	评价空间学习记忆能力和选择性注意力 Evaluation of spatial learning and memory ability and selective attention
震惊反射前脉冲抑制[76, 96] Pre-pulse inhibition of acoustic startle response[76, 96]	内设震惊反射检测装置、噪音喇叭的密闭隔音箱 Internal shock reflection detection device, noise, the speaker airtight soundproof box	前脉冲抑制率 Epulse suppression rate	(1)具有较好的重复性和可靠性； (2)操作简单、反应直观 (1) It has good repeatability and reliability; (2) Operation is simple and the reaction is intuitive	(1)设备成本较高； (2)数据解释复杂 (1) High equipment cost ; (2) Complex data interpretation	评价反应能力和选择性注意力 Evaluation reflect the ability and selective attention
新物体识别测试[34, 63, 97] Novel object recognition test[34, 63, 97]	内有两个类似小物体的立方体箱子 There were two small objects like cube box	对新旧物体的探索时间和次数 Time and times for new and old objects	(1)操作简便、成本低廉； (2)实验周期短 (1) Simple operation and low cost; (2) Short experiment period	实验结果可能受到动物探索性和新奇刺激吸引力的影响 Results may have been influenced by the attractiveness of the exploratory and novel stimuli of the animals	评价记忆力和选择性注意力 Memory and selective attention were evaluated

续表 2

简介 Introduction	实验装置 Device	评价指标 Evaluation	优点 Advantage	缺点 Disadvantage	应用 Application
旷场测试[82, 98-99] Open-field test[82, 98-99]	露天立方体箱子 Open-air cube box	运动总距离、进入中央区潜伏期、中央区停留时间 Total distance moved, freezing time, time spent in the center	原理、操作与数据处理简单,廉价,实验效果较好 Simple principle, operation and data processing are, cheap, better outcomes	(1)评估指标单一; (2)主要用于评估行为与活动能力和焦虑情况 (1)Single evaluation index; (2)Mainly used to evaluate behavior and activity ability and anxiety.	评价行为活动能力、焦虑状态和选择性注意力 Behavioral activity, anxiety state, and selective attention were evaluated
高架迷宫测试[34, 55, 100] Elevated plus maze test[34, 55, 100]	距地面 50 cm 高的十字迷路箱 A cross labyrinth box 50 cm above the ground	进入开放臂和封闭臂的次数、开放臂探头次数、开闭臂停留时间 Entering times of open arm, Probe head times of open arm, time spent in the open arm and close arm	(1)测试操作简单,可在短时间内完成; (2)基于动物的自然探索行为和对开放空间的本能性避让,因此能较好反映动物的焦虑状态 (1)To test the operation is simple, it can be finished in a short period of time; (2)Based on the natural exploration behavior of animals and the instinctive avoidance of open space, it can better reflect the anxiety state of animals	实验结果可能受动物运动能力和平衡感影响 Results may be influenced by the motor ability and balance of the animals	评价焦虑状态 Evaluating anxiety
新型水箱测试[87, 101-103] Novel tank test[87, 101-103]	外侧用水平虚线标记的矩形玻璃水箱 Rectangular glass tanks marked with horizontal dashed lines on the outside	进入顶部的次数、在顶部花费的时间、进入顶部的潜伏期 Number of top entries, time spent in top , the latency to enter the top	操作简单,无需复杂设备 Operation is simple and no complex equipment is needed	行为评估能力有限,主要关注焦虑行为 Behavior assessment ability is limited, mainly focus on anxious behavior	评价行为活动能力和焦虑状态 Behavioral activity and anxiety were evaluated
明暗箱测试[104-105] Light-dark test[104-105]	左右两侧用白色和黑色覆盖的矩形玻璃水箱 Rectangular glass tanks covered with white and black on the left and right sides	明箱停留时间、从暗箱进入明箱次数及停留时间 Time spent in the light side , the number of entries to the light and the presence of freezing	(1)操作简单; (2)基于斑马鱼对光照的自然偏好,主要用于评估焦虑与应激 (1)Easy to operate ; (2)Based on the zebrafish's natural preference for light, it is mainly used to assess anxiety and stress	结果可能受环境因素影响 Results may be affected by environmental factors	评价焦虑状态 Evaluation state of anxiety
聚群测试[106-107] Shoaling test[106-107]	矩形玻璃水箱 Rectangular glass tank	平均鱼间距离 An average inter-fish distance	适用性广,可评估多种因素对社交行为的影响 It has wide applicability and can evaluate the influence of various factors on social behavior	(1)空间需求大; (2)需要一定数量的斑马鱼; (3)数据分析复杂 (1)Large space requirements ; (2)A certain number of zebrafish is required ; (3)Omplex data analysis	评价焦虑状态 Evaluation State of anxiety

出,这些模型大多都使用了一个框架,即一个诱发因素(主要为老年小鼠或大鼠)和或叠加一个促发因素(包括药物、麻醉和手术等)以模拟急性事件触发的人类谵妄现象。其中腹腔注射东莨菪碱、LPS 以及麻醉下的腹部手术是目前构建谵妄动物模型较为成熟的方法[88]。这些模型在一定程度上复制

了谵妄的关键特征,如注意力缺陷、思维紊乱、认知功能障碍及睡眠-觉醒周期的改变。并通过免疫学方法、神经病理学检查及电生理学评估揭示了其与炎症反应、氧化应激和神经递质失衡密切相关的潜在病理机制。

尽管取得了一定进展,但当前谵妄动物模型仍面临诸多挑战和限制。首先,谵妄的临床表现高度异质,而现有模型大多只通过单一致病因素诱导谵妄并且只能模拟其中的部分特征,难以全面反映疾病的复杂性。此外,大多数模型侧重于老年动物,对于其他风险因素(如合并症)导致的谵妄,模型的建立和验证仍相对缺乏。再者,动物行为学评估方法的客观性和标准化亟待提高,以更准确地反映谵妄的临床现象。

针对现有谵妄动物模型的局限,未来的研究需要从以下 4 个方向进行突破和创新:(1)多因素模型:鉴于谵妄病因复杂多样,未来其模型构建应更加注重多因素模型的应用,从而更准确地反映谵妄的复杂病理过程并提高研究的真实性和临床相关性;(2)跨种属模型:除了传统的啮齿动物模型外,应更多向斑马鱼及其他领域迈进,为模拟人类谵妄提供更加准确的平台;(3)高精度行为评估技术:运用计算机视觉、机器学习等先进技术,开发更加客观、精确的行为学评估工具,以提高模型的评价效率和可靠性;(4)机制与治疗并行研究:在深入揭示谵妄复杂机制的同时,积极探索基于模型的预防和干预策略,加速从基础研究向临床应用的转化。

总之,尽管面临挑战,但通过持续的努力和创新,谵妄动物模型的研究有望为谵妄的机制解析和治疗开发提供更加坚实的科学基础。

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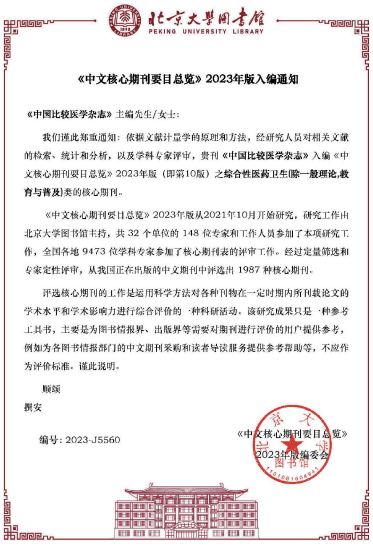
依据文献计量学的原理和方法,经研究人员对相关文献的检索、统计和分析,以及学科专家评审,《中国比较医学杂志》再次入编《中文核心期刊要目总览》2023 年版(即第 10 版)综合性医药卫生类的核心期刊!

《中文核心期刊要目总览》采用定量评价和定性评的学术水平和学术影响进行综合评价,受到学术界的广泛认同。

目前,本刊为中国学术期刊综合评价数据库来源期刊、中国学术期刊综合评价数据库(CAJCED)统计源期刊、《中国学术期刊文摘》来源期刊;被中国生物学文献数据库、《中国核心期刊(遴选)数据库》、《中国科技论文统计源期刊》(中国科技核心期刊)、《中文核心期刊要目总览》等数据库收录。

感谢编委、专家们的帮助与支持,感谢广大作者和读者朋友们的厚爱与信任。本刊编辑部将始终坚守办刊宗旨,不忘初心,严谨办刊,开拓进取,不断创新,向世界一流期刊看齐。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《中文核心期刊要目总览》2023年版入编通知

《中国比较医学杂志》主编先生/女士:

我们谨此郑重通知:依据文献计量学的原理和方法,经研究人员对相关文献的检索、统计和分析,以及学科专家评审,贵刊《中国比较医学杂志》入编《中文核心期刊要目总览》2023年版(即第10版)之综合性医药卫生[除一般理论,教育与普及]类的核心期刊。

《中文核心期刊要目总览》2023年版从2021年10月开始研究,研究工作由北京大学图书馆主持,共32个单位的148位专家和工作人员参加了本项研究工作,全国各地9473位学科专家参加了核心期刊表的评审工作。经过定量筛选和专家定性评审,从我国正在出版的中文期刊中评选出1987种核心期刊。

评选核心期刊的工作是运用科学方法对各种刊物在一定时期内所刊载论文的学术水平和学术影响力进行综合评价的一种科研活动。该研究成果只是一种参考工具书,主要是为图书情报界、出版界等需要对期刊进行评价的用户提供参考,例如为各图书情报部门的中文期刊采购和读者导读服务提供参考帮助等,不应作为评价标准。谨此说明。

顺颂

撰安

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《中文核心期刊要目总览》2023年版编委会