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抑郁症啮齿动物模型的建立及评价

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【摘要】 抑郁症是一种高复发率、高自杀率的常见精神障碍,严重危害人类身心健康。抑郁症动物模型可以模拟人类抑郁症的疾病表型,帮助人类研究疾病发病机制,开发新的抗抑郁药物。尽管既往研究已构建多种抑郁症啮齿动物模型,但现有的单一模型都不能很好地模拟疾病的全貌,复合模型的发展为更全面地解析抑郁症提供了手段以及更高的可靠性,但也存在实际操作复杂、一致性差等问题。因此,为了筛选更符合实验要求的动物模型,本综述回顾了截至 2021 年发表的抑郁症啮齿动物模型相关文章,对比了近 5 年各模型的使用频率,从抑郁症的病因学与病理生理学机制出发,全面汇总了其建模方法、可靠性评价、优缺点对比及现阶段应用情况等,系统地回顾了目前常用的抑郁症啮齿动物模型(包括应激模型、药理学模型、遗传模型、手术损伤模型、复合模型及其他模型)。此外,同时展望了未来抑郁症啮齿动物模型的建立和使用时所面临的挑战,旨在为研究人员提供更可行的抑郁症建模参考、优选方案和创新方向。

【关键词】 抑郁症;动物模型;模型建立;模型评价
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Establishment and evaluation of rodent models of depression

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【Abstract】 Depression is a common mental disorder with a high recurrence and suicide rate and is a serious threat to human physical and mental health. Animal models of depression mimic the disease phenotype of human depression, helping humans to study the pathogenesis of the disease and develop new antidepressant drugs. Although several rodent models of depression have been established, none of the existing single models simulate the whole disease well. The development of compound models allows researchers to more comprehensively analyze depression with higher reliability, but

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there are also problems such as complicated practical operations and poor consistency. Therefore, to select animal models that better meet experimental requirements, we reviewed articles related to rodent models of depression published up to 2021, compared the frequency of use of each model in the previous 5 years, and comprehensively summarized their modeling method , reliability evaluation, advantages and disadvantages, and current applications from the etiological and pathophysiological mechanisms of depression. We also systematically reviewed the current commonly used rodent models of depression. Additionally, the current rodent models of depression, including stress, pharmacological, genetic, surgical injury, composite, and other models, were systematically reviewed. Challenges in the establishment and use of future rodent models of depression are also presented to provide researchers with more feasible references, preferred options, and innovative directions to model depression.

【**Keywords**】 depression; rodent model; model establishment; model evaluation

Conflicts of Interest: The authors declare no conflict of interest.

抑郁症是一种高复发率、高自杀率的常见精神障碍,其典型症状包括情绪低落,兴趣减退,快感缺失,认知障碍和躯体症状等[1]。据世界卫生组织统计,2019 年全球约有 2.8 亿(患病率 4.4%)抑郁症患者[2]。2019 年,Huang 等[3]调查显示我国心境障碍终生患病率为 7.37%,12 月患病率为 4.06%,抑郁症的终生患病率为 3.4%。抑郁症因其高发病率和高致残率,为家庭和社会带来了沉重的经济负担。预计到 2030 年,抑郁症将成为全球第一大疾病负担。然而,该病发病机制复杂,目前尚无一种假说可以全面解释抑郁症的发病机制[4]。现有抗抑郁药物研发大多基于“单胺类神经递质假说”[5],但由于其具有高度异质性,目前针对假说研发的抗抑郁药物,如 5-羟色胺再摄取抑制剂(selective serotonin reuptake inhibitors, SSRIs)、5-羟色胺及肾上腺素再摄取抑制剂(serotonin and noradrenaline reuptake inhibitors, SNRIs),对部分亚型的抑郁症疗效差[6],在临床上有 30%的患者显示对这些药物无效[7],提示我们对抑郁症神经生物学机制的了解并不清晰。

建立合适的啮齿类动物模型是解锁疾病病理机制的重要工具和手段,可以帮助研究者探索抑郁症发病机制、筛选抗抑郁新药。迄今为止,尚无一种动物模型能够全面地刻画抑郁症表型,因此需要对现有的抑郁症啮齿动物模型进行总结、归纳、评价及优化。本文将回顾既往抑郁症啮齿动物模型的研究进展,对常用的模型建立方法进行综述。

1 抑郁症啮齿动物模型近 5 年使用情况分析及评价标准

为对抑郁症啮齿动物模型使用情况进行梳理分析,作者于 2022 年 1 月通过 pubMed、embase、web of science 数据库检索 2017 年 1 月~2021 年 12 月发表有关于应用抑郁症啮齿动物模型的文章,关键词包括“depression”、“depressive disorder ”、“animal model”、“rats”、“mice” 等及其缩写和衍生词;以(1)公开发表关于抑郁症的动物实验或动物模型的相关文献,(2)实验建立模型目的为建立仅抑郁症模型或模拟抑郁样症状,(3)建立模型所使用的动物为啮齿动物(大鼠或小鼠)为纳入标准;以(1)以非英文语言为研究语种,(2)发表形式为综述,(3)专家评论、会议报告以及信函等,(4)研究抑郁症与其他疾病共病的模型,(5)与建立或使用抑郁症啮齿动物模型无关为排除标准进行文献筛选,最后纳入的文献共计 1581 篇。

目前建立抑郁症啮齿动物模型的方式多是基于抑郁症病因学和病理生理学机制,最常见的手段是通过急、慢性应激暴露、外源性给药、遗传操作和神经损伤等方法,建立应激模型(996 篇,63.00%)、药理学模型(193 篇,12.21%)、遗传模型(168 篇,10.63%)、手术损伤模型(48 篇,3.04%)以及复合模型(37 篇,2.34%)等。2017~2021 年抑郁症建模方法具体分布见图 1。目前,在建立抑郁症啮齿动物模型时,人们更倾向于选择应激模型,尤其是慢性不可预知温和应激模型(chronic unpredictable mild stress,CUMS)使用频率较高疾病动物模型的可靠性评价指标包括表面效度、结构效度和预测效度[8]。表面效度是指动物模型的行为现象与患者相应症状的相似性;结构效度是指动物模型与患者具有相似的病理和生物学机制;预测效度是指对动物干预效果或疗效与对患者对应干预效果之间的相似性,其研究成果可为临床抗抑郁新药的开发和筛选提供依据。这 3 个指标可综合反映动物模型的可靠性和建模效率,以此标准可对疾病动物模型进行评价。本文根据评价其可靠性的 3 个指标,分析对比上述各模型的优缺点,详见表 1。

表 1　常见抑郁症啮齿动物模型的优劣势分析及可靠性评价

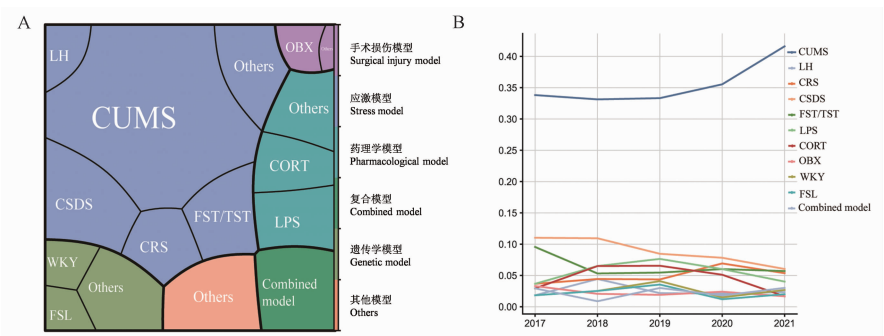
Table 1　Advantages and disadvantages analysis and reliability evaluation of common rodent models of depression

模型种类 Types of models		优势 Advantages	劣势 Disadvantages	可靠性评价 Reliability assessment
应激模型 Stress models	慢性应激模型 Chronic stress models	1. 贴近人类抑郁症的发病过程,能模拟多数发病机制及临床症状; 2. 突出了快感缺失是一个关键性且可量化的特征; 3. 展示了诱发抑郁症的多方面因素; 4. 其中早期应激模型的持续时间是长期性的,甚至是终生性的,如 MD; 5. 最适合与其他类型模型联合或同类型多方法联合。 1. Fitting the pathogenesis of human depression, simulating most pathogenic mechanisms and clinical symptoms; 2. Highlighting the absence of pleasure as a key and quantifiable feature; 3. Demonstrating the multifaceted factors that induce depression; 4. In which the duration of the early stress model is long-term or even lifelong, such as MD; 5. Where it is best suited for combination with other types of models or multi-method combinations of the same type.	1. 多数模型抑郁状态持续时间相对较短; 2. 短期造成的焦虑状态可能与抑郁症状混淆; 3. 不同品系动物对不同应激做不同反应,故该类型的抑郁症易感性存在差异; 4. 不同的实验环境和评估标准可能会导致效果存在偏差; 5. 部分模型相对需要更多的人力物力和时间,如 CUMS。 1. The duration of the resulting depressive state is relatively short; 2. Short-term causes of anxiety states may be confused with depressive symptoms; 3. Different strains of animals do different responses to different stresses, so there are differences in susceptibility to that type of depression; 4. Different experimental settings and assessment criteria may lead to biased effects; 5. Some models relatively require more human resources and time, such as CUMS.	高表面效度 高结构效度 高预测效度 High surface validity High structural validity High predictive validity
	急性应激模型 Acute stress models	1. 可以评估模型和药物治疗效率; 2. 廉价而快速。 1. Allows assessment of model and drug treatment efficiency; 2. Cheap and fast.	1. 不能评估抑郁症病因机制; 2. “不动时间”的概念是主观的,不易准确测量。 1. The etiological mechanism of depression cannot be assessed; 2. The concept of “immobility time” is subjective and not easily measured accurately.	中表面效度 低结构效度 高预测效度 Medium surface validity Low structural validity High predictive validity
药理学模型 Pharmacological models		1. 基于分子生物学模拟抑郁症; 2. 动物痛苦小; 3. 时间短、操作简单; 4. 可重复性高,可控性好; 5. 使用皮质醇皮下注射可避免个体 HPA 轴差异的影响。 1. Molecular biology-based simulation of depression; 2. Low animal suffering; 3. The short duration and simple operation; 4. High reproducibility and good controllability; 5. The use of cortisol subcutaneous injection can avoid the effect of individual HPA axis differences.	1. 不能自然还原抑郁症的发展过程; 2. 药物副作用或许对实验有影响。 1. The inability to naturally restore the development of depression; 2. The side effects of the drug might have an impact on the experiment.	高表面效度 低结构效度 中预测效度 High surface validity Low structural validity Medium predictive validity
手术损伤模型 Surgical injury models		1. 时间短; 2. 生理学和行为学的改变与人类抑郁症相似。 1. Short duration; 2. Physiological and behavioral changes similar to human depression.	1. 不能自然还原抑郁症的发展过程; 2. 外科技术要求高; 3. 动物死亡率较高; 4. 术后恢复期较长; 5. 病理生理学机制不甚清晰。 1. Cannot naturally restore the development of depression; 2. High surgical technique requirements; 3. Higher mortality rate in animals; 4. Longer postoperative recovery period; 5. The pathophysiological mechanisms are not well understood.	高表面效度 中结构效度 低预测效度 High surface validity Medium structural validity Low predictive validity

续表1

模型种类 Types of models	优势 Advantages	劣势 Disadvantages	可靠性评价 Reliability assessment
遗传学模型 Genetic models	1. 可操作性强、易于跟踪观察； 2. 伦理道德问题较少； 3. 重复了与人类的抑郁症相似的遗传倾向； 4. 探索特定基因在抑郁症中的特定作用。 1. Operability and ease of follow-up; 2. Less ethical and moral issues; 3. Replicates a genetic predisposition to a depression similar to that of humans; 4. Explores the specific role of specific genes in depression.	1. 不能自然还原抑郁症的发展过程； 2. 耗时，费力，成本高； 3. 遗传操作影响动物全身，而不仅仅是与病理生理机制相关的大脑区域； 4. 抑郁症并不是单一基因改变，其适用性或许受到限制。 1. Cannot naturally restore the development process of depression; 2. Is time-consuming, laborious, and costly; 3. Genetic manipulation affects the whole body of the animal, not only the brain regions associated with pathophysiological mechanisms; 4. Depression is not a single genetic alteration and its applicability may be limited.	高表面效度 高结构效度 高预测效度 High surface validity High structural validity High predictive validity
复合模型 Composite models	1. 灵活，可根据实验条件和需要进行联合和调整； 2. 成功率高； 3. 多类型模型的联合提高了模型的可靠性，多维度模拟抑郁症。 1. Flexibility to combine and adapt to experimental conditions and needs; 2. High success rate; 3. The combination of multiple types of models improves the reliability of the model and multi-dimensional simulation of depression.	1. 耗时且操作复杂； 2. 一致性较难保证。 1. Time-consuming and complex to operate; 2. Consistency is more difficult to guarantee.	依据具体联合方法判断 Judgment based on the specific combination of methods

注：MD：母体剥夺；CUMS：慢性不可预知温和应激；HPA：下丘脑-垂体-肾上腺皮质。
Note. MD, Maternal deprivation. CUMS, Chronic unpredictable mild stress. HPA, Hypothalamic-pituitary-adrenal.



注：A：近 5 年发表文献所采用抑郁症建模方法分布图；B：近 5 年各模型使用频率折线图。CUMS：慢性不可预知温和应激；LH：习得性无助；CRS：慢性束缚应激；CSDS：慢性社会失败应激；FST/TST：强迫游泳/悬尾；LPS：脂多糖诱导；CORT：糖皮质激素诱导；OBX：嗅球切除；WKY：Wistar-Kyoto；FSL：Flinder Resistant Line。

图 1 近 5 年抑郁症建模方法分布及年度使用频率趋势

Note. A, Distribution of depression modeling methods used in the last five years of published literature. B, Line graph of the frequency of use of each model in the last five years. CUMS, Chronic unpredictable mild stress. LH, Learned helplessness. CRS, Chronic restraint stress. CSDS, Chronic social defeat stress. FST/TST, Forced swim/tail suspension. LPS, Lipopolysacharide-induced. CORT, Corticosterone-induced. OBX, Olfactory bulbectomized. WKY, Wistar-Kyoto. FSL, Flinder Resistant Line.

Figure 1 Distribution of depression modeling methods and annual usage frequency trends in the past five years

2 应激模型

应激暴露是基于病因学而诱导动物产生抑郁样行为的常用方法。生活逆境史以及在青春期或成年生活中经历过压力或创伤是人类公认的抑郁症的危险因素[9]。基于环境危险因素对抑郁症的影响建立的应激模型在很大程度上还原了人类在患病前的经历，以此来获得更高的可靠性。对动物施加慢性应激的常用范式包括慢性不可预知温和应激（chronic unpredictable mild stress，CUMS）、慢性

社会失败应激(chronic social defeat stress,CSDS)和慢性束缚应激(chronic restraint stress,CRS)。此外,急性应激模型主要包括习得性无助(learned helplessness,LH)、强迫游泳实验(forced swim test,FST)和悬尾实验(tail suspension test,TST)也能迅速诱发啮齿动物的抑郁样行为。

2.1 慢性应激模型

2.1.1 慢性不可预知温和应激模型

慢性不可预知温和应激模型应用广泛,近 5 年内使用频次大幅领先其他动物模型且呈逐年上升趋势(图 1A、1B)。该模型是利用长期慢性低水平刺激,将动物持续暴露于一系列未知的温和刺激(如闪光、电击、冷水游泳、潮湿、倾斜笼子等),以及每日随机断水或断食,时长为 3 周~3 个月不等,从而模拟现实生活中患者的发病环境[10](图 2A)。该模型动物最明显的特征是快感缺乏,这可用蔗糖偏好实验来评估,大多数抗抑郁药可以达到逆转蔗糖消耗减少的效果[11]。这种应激范式可以避免单一重复刺激使动物产生适应性,且使其保持长期有效的抑郁状态。该模型表现出前额叶皮层星形胶质细胞弥散和缝隙连接异常超微结构减少,抗抑郁药物可以逆转缝隙连接功能障碍和连接蛋白 43 基因表达。此外,利用该模型还发现应激后促炎细胞因子的水平上调,抗炎细胞因子如转化生长因子-β 和白介素-10 受到抑制,海马和下丘脑中的脑源性神经营养因子(brain-derived neurotrophic factor,BDNF)基因表达降低,可能是由于影响神经元再生的细胞因子失衡所致[12]。该模型是具有较高可靠性的经典模型,与西医临床诊断标准吻合度可达到 70%以上,与中医诊断标准吻合度可达到 80%以上[13]。

2.1.2 慢性社会失败应激模型

社会失败应激模型(图 1A)是在社会层面上模拟抑郁症的发病机制,实现了更高的结构效度。该模型是将动物反复暴露在更强壮、更具攻击性的同类动物面前,导致其快感丧失和焦虑[14](图 2B)。在频繁刺激的情况下,屡次战败的模型动物表现出应激反应,从而产生长期的行为变化(如与群体交流的频率降低、性行为减少[15])和生理变化(如神经细胞增殖减少、海马体积降低[16])。还有研究表明,慢性社会失败模式导致的大脑奖赏环路改变与抑郁样行为的易感性增加有关[17]。值得注意的是,由于雌性动物在上述实验环境中不易产生攻击性行为,因此该范式被应用在雌性动物时需要做出调整。在建立模型前 1 周,收集、过滤、储存不同雄性鼠的尿液,并在建立模型前使用 30 μL 尿液浸泡雌鼠尾巴根部和阴部[18]。所有雌鼠均使用不同的雄性尿液,致使攻击鼠不会遇到两次相同的尿液的战败鼠。此外要注意区分本实验可能会产生假阳性结果,因为实验处理时间过短仅能导致表面上的焦虑。

2.1.3 慢性束缚应激模型

慢性束缚应激模型(图 1A)的优势在于简便、廉价,与其他慢性应激动物模型相比,所需时间、成本和人力更少。动物被束缚在通风良好的有机玻璃管内(管的大小取决于动物的体重),每天 3~6 h 且不被提供食物和水。为了避免昼夜节律波动的干扰,大多数研究是在每日固定的时间段内进行 CRS。持续 3~4 周的应激会减少动物探索行为和自主活动,并逐渐出现紧张、焦虑、抑郁等不良情绪。CRS 可通过参与肾上腺皮质 5-羟色胺样免疫反应和上调 5-羟色胺 7 受体,诱导皮质酮分泌敏化及 5-羟色胺水平升高。选择性 5-羟色胺 7 受体拮抗剂可使 CRS 诱导皮质酮分泌恢复到对照水平,从而表明皮质酮分泌加剧的机制可能涉及 CRS 诱导的肾上腺皮质 5-羟色胺的释放[19]。研究表明该范式存在物种差异性,与小鼠相比,大鼠对束缚应激更敏感;性别因素对该范式诱导的抑郁样行为同样也有显著影响,在应激源下,雌性比雄性表现出更多的运动[20]。

2.2 急性应激模型

2.2.1 习得性无助模型

习得性无助状态(图 1A)是指动物暴露在无法预知且不能挣脱的伤害环境中导致其表现出低意愿的逃避行为,该状态可影响实验动物神经系统和相关生物大分子的改变[21]。该模型最常用的刺激方法是每天以约 0.3 mA 的电流进行足部或尾部电击,每次电击时间与间隔时间不规律(图 2C),通过动物低意愿逃避的行为改变来反映抑郁严重程度以及药物的抗抑郁作用。习得性无助模型对常用抗抑郁药作用具有较高的灵敏度和特异性,并且可以解释创伤性应激障碍和重度抑郁并存的症状。该应激导致中缝背核 5-羟色胺神经元的强烈激活,杏仁核、中脑导水管周围灰质背侧和伏隔核中 5-羟色胺的急剧释放,以及神经营养因子的变化和皮质酮水平升高。抑郁症患者的功能神经成像也发现

了类似的神经生物学变化,这突显了该模型的高结构效度。此外,该范式也可以成为转基因动物基因-表型关系的测试模型,如 C1q(经典补体途径的启动子)基因敲除小鼠更容易产生习得性无助[22]。

2.2.2 行为绝望模型

行为绝望模型(主要包括 FST 和 TST,图 1A)是通过强迫动物的活动直至其出现绝望状态的方法建立模型。FST 是将动物置于高约 40 cm、半径 10~15 cm、水深 20 cm 的光滑玻璃筒内进行强迫游泳训练(图 2D)[23];TST 是将动物头部向下悬挂(图 2D),二者均是将动物置于无法挣扎逃脱的环境中[24],以增加的不动时间作为反映抑郁的严重程度的量化标准。该模型具有操作简单、灵敏度和成功率高等优点。同时,它也常作为筛选模型来评估其他抑郁症啮齿动物模型的建立是否成功及抑郁程度。该模型也存在如对“不动”的判定易带有主观性或单一应激方法有局限性等缺点。

3 药理学模型

抑郁症可以导致多种生化指标的改变,因此改变特定的物理分子的浓度也是建立抑郁症啮齿动物模型的一种重要手段。该类模型虽具有较高的表面效度,但由于其无法还原抑郁症的发生发展过程,且建立机制与抑郁症的发病机制并不完全吻合,这或许会影响其结构效度。目前最常用的抑郁症药理学模型有脂多糖(lipopolysacharide,LPS)、糖皮质激素(corticosterone,CORT)、利血平等诱导的模型(图 1A)。

脂多糖诱导模型被用于建立与炎症相关的抑郁症模型,其机制是激活动物的外周或中枢免疫系统,促进炎症因子释放,产生神经炎症,进而出现自发活动减少、快感缺失等抑郁样行为[25]。建立模型的方法可选择腹腔注射或脑室内注射[26-27],单次注射剂量通常为 0.5~0.83 mg/kg。已证实该模型存在前额叶皮层和海马区 BDNF 水平下降,皮质酮增加及皮质边缘结构中单胺类物质的变化[28-29]。

抑郁症患者下丘脑-垂体-肾上腺皮质(hypothalamic-pituitary-adrenal,HPA)轴功能紊乱致使血清皮质醇含量升高。内源性或外源性皮质醇/皮质酮增加时,人/动物会出现与抑郁症相似的表征[30-31]。多数采用皮下注射外源性皮质酮(20 mg/kg)3 周的方法建立动物模型。长期给予皮质醇可以通过改变一组选定的微核糖核酸(microRNAs,miRNAs)及相关网络以诱导抑郁症表型[32],预测其靶基因的功能聚类可能与抑郁症相关的发育、炎症和心理等疾病有关。

利血平作为一种囊泡重摄取抑制剂,可以阻断突触前膜重摄取的过程。当递质被阻挡在囊泡外时,会被单胺氧化酶降解,进而脑中儿茶酚胺和 5-羟色胺的含量迅速降低,引发动物上睑下垂、体温过低和运动抑制等变化[33]。通过腹腔注射的方法以约 4 mg/(kg·d)建立急性模型或以 0.1~0.6 mg/(kg·d)建立慢性模型[34-35]。利血平可诱导氧化应激和炎症反应增加,神经发生减弱,单胺能系统损伤以及组织病理学改变,具体包括丙二醛升高,还原型谷胱甘肽升高,肿瘤坏死因子-α 降低,BDNF 皮质和海马区升高,CBL 蛋白激酶 A(PKA)和核因子 κB 皮质和海马区蛋白表达升高[36]。

4 遗传模型

抑郁症由复杂的遗传和环境交互作用引起。遗传学研究表明,个体患抑郁症的风险受其基因构成的影响。抑郁症的动物模型可以帮助研究人员为人类遗传学的研究寻找与抑郁症相关的候选基因。

Wistar-Kyoto(WKY)大鼠模型最初来源于自发性高血压大鼠,后发现其抑郁样行为表现,对应激表现出更高的情绪性和反应性。由于其先天对应激环境具有高敏感度,表现在临床抑郁症相关的特定功能领域,包括精神运动发育迟缓、行为抑制、习得性无助、社交退缩和生理功能障碍,且对 SSRIs 类抗抑郁药物不敏感,因此它可成为开发针对难治性抑郁症的个性化抗抑郁疗法的模型[37]。

研究发现,抑郁症患者比健康人对胆碱能激动剂更敏感,胆碱能-肾上腺素能平衡的改变会导致加深抑郁状态或减轻躁狂状态。Flinders 敏感品系(Flinder sensitive line,FSL)大鼠选育自 SD 品系,对抗胆碱酯酶药物,尤其是二异丙基氟磷酸盐敏感,可产生明显的抑郁样表型[38]。FSL 大鼠与对照 Flinders 抗性品系(Flinder Resistant Line,FRL)大鼠之间存在脑区差异表达的基因可能使动物易出现抑郁样行为,目前该模型已被用于抑郁症发生的基因与环境交互作用的研究[39]。此外,FSL 大鼠显示出结构性一氧化氮合酶系统激活,证实 N-甲基-D-天冬氨酸-一氧化氮级联是 FSL 大鼠抑郁表型的重要易感因素[40]。

基于食物竞争社会互动显性-顺从关系测试的 Sabra 小鼠谱系选择性育种方法的显性(Dom)和顺从(Sub)小鼠可以表现出强烈而稳定的显性或顺从行为特征[41],具有显著不同的应激相关行为和内分泌水平,以及对抗抑郁药物的不同反应。据报道,在应激或药物暴露下,Dom 和 Sub 小鼠在记忆编码相关基因的调控上存在显著差异,应激顺应性的潜在机制在于记忆编码的差异[42]。

先天性习得性无助(congenital learned helplessness,cLH)品系的促黄体生成素遗传模型是通过多代逃逸失败筛选和繁殖而获得,且对抗抑郁药物(除大剂量单胺氧化酶-B 外)具有耐药性[43]。神经成像研究显示,cLH 大鼠代谢和功能连接的变化与重度抑郁症和难治性抑郁症患者的变化非常相似。

作为一种合并抑郁症和酒精中毒的动物模型,Fawn-Hooded 大鼠存在遗传控制中枢和外周 5-羟色胺缺乏,血小板 5-羟色胺储存异常。该模型表现出在 FST 中高不动性和高自愿乙醇摄入量[44],HPA 轴过度活跃和血清皮质酮异常升高,且长期使用抗抑郁药物可减轻或正常化上述变化。

此外,随着对疾病遗传机制研究的深入,遗传模型也为特定基因参与抑郁症病理生理的概念提供证据,如被研究最多的单胺类基因 5-羟色胺转运体基因(5-HTTLPR)启动子区域的功能多态性。随着应激事件频率的增加,5-HTTLPR 基因短等位基因纯合子的个体相对于长等位基因纯合子的个体患抑郁症的风险增加,杂合子也显示出中等水平的风险[45]。α2-肾上腺素能受体基因敲除小鼠和环磷酸腺苷(cyclic adenosine monophosphate,cAMP)反应元件结合蛋白高表达的小鼠也更容易在应激环境中出现抑郁样症状[46-47]。然而,抑郁症是一种多基因疾病,基因的影响与环境因素有很强的交互作用,或许带有特定基因单一突变的遗传模型不能概括抑郁症的遗传病因。

5 手术损伤模型

边缘系统的神经损伤会导致大脑奖惩系统异常,从而导致抑郁样症状,因此可通过手术损伤建立动物模型,其中嗅球切除模型(olfactory bulbectomy,OBX)(图 1A)最为经典。嗅球位于端脑前部,与边缘系统功能相关。研究显示抑郁症患者嗅觉敏感度显著降低,且降低程度与症状严重程度有关[48]。其建模方法是将电热探头立体定位插入并破坏嗅球区域(图 2E),而后动物有快感减退、被动回避学习能力降低、条件性味觉厌恶和食物动机行为的缺陷等表现[49],长期使用抗抑郁药物可以在部分程度上纠正嗅球切除术后发生的一系列变化[50]。手术切除嗅球也会在神经生物学层面上产生变化。据报道,投射到嗅球的皮质边缘网络区域出现进行性神经性变,以及炎症反应和皮质酮水平升高,以及 5-羟色胺能神经传递的变化[51]。去嗅球大鼠神经肽 Y、ChAT、去甲肾上腺素和谷氨酸水平也降低。嗅球切除 16 d 后,海马区和额叶皮质 BDNF 水平也有增加的报道[52]。这些证据表明,OBX 模型为研究抑郁症的神经生物学和抗抑郁机制提供了工具,但因其所致抑郁的病理机制暂未明确,并且对抗抑郁药物的预测效度较低,术后发病率较高[53],故该模型目前应用受限。

6 复合模型

单一模型或许不能模拟抑郁症的全貌,但不同模型多维度联合可能更有助于诱导动物出现类似抑郁症的状态,并为深入理解抑郁症全貌提供机会。复合模型(图 1A)的联合方法多样,单一类型的不同方法联合以提高建模成功率,如母体剥夺(maternal deprivation,MD)联合 CUMS 模型[54]、MD 联合 CSDS 模型[55]等;多类型交叉联合的范式不仅仅能够提高建模成功率,也增加了模型可靠性和实验数据的准确性,如(1)药物诱导联合环境应激模型:注射 LPS 与 CUMS 联合,与单一 CUMS 模型相比,动物表现出更严重的快感缺失,同时 CUMS 可消除 LPS 耐受性增强所致的海马区炎症[56];(2)环境应激联合遗传模型:CUMS 与 MD 联合垂体腺苷酸环化酶激活多肽(pituitary adenylate cyclase-activating polypeptide,PACAP)基因突变,该模型中基因突变模拟了遗传易感性,MD 模拟了早期生活中的逆境,CUMS 作为第 2 次环境应激与遗传易感性和病史相叠加,更拟合抑郁症的发病条件,与表观遗传学一致,通过生理、内分泌、行为和功能形态学工具对该新模型的有效性进行了检验,认为其具有更高的可靠性[57]。

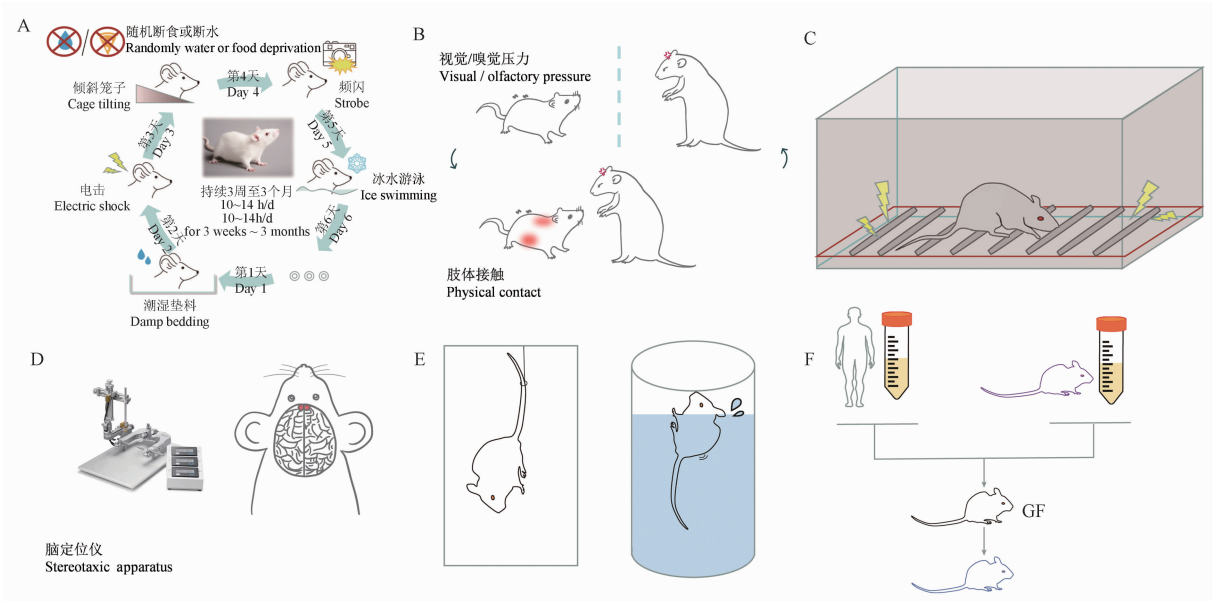
7 其他模型

除上述经典模型外,近年来一些新模型也亟待发展。(1)光遗传模型是通过光遗传工具以高度的

解剖学、遗传学及时间精度来阻断或刺激神经元活动的方法,进而有效地诱导抑郁样行为或增加对应激的敏感性,如抑制纹状体尾状核床核的前腹部[58]、刺激前扣带皮层的锥体神经元[59]、抑制伏隔核 D1 受体表达的中棘神经元或慢性刺激内侧前额皮层[60-61]的等手段。但该模型对技术要求具有挑战性且成本较高;(2)粪便微生物移植(fecal microbiota transplantation ,FMT)是重建肠道菌群和宿主功能的有效方法。从抑郁症患者或抑郁样动物到无菌动物的 FMT 可导致受体动物出现抑郁样行为(图 2F)[62-63];(3)抑郁症患者经常表现出昼夜节律和睡眠/觉醒周期紊乱[64]。稳定昼夜节律对抑郁症状有积极影响,而扰乱动物的昼夜节律可能导致抑郁样症状[65]等。

8 展望与挑战

目前,CUMS 模型被公认为是经典的抑郁症啮齿动物模型之一,不仅因为其建模方法易于实现,而且其建模效果和症状维持时间也相当可观。但抑郁症发病机制复杂,任何动物模型都有一定的局限性,围绕单一模型只能表现抑郁症的某些方面,实验结果也容易受到主观偏好的影响,导致假阳性结果的发生率增加。因此,建议多模型联合应用效果更好、可靠性更高。由于复合模型的建模过程复



注:A:慢性不可预知温和应激模型,动物每天暴露于不同的温和刺激,其顺序是随机的、不可预测的,同时还伴有间歇性的断食或断水,多为期 3~9 周;B:社会失败应激模型,该模型通过将实验动物直接暴露在另一只更强壮、更具攻击性的同类动物面前,每天接触时间为 5 min,其余时间越过透明屏障保持感官接触的方法,约在 10~15 d 成功诱导抑郁症状(图中战败鼠身有淤红由攻击鼠侵略所致);C:习得性无助模型,动物连续 5~7 d 被束缚在电击箱中被迫接受无法预知的刺激,而后被转入无刺激的电击箱中,表现出逃避行为缺陷和抑郁症状;D:手术损伤模型,嗅球切除模型(图中红色标记位置为嗅球),该模型通过破坏嗅球的方法诱导动物产生抑郁样症状;E:悬尾模型和强迫游泳模型,该类模型通过将动物置于无法挣扎逃脱的绝望境地,从而诱导抑郁样行为;F:粪便微生物群移植模型,从抑郁症患者或有抑郁样行为动物的粪便中提取肠道菌液移植到无菌动物体内,可致受体动物出现抑郁样行为。GF:无菌动物。

图 2 常见抑郁症啮齿动物模型建模方法

Note. A, Chronic unpredictable mild stress model. Animals are exposed to different mild stimuli in a random and unpredictable sequence every day, accompanied by intermittent food or water deprivation, mostly for 3 to 9 weeks. B, Social defeat stress model. This model successfully induces depressive symptoms for approximately 10 to 15 days by exposing the experimental animal directly to another stronger, more aggressive counterpart for 5 minutes per day and maintaining sensory contact across a transparent barrier for the rest of the day. C, Learned helplessness model. Animals were restrained in a shock box for 5 to 7 consecutive days and forced to receive unpredictable stimuli, and then transferred to a stimulus-free shock box, exhibiting avoidance behavioral deficits and depressive symptoms. D, Tail suspension model and forced swimming model. These models induce depression-like behavior by placing the animal in a desperate situation where it cannot struggle to escape. E, Surgical injury model: olfactory bulbectomized model (the location marked in red in the figure is the olfactory bulb). This model induces depression-like symptoms in animals by destroying the olfactory bulb. F, Fecal microbiota transplantation model. Transplantation of intestinal fluids from the feces of depressed patients or animals with depressive-like behaviors into germ-free animals can cause depressive-like behaviors in the recipient animals. GF, Germ-free animal.

Figure 2 Modeling methods for common depression rodent models

杂,现使用频率仍然较低,建议建立一种能够同时兼顾简单易操作和足够可靠性的复合模型以用于抑郁症研究。其次,现有的抑郁症模型大多选用雄鼠建立。然而,抑郁症在女性中的发病率远高于男性[66],将对抑郁症的研究仅局限于男性可能会导致研究的不全面或忽略了仅匹配女性的关键信息。未来建立模型时应多基于性别比较或控制性激素波动,重点关注和识别性别特异性的生物标记物以探索相关机制。最后,随着近年来关于抑郁症与炎症、细胞凋亡、生长因子、遗传和表观遗传调控、环境等方面的研究日益增多,未来应围绕这些潜在机制以开发出更个体化的建模方案。

综上所述,研究者要掌握不同模型动物的特点,选择最合适的动物模型;同时,应不断创新和优化抑郁症模型,以期构建更完善的研究工具,为探索抑郁症机理、提高抗抑郁药的研发水平提供更有价值的信息。

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