Sigma-1受体作为抗焦虑药物靶点的研究现状

段 敏, 李 阳*

(北京协和药厂有限公司, 北京 102600)

摘要: 焦虑障碍是一种具有高患病率、慢性迁延性和高共病率特征的精神疾病。现有临床治疗药物存在明显的局限性, 如选择性5-羟色胺重摄取抑制剂、5-羟色胺−去甲肾上腺素重摄取抑制剂和苯二氮卓类药物等, 常受到疗效有限、不良反应明显和耐药性等问题的限制。近年来, sigma-1受体作为新型抗焦虑药物靶点备受关注, 其配体已在多种动物模型中展现出明显的缓解焦虑样行为的作用, 为突破当前治疗困境带来了新的希望。然而, 目前尚无以sigma-1受体为靶点的抗焦虑药物进入临床研究阶段。基于此, 本文综述了近年来sigma-1受体在焦虑疾病中的分子作用机制, 并对其配体在动物模型中的药效学研究进展进行总结, 以期为基于sigma-1受体的新型抗焦虑药物研发提供理论依据和研究思路。

关键词: sigma-1受体; 焦虑障碍; 配体; 作用机制; 临床研究

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Current research status of sigma-1 receptor as a therapeutic target for anxiety disorders

DUAN Min, LI Yang*

(*Beijing Union Pharmaceutical Factory Ltd., Beijing 102600, China*)

Abstract: Anxiety disorder, as a psychiatric condition characterized by high prevalence, chronic progression, and frequent comorbidities, faces significant limitations with current clinical treatments such as selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and benzodiazepines. These therapies are often constrained by limited efficacy, notable side effects, and issues of drug resistance. In recent years, the sigma-1 receptor has emerged as a promising target for novel anti-anxiety medications, with its ligands demonstrating significant anxiolytic effects in various animal models, offering new hope for addressing current therapeutic challenges. However, no anti-anxiety drugs targeting the sigma-1 receptor have advanced to clinical research stages. Therefore, this article reviews recent progress in understanding the molecular mechanisms of the sigma-1 receptor in anxiety disorders and summarizes the pharmacological efficacy of its ligands in animal models, aiming to provide a theoretical foundation and research directions for the development of innovative anti-anxiety drugs targeting the sigma-1 receptor.

Key words: sigma-1 receptor; anxiety disorder; ligand; mechanism of action; clinical study

焦虑症是最常见的一种精神疾病, 又称焦虑障碍或病理性焦虑[1], 其主要特征为过度的恐惧和焦虑, 或回避感知到的持续有害的威胁。在中国成年人中, 焦虑障碍的终生患病率约为7.6%[2], 且女性患病率明显高于男性[3,4]。由于焦虑症的高患病率、长期性和共病性, 世界卫生组织将其列为导致残疾的第九大健康原因。目前, 临床抗焦虑药物主要有5-羟色胺重摄取抑制剂、5-羟色胺−去甲肾上腺素重摄取抑制剂和苯二氮卓类药物等, 但治疗耐药和严重的不良反应是临床上的重大挑战[3]。因此, 急需寻找新的药物靶点。

Sigma-1受体是一种分子伴侣蛋白, 能够与多种蛋

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*通讯作者 Tel: 15811252399, E-mail: liyangkrystal@163.com
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白相互作用, 并参与多种细胞信号通路的调节。近年来, 因作为神经精神疾病领域的潜在治疗药物靶点而备受关注[5,6]。全基因组研究[7]发现, sigma受体基因在焦虑相关的遗传信号中高度富集。同时, sigma-1受体基因敲除的小鼠也表现出了焦虑样行为[8]。此外, 多项动物实验[9-11]研究结果表明, sigma-1受体配体可明显缓解焦虑样行为。尽管目前尚未有临床试验验证该靶点在人体中的有效性和安全性, 但现有研究结果提示调节sigma-1受体可能对焦虑的治疗具有潜在益处。因此, 本文旨在对sigma-1受体在焦虑疾病中的研究现状进行综述, 讨论sigma-1受体成为焦虑治疗药物靶点的潜力。

1　Sigma-1受体的基本信息

Martin等[12]在研究吗啡样和烯丙吗啡样药物的药理效应时, 发现烯丙吗啡样药物SKF-10047产生了与吗啡和酮佐辛等传统阿片类药物不同的药理效应 (如致幻作用)。由于这些效应可被纳洛酮拮抗, 他们最初推测该受体可能是阿片受体家族的一个新亚型, 并将其命名为sigma阿片受体。然而, 1982年, Su[13]通过放射性配体结合实验发现, 传统阿片类药物如吗啡、埃托啡和纳洛酮等对[^{3}H]SKF-10047结合位点的抑制作用较弱, 非阿片类药物如氟哌啶醇等则表现出强效抑制作用, 这一结果表明, 此结合位点并非阿片受体, 于是Su正式将其命名为sigma受体。根据分子大小和配体结合特征, sigma受体被分为sigma-1和sigma-2两种亚型[5,14]。随着sigma-1受体高亲和力、高选择性放射性配体[^{3}H](+)-喷他佐辛的开发[15], 极大地推动了sigma-1受体的基础及药理学研究。Sigma-1受体广泛分布于脑、肝脏、肾脏、肺、肌肉、膀胱及内分泌、免疫和生殖组织, 主要在中枢神经系统 (海马、下丘脑、中脑、嗅球)中表达[6], 是一种位于线粒体相关内质网膜上的分子伴侣蛋白。生理状态下, sigma-1受体与免疫球蛋白结合蛋白 (binding immunoglobulin protein, BiP) 结合形成复合物, 此时的sigma-1受体不具有分子伴侣活性。当内质网Ca^{2+}耗竭或在配体刺激下, sigma-1受体从BiP解离, 转移至内质网膜、线粒体膜、细胞核膜或细胞膜上, 并与相应细胞器的客户蛋白如受体、离子通道和激酶等相互作用, 以进一步介导细胞信号通路的调节[5,16]。

2　Sigma-1受体与焦虑的关系

Sigma-1受体在神经精神疾病的病理生理学中起着重要作用。有研究发现sigma-1受体敲除的小鼠表现出明显的焦虑迹象[8,17,18]。同时, Zhang等[18]发现短链脂肪酸可改善甲基苯丙胺 (methamphetamine, METH) 诱导的小鼠焦虑和抑郁样行为, 但对sigma-1受体敲除的小鼠无法发挥其抗焦虑的作用。此外, Chen等[19]将慢病毒编码的miR-153-3p反向互补序列注射到经单一延长应激处理的SD大鼠的侧脑室, 可上调大鼠海马体中sigma-1受体的表达水平, 缓解大鼠的焦虑行为。上述研究提示, sigma-1受体在焦虑相关疾病的发病机制中扮演着十分重要的角色。此外, 研究显示焦虑障碍与抑郁症、双相情感障碍、阿尔茨海默病、脆性X染色体综合征、创伤后应激障碍或其他类型的焦虑障碍等疾病之间存在较高的共病率[20-22]。全基因组关联研究也显示焦虑、抑郁和神经质患者之间存在较高的遗传相关性[3]。所以, 与上述疾病相关的研究有助于研究者对焦虑障碍的整体理解。本综述中出现的疾病模型不仅仅局限于焦虑障碍, 还包括与焦虑高度重合的共病动物疾病模型如抑郁、创伤后应激障碍和疼痛等。本文将从机制、配体和临床试验三方面综述sigma-1受体与焦虑的关系。

2.1　Sigma-1受体影响焦虑样行为的机制

2.1.1　神经保护　脑源性神经营养因子 (brain-derived neurotrophic factor, BDNF) 作为调控轴突生长、突触可塑性和情绪调节的关键分子, 其表达水平的改变与焦虑样行为密切相关。有研究[23]表明携带*BDNF Met*等位基因的小鼠 ($BDNF^{Met/Met}$和$BDNF^{+/Met}$) 表现出活动依赖性BDNF释放减少、齿状回神经元树突复杂性降低以及海马体体积缩小等特征, 并呈现出与人类携带者相似的焦虑样行为。这些发现证实了BDNF在焦虑调控中的核心作用。近年来研究发现, sigma-1受体可通过调控BDNF信号通路发挥抗焦虑作用。具体而言, sigma-1受体变构调节剂[24]及激动剂[25,26]均可通过增加小鼠海马体中BDNF的水平, 实现缓解小鼠焦虑样行为的作用。此外, BDNF通过与其特异性受体原肌球蛋白相关激酶受体B (tropomyosin related kinase receptor B, TrkB) 结合, 在神经元保护和修复中发挥重要作用。已有研究证明上调BDNF/TrkB通路, 可减轻大鼠海马区的神经元损伤, 从而显著改善焦虑和抑郁样行为[27]。Zhang等[18]研究发现, sigma-1受体敲除的小鼠, 海马体中BDNF和磷酸化TrkB (p-TrkB) 的蛋白表达量低于野生型小鼠, 且表现出明显的焦虑迹象。Tong等[28]进一步证实, sigma-1受体激动剂可逆转大鼠额叶BDNF及p-TrkB蛋白表达水平的降低。上述研究表明, sigma-1受体激活, 可上调大脑中BDNF/p-TrkB水平, 发挥神经保护和抗焦虑作用。为深入探索上下游信号分子, Ji等[29,30]在此基础上进一步检测了细胞外信号调节激酶 (extracellular signal regulated kinase, ERK)、环磷腺苷效应元件结合蛋白 (cAMP response element binding protein, CREB)

和 *N*-甲基-*D*-天冬氨酸受体 2A (*N*-methyl-*D*-aspartate receptor subunit 2A, NR2A)。研究发现, sigma-1 受体激动剂降低了大鼠杏仁核区域的 BDNF、p-TrkB 和磷酸化 ERK 的水平, 同时上调了海马体中 BDNF、磷酸化 CREB 水平和 NR2A 的表达。因此, sigma-1 受体激活可能通过调节 NR2A-CREB-BDNF-TrkB-ERK 信号通路来保护神经细胞, 进而发挥抗焦虑作用。然而, 该信号通路并非简单的线性结构, NR2A 既可作为上游信号分子调节 BDNF 的水平, 又可作为下游分子被 BDNF 所调节[31]。此外, sigma-1 受体还可以直接作用于 TrkB, 调节其磷酸化水平, 促进神经元突起延长[32] (机制见图 1)。由此可见, sigma-1 受体在神经细胞保护和抗焦虑作用中的机制比较复杂, 其具体细节仍有待进一步探索。另外, 值得注意的是, 在上述研究中 sigma-1 受体激动剂 PRE084[28-30]对 BDNF 和 p-TrkB 表达的调控作用表现出显著的脑区差异性, 这可能与焦虑状态下不同脑区的功能状态有关。研究表明, 与健康人相比, 精神疾病患者额叶皮层呈现低激活状态, 而杏仁核则表现为高激活[21]。Song 等[27]研究发现, 焦虑大鼠海马体中 p-TrkB 水平呈现先升高后持续下降的动态变化。这些发现提示, BDNF 和 p-TrkB 的表达水平不仅与特定脑区的功能状态密切相关, 还可能受到疾病病程的影响。因此, sigma-1 受体对相关蛋白的调控并非简单的单向调节, 而是根据疾病状态下不同脑区的激活情况, 对特定蛋白进行精确调控。

焦虑障碍以突触病理改变为特征, 可能涉及突触可塑性相关分子如突触后密度 95 (postsynaptic density 95, PSD95) 等蛋白的异常表达[33]。PSD95 作为突触形成和树突棘密度调控的核心蛋白, 其表达水平与焦虑状态密切相关。研究发现, 在壬基酚诱导的大鼠焦虑模型中, 海马体 PSD95 蛋白和 mRNA 的表达显著下调[34]。Chen 等[19]发现, sigma-1 受体激动剂显著提升大鼠海马体中磷酸化哺乳动物雷帕霉素靶蛋白 (phosphorylated mammalian target of rapamycin, p-mTOR) 和 PSD95 的表达水平, 且该作用可被 mTOR 信号通路抑制剂雷帕霉素预处理所逆转。因此, sigma-1 受体可能通过调控 mTOR/PSD95 信号通路来调节突触可塑性, 进而发挥抗焦虑作用。综上, sigma-1 受体激活具有抗焦虑作用, 其机制可能是通过调节 PSD95 蛋白表达, 以恢复神经可塑性。这些发现为深入理解 sigma-1 受体在焦虑障碍中的作用机制提供了重要依据。

2.1.2 神经递质系统 焦虑障碍的发生与多个脑区及神经递质系统的复杂相互作用密切相关。焦虑的调节需要多种神经递质通路的动态平衡, 包括谷氨酸 (glutamate, Glu)、γ-氨基丁酸 (gamma-aminobutyric acid, GABA)、5-羟色胺和去甲肾上腺素等[35]。研究发现 sigma-1 受体激动剂可恢复产后抑郁/焦虑小鼠海马体星形胶质细胞中 Glu 和 GABA 的水平, 并调节海马

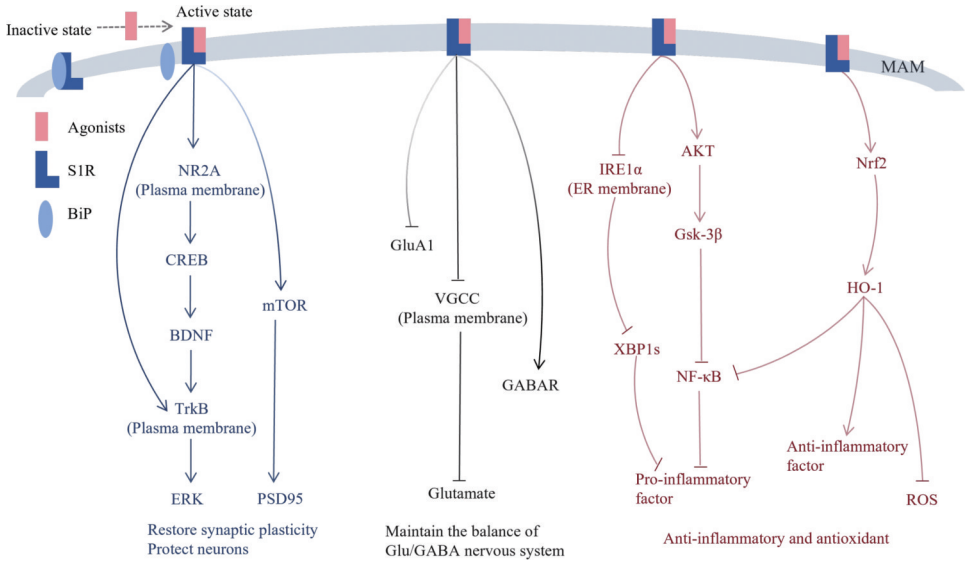


Figure 1 Mechanism of sigma-1 receptor agonists in the treatment of anxiety disorders. S1R: Sigma-1 receptor; BiP: Binding immunoglobulin protein; MAM: Mitochondrion-associated membrane; NR2A: *N*-Methyl-*D*-aspartate receptor subunit 2A; CREB: cAMP response element binding protein; BDNF: Brain-derived neurotrophic factor; TrkB: Tropomyosin related kinase receptor B; ERK: Extracellular signal regulated kinase; mTOR: Mammalian target of rapamycin; PSD95: Postsynaptic density 95; GluA1: Glutamate receptor subunit A1; VGCC: Voltage gated calcium channels; GABAR: Gamma-aminobutyric acid receptor; IRE1*α*: Inositol-requiring enzyme 1*α*; XBP1: X-box binding protein 1; AKT: Protein kinase B; Gsk-3*β*: Glycogen synthase kinase-3*β*; Nrf2: Nuclear factor erythroid 2-related factor 2; HO-1: Heme oxygenase-1; ROS: Reactive oxygen species; NF-*κ*B: Nuclear factor kappa B

体中谷氨酸受体A1亚基的磷酸化水平和GABA受体的表达[26]。激活后的sigma-1受体通过抑制电位依赖性Ca^{2+}通道功能, 减少Ca^{2+}内流, 从而抑制Glu的释放。此外, sigma-1受体激动剂还可能通过调节神经末梢突触前转运体或突触囊泡的酸化, 进而调节Glu/GABA的摄取和释放[36-38]。另外, 研究发现sigma-1受体激动剂通过增强sigma-1受体和NR2A间的直接作用, 促进大鼠海马体中NR2A蛋白的合成, 并介导其向细胞表面转运[30,39]。然而, NR2A作为大脑主要兴奋性神经递质谷氨酸的受体, 研究者通常认为其在大脑相关区域的上调会引起焦虑, 这一矛盾现象可以从两个方面加以分析。一方面, NR2A不仅是谷氨酸受体, 同时也在神经突触的发育、功能调节及突触可塑性方面发挥重要作用, NR2A表达的降低可能会削弱神经元之间的信息共享, 影响神经网络活动, 最终导致情绪调节功能受损[30]; 另一方面, 尽管sigma-1受体的激活会促使NR2A介导的Ca^{2+}内流增加, 从而增强神经系统兴奋性, 但sigma-1受体的激活同样也能促进Ca^{2+}进入线粒体, 以此维持细胞内Ca^{2+}浓度的平衡, 从而维持神经系统的正常兴奋性[40]。另外, 除上述神经递质通路外, Hong等[41]发现sigma-1受体激动剂可促进sigma-1受体多聚体解离成单体, 然后与多巴胺转运体 (dopamine transporter, DAT) 相互作用, 改变DAT构象, 促进其与可卡因的结合, 从而增强可卡因自我给药行为的敏感性。虽然目前尚无研究直接证实这一机制在焦虑中的调控作用, 但多巴胺能系统可能参与sigma-1受体调节焦虑的潜在机制仍值得关注。综上, sigma-1受体通过整合多个神经递质系统的功能, 在焦虑障碍的病理生理过程中发挥重要的调节作用。这一发现为开发基于sigma-1受体的新型抗焦虑药物提供了重要的理论依据和研究方向。

2.1.3　神经炎症　焦虑和抑郁患者的外周和脑脊液中存在明显的炎症因子水平异常。促炎因子如白细胞介素 (interleukin, IL)-1β、IL-6、IL-8、肿瘤坏死因子-α (tumor necrosis factor-alpha, TNF-α) 和C反应蛋白 (C-reactive protein, CRP) 显著升高, 而抗炎因子包括IL-4、IL-10呈现下降趋势, 这些变化与患者的临床症状严重程度和病程进展密切相关[42]。这一现象在动物模型中也得到了验证, Ma等[43]研究发现, 束缚应激诱导的焦虑和抑郁模型小鼠海马体中IL-1β和IL-6水平显著升高, 提示炎症反应在焦虑发生机制中的重要作用。Sigma-1受体激动剂[44]可降低小鼠前额叶皮质IL-1β和NOD样受体蛋白3的表达水平。在细胞水平研究中, 激动剂可抑制脂多糖诱导的BV2小胶质细胞*IL-1β*和*IL-6* mRNA水平上调。另有研究发现, sigma-1受体拮抗剂可抑制纤维肌痛样小鼠脊髓星形胶质细胞和小胶质细胞增生和活化, 降低慢性骨关节炎疼痛小鼠内侧前额叶皮层中小胶质细胞的数量, 产生抗焦虑和抑郁样行为的作用[45,46]。从作用机制而言, 有研究指出sigma-1受体激活可上调蛋白激酶B和糖原合成酶激酶-3β磷酸化水平, 降低NF-κB (nuclear factor kappa B) 的磷酸化水平, 从而下调炎症因子[47]。此外, sigma-1受体激活可直接结合核因子E2相关因子2 (nuclear factor erythroid 2-related factor 2, Nrf2), 上调其mRNA及蛋白表达水平, 并促进Nrf2核转位, 结合抗氧化反应元件, 进而上调血红素加氧酶-1 (heme oxygenase-1, HO-1), 通过抑制NF-κB或直接抑制促炎因子, 激活抗炎因子, 以恢复抗炎/促炎系统的平衡[48-50]。另外, sigma-1受体敲除后, 内质网应激蛋白肌醇依赖性激酶 (inositol-requiring enzyme, IRE) 1α内切酶活性增加, 剪接X-盒结合蛋白1 (X-box binding protein 1, XBP1) mRNA, 生成具有转录活性的*XBP1s*, 进而上调炎症因子水平。IRE1α抑制剂能有效地减弱sigma-1受体敲除细胞的炎症增强反应, 表明IRE1α在sigma-1受体调控炎症因子的通路中具有重要作用[51]。另外, 值得注意的是, sigma-1受体激动剂[47,52]和拮抗剂均具有调节胶质细胞活性和炎症因子水平的药理作用。如sigma-1受体拮抗剂 (+)-2*R/S*-LP2可降低星形胶质细胞和小胶质细胞的数量和活性, 并降低IL-6水平[53]。此外, 拮抗剂MR309 (E-52862) 显著降低脊髓组织中TNF-α和IL-1β的水平, 并减少内侧前额叶皮质中小胶质细胞的数量[46,54]。综上, sigma-1受体在中枢神经系统炎症因子水平的调控中扮演着重要角色, 可能是其产生抗焦虑效应的重要机制之一。然而, 目前sigma-1受体调节炎症因子的双向作用机制尚不清楚, 未来仍需进一步探索sigma-1受体在不同病理状态下对炎症反应的调节机制, 以更好地理解其在焦虑疾病中的作用。

2.1.4　氧化应激　研究表明, 在精神疾病中活性氧 (reactive oxygen species, ROS)的生成超过了大脑的抗氧化防御能力[55]。此外, 有报道[56]表示一些具有抗氧化活性的化合物如*N*-乙酰半胱氨酸和银杏叶提取物EGb761等在啮齿类动物中表现出抗焦虑作用。因此, 氧化损伤可能在神经精神疾病的病理生理过程中起着关键作用。Li[57]发现三氟淫羊藿素 (trifluoro-icaritin, ICTF) 与sigma-1受体结合能力与经典配体PRE084相近, 并可显著降低神经病理性疼痛焦虑大鼠海马体中sigma-1受体的表达, 调节氧化应激指标如降低丙二醛, 升高超氧化物歧化酶, 有效缓解大鼠机械痛敏和焦虑样行为。为进一步验证sigma-1受体的作用, 研究者

采用基因编辑技术特异性敲低大鼠海马体CA1区sigma-1受体的表达, 成功复现了上述治疗效果。然而, 体外细胞实验发现ICTF对sigma-1受体的表达具有双向调节作用 (既可上调也可下调), 但均能显著抑制活性氧的生成。这种矛盾现象在当前研究中也普遍存在, 有研究发现METH诱导的原代大鼠星形胶质细胞中sigma-1受体蛋白表达上调, 同时激活星形胶质细胞并诱导氧化应激的产生[58]。也有研究发现sigma-1受体基因敲除后, 小鼠的氧化应激水平升高[59]。这提示sigma-1受体在氧化应激中的表达水平可能因细胞类型、实验条件或生理病理状态的不同而存在明显差异。另外, 大量研究表明, sigma-1受体激动剂可通过多种途径改善氧化应激水平, 如上调Nrf2/HO-1信号通路、恢复线粒体复合物Ⅰ和Ⅳ的生理功能等[50,60,61]。但是, 拮抗剂的抗氧化作用在不同研究中结果并不一致。拮抗剂NE100无法抑制淀粉样蛋白A$\beta_{1\text{-}42}$诱导的ROS水平升高[61]。而拮抗剂BD1047能够抑制METH诱导的原代大鼠星形胶质细胞增生, 从而发挥抗氧化作用[58]。综上所述, sigma-1受体可能通过调节氧化应激反应, 在抗焦虑过程中发挥一定作用。然而, sigma-1受体的表达水平与氧化应激间的具体关系尚未完全明确。此外, sigma-1受体激动剂与拮抗剂抗氧化作用机制亦有待进一步探索。

2.2 Sigma-1受体配体对焦虑样行为的影响

目前, 已有多种sigma-1受体配体在不同动物模型中显示出抗焦虑效应 (表1[9,10,24,26,28-30,44-46,62,63])。然而, 除PRE084外, 表中的激动剂均为多靶点药物, 不仅作用于sigma-1受体, 还可作用于组胺H3受体、5-羟色胺受体1A、毒蕈碱受体和单胺氧化酶A等, 这些靶点同样被认为是焦虑障碍的潜在治疗靶点[64-67]。因此, 观察到的抗焦虑效应可能并非完全由sigma-1受体介导。此外, 即使抗焦虑效应与sigma-1受体有关, 也未必直接源于sigma-1受体的激活, 而可能是通过间接参与抗焦虑相关的信号传导通路实现的。尽管目前仍需要更多数据来充分阐明sigma-1受体与H3受体、5-羟色胺受体1A及毒蕈碱受体等之间在抗焦虑作用中可能存在的相互作用, 但值得注意的是fabomotizole、pitolisant和YL-0919等激动剂的抗焦虑效应可被sigma-1受体拮抗剂BD1047或NE100所阻断。此外, 高选择性sigma-1受体激动剂PRE084表现出明显的抗焦虑作用, 这仍然提示sigma-1受体在焦虑相关疾病病理生理机制中的关键作用, 它依旧有望成为治疗焦虑障碍的重要靶点。不仅sigma-1受体激动剂具有抗焦虑效应, 变构调节剂SOMCL-668也在动物模型中显示出明显的缓解焦虑样行为的作用。然而, sigma-1受体拮抗剂对于焦虑样行为的缓解作用在不同研究中结果存在差异, 这种差异可能源于拮抗剂的不同化学结构与sigma-1受体的亲和力不同, 诱导的结合位点构象变化不同, 进而影响受体功能, 导致拮抗剂产生不一致的药理作用[68]。另外, 目前研究多采用行为学实验方法对动物焦虑状态进行评价, 但此类评价方法易受研究者主观偏见、实验环境和检测装置等诸多因素的干扰, 从而影响实验结果的稳定性和可重复性。如光照强度和动物初始放置位置 (黑暗侧/明亮侧) 能显著影响大鼠在明暗箱中的行为表现[69]。同样, 高架十字迷宫测试装置的闭臂颜色对小鼠行为也具有显著影响。对比黑色闭臂, 小鼠在透明闭臂条件下表现出开放臂探索行为的显著增加[70]。由此可见, 实验参数的选择对实验结果的准确性和可重复性具有重要意义。另外, 行为学实验通常通过多种方法的结合来综合评估焦虑行为。然而, 连续的行为测试可能会导致动物的行为适应性发生变化, 从而影响实验结果的准确性。已有研究建议, 不同测试之间至少间隔两天, 以减少累积压力对小鼠行为的潜在影响[71-73], 从而保证实验的结果真实性和可靠性。

2.3 Sigma-1受体在焦虑障碍中的临床研究

焦虑障碍作为一种全球范围内患病率高、疾病负担重的精神疾病, 其药物研发却相对滞后。近年来, 针对焦虑症的临床研究项目涉及的新靶点及药物[74], 包括但不限于大麻素受体调节剂大麻二酚、鼻腔化学感受器激活剂PH94B、痕量胺相关受体1激动剂SEP-363856及其他靶点尚未完全明确的药物如布格呋喃 (AF-5) 等。尽管目前尚无以sigma-1受体为靶点的抗焦虑药物进入临床研究阶段, 但该受体靶点在癫痫、抑郁、Rett综合征、亨廷顿病和阿尔茨海默病等其他神经精神疾病领域已显示出潜在治疗价值[75,76]。然而, 相关药物至今尚未成功上市, 这可能与焦虑障碍的病理生理机制尚未完全阐明、动物模型临床转化失败率高和特异性生物标志物缺乏等研发瓶颈密切相关。

临床中的焦虑障碍发病机制极为复杂, 是由基因、环境和生理失衡等多种因素共同作用的结果。然而, 当前大多数焦虑动物模型的构建方法主要依赖于躯体应激或药物诱导[71], 这些方法仅能模拟单一应激源诱发的焦虑样行为, 无法复现人类焦虑障碍中多病因相互作用的复杂情况。此外, 焦虑状态评价采用的动物行为学指标仅能反映部分症状 (如回避行为), 无法捕捉人类过度担忧和不安等复杂情绪。为弥补动物模型的局限性, 有研究者提出在Ⅰ期和Ⅱ期临床试验之间引入健康人焦虑模型, 以提升临床前预测效度[77,78]。另外, 尽管目前发现了部分标志物, 如前扣带回皮层和杏

Table 1　The effect of sigma-1 receptor ligand on animal anxiety like behavior. PTSD: Post-traumatic stress disorder; CUMS: Chronic unpredicted mild stress; ASI: Acidified saline intramuscular injections; EPM: Elevated plus maze test; OE: Open arm entries; TOA: Time in open arms; LOA: Latency to open arms; OFT: Open field test; TD: Total distance; TC: Time in the center; DC: Distance in the center; CE: Center entries; LDB: Light dark box; TID: Time in dark; NOT: Number of transitions; ZMT: Zero maze test. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ *vs* model group

S1R ligand	Ligand type	Animal	Model	Anxiety assessment	Ref.
Fabomotizole	Agonist	BALB/c mice	—	EPM (OE***, %OE***, TOA***, %TOA***)	[10]
PRE084	Agonist	SD rat	Single prolonged stress induced PTSD	OFT (TD, %TC*, DC*), EPM (%TOA*, %OE*)	[28-30]
Pitolisant	Agonist	CD-1 mice	Corticosteroid induced depression	EPM (TOA*, OE*)	[9]
YL-0919	Agonist	C57BL/6J mice	Lipopolysaccharide induced depression	OFT (TD, TC**, CE*)	[44]
	Agonist	C57BL/6 mice	Postpartum depression	OFT (TD, CE*), EPM (%OE*)	[26]
SOMCL-668	Allosteric modulator	C57BL/6 mice	Methamphetamine induced anxiety like behavior	LDB (TID***, NOT), EPM (TOA*, OE)	[62]
			CUMS induced anxiety like behavior	OFT (TC*)	[24]
E-52862	Antagonist	CD-1 mice	Monosodium iodoacetate induce osteoarthritis pain	EPM (LOA, %TOA, %OE), ZMT (LOA, %TOA)	[46]
Compound 3	Antagonist	SD rat	Binge eating model	OFT (CE, DC)	[63]
BD1063	Antagonist	CD-1 mice	Reserpine induced myalgia	LDB (%TID**)	[45]
			ASI induced fibromyalgia	LDB (%TID)	

仁核的较低反应性可作为预测患者对文拉法辛治疗产生积极反应的潜在指标[79], 而IL-6/CRP基线水平较高的焦虑患者可能对抗炎治疗的敏感性更高[42]。然而, 现有标志物在神经精神疾病鉴别诊断中仍缺乏足够的特异性, 难以有效解决焦虑障碍的高临床异质性和疗效评估过度依赖主观量表等问题。综上所述, 焦虑障碍的药物研发面临着诸多挑战。未来需要进一步深化对焦虑障碍病理生理机制的基础研究, 开发更贴近人类疾病特征的转化模型, 并探索具有鉴别诊断价值的生物标志物, 以推动抗焦虑药物研发的突破, 为患者提供更精准有效的治疗选择。

3　展望

近年来, sigma-1受体在基础研究领域取得了显著进展, 其作为潜在抗焦虑治疗靶点的重要性日益凸显。大量研究表明, sigma-1受体可通过保护神经细胞、调控神经递质系统和调节炎症因子等多种途径发挥抗焦虑效应。尽管基础研究取得了丰硕成果, 但仍存在较多问题亟待解决。现有研究表明, sigma-1受体作为分子伴侣蛋白可通过多种途径发挥抗焦虑作用, 但各途径的相对贡献、各机制间的相互关联及具体分子机制等均尚未明确。更重要的是, 当前对焦虑症病理生理学机制的理解仍存在显著不足, 这是抗焦虑药物开发过程中的重要障碍。同时, 有效且可靠生物标志物的缺乏, 以及现有焦虑动物模型在转化医学价值方面的局限性, 进一步制约了新型抗焦虑药物的开发进程[80]。但是, 基于目前所发表的研究成果, 仍可合理推断sigma-1受体在焦虑障碍的病理生理过程中扮演着关键角色, 这将为焦虑障碍的治疗药物开发提供新的研究方向。

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