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食欲素系统相关分子通路在神经精神疾病中的研究进展

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摘要 神经精神疾病(如抑郁、焦虑、失眠、创伤后应激障碍)已成为全球范围内日益严重的公共卫生问题, 给患者及其家庭带来了巨大的痛苦, 同时也给社会带来了沉重的经济负担。这些疾病严重损害患者的生活质量以及社会功能, 并导致患者劳动力丧失。因此, 寻找有效的治疗策略一直是医学界关注的焦点。近年来, 食欲素(orexin, OX)及其受体(OX1R和OX2R)在神经精神疾病中的作用机制研究取得了重要进展。随着对食欲素受体拮抗剂在相关中的研究不断深入, 其作用也逐渐受到广泛关注。该综述基于近年来该领域的前沿进展, 对食欲素系统在神经精神疾病领域的研究动态及其作用机理进行了系统梳理与简明阐述, 重点解析了其在相关疾病病理机制中的调控作用。

关键词 神经精神疾病; 食欲素系统; 分子通路; 焦虑; 抑郁

Research Advances in Molecular Pathways Related to the Orexin System in Neuropsychiatric Disorders

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Abstract Neuropsychiatric disorders, including depression, anxiety disorders, insomnia, and PTSD, now represent a pressing global public health crisis, inflicting profound distress on affected individuals and families alongside significant socioeconomic costs. These diseases severely impair the patients' quality of life and social functioning, and lead to loss of labor capacity. Consequently, the quest for efficacious therapeutic strategies has remained a paramount focus in medicine. Recent advances have illuminated the orexin system, particularly OX1R and OX2R, as critical modulators in neuropsychiatric pathophysiology. Growing evidence supports the therapeutic potential of orexin receptor antagonists, positioning them as promising intervention targets. This review, based on recent cutting-edge advancements in the field, systematically outlines and concisely elaborates on the research dynamics and mechanistic roles of the orexin system in neuropsychiatric disorders, with a focused analysis of its regulatory functions in the pathological mechanisms of related diseases.

Keywords neuropsychiatric disorders; orexin system; molecular pathway; anxiety; depression

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抑郁、焦虑、失眠和创伤后应激障碍等神经精神疾病, 已成为全球范围内的重大公共卫生问题。根据世界卫生组织《2024年世界精神卫生报告》, 全球约有八分之一的人患有各类精神障碍, 其中儿童青少年患病率呈上升趋势, 而焦虑症和抑郁症(major depressive disorder, MDD)则是最为常见的类型。这些疾病严重损害患者的生活质量以及社会功能, 并导致患者劳动力丧失。传统治疗方法虽然在一定程度上缓解了症状, 但普遍存在疗效局限及不良反应显著的问题。选择性5-羟色胺(5-hydroxytryptamine, 5-HT)再摄取抑制剂是抑郁症、焦虑症一线用药, 但起效慢, 部分患者易出现治疗抵抗性[1]。对于创伤后应激障碍(post-traumatic stress disorder, PTSD), 传统治疗如暴露疗法可能加重患者的创伤体验, 导致患者退出率高[2]。因此, 寻找更安全、有效的治疗策略一直是医学界关注的焦点。近年来, 食欲素(orexin)系统因其在调节睡眠、情绪和应激反应中的关键作用, 成为神经精神疾病研究的热点。食欲素系统由食欲素1受体和食欲素2受体及其配体食欲素A(orexin A, OXA)和食欲素B(orexin B, OXB)组成。其功能异常与多种神经精神疾病的病理机制密切相关[1-6]。此外, 食欲素及其受体在失眠、创伤后应激障碍等疾病中的研究也取得了显著成果[7]。综上所述, 深入了解食欲素及其受体在神经精神疾病中的作用机制, 对于研发新型治疗药物, 改善神经精神疾病患者的生活质量具有重要意义。本综述旨在简要总结食欲素系统在神经精神疾病中的研究现状, 并探讨其在相关疾病中的作用机制。

1 食欲素系统概述

食欲素系统在调节睡眠、情绪、应激反应、代谢以及奖赏机制等多方面发挥重要作用[8]。食欲素神经元主要起源于下丘脑外侧区(lateral hypothalamic area, LHA), 并通过广泛的投射作用影响其他脑区的功能。食欲素系统包括食欲素A和食欲素B两种神经肽亚型, OXA由33个氨基酸组成, 结构上含有2个链内二硫键, 使其相对稳定; 而OXB则为28个氨基酸构成的线性肽, 尽管两者在氨基酸序列上存在同源性, 但在分子构象层面呈现显著差异[3]。这种差异导致二者对受体的亲和力不同。它们通过激活两种G蛋白偶联受体——食欲素1型受体(orexin receptor-1, OX1R)和食欲素2型受体(orexin receptor-2, OX2R)来发挥作用。这两种受体在序列同源性上约为64%, 但在配体选择性和生理功能上存在显著差异[9], 如图1所示。研究表明, OX1R受体对OXA的亲和力高于OXB, 而OX2R受体对OXA和OXB的亲和力相似[10]。

食欲素受体在中枢神经系统中广泛表达, 其中OX1R和OX2R的表达具有显著的区域选择性(如图2所示)。OX1R主要集中在蓝斑(locus coeruleus, LC)以及扣带皮层等特定脑区, 这些区域在摄食行为调控、学习记忆过程及奖赏机制中扮演关键角色; 而OX2R则选择性表达于下丘脑后部的结节乳头核、下丘脑室旁核以及伏隔核等区域, 主要负责唤醒功能[1,11-12]。尽管OX1R和OX2R存在上述表达差异, 但它们在中枢神经系统中也有广泛的共表达区域, 涵盖下丘脑外侧区、内侧前额叶皮层、海马体、中央杏仁核、终纹床核、背侧中缝核、腹侧被盖区、外侧背被盖核以及孤束核等多个关键脑区。两者的表达分布差异表明促食欲素与两种受体结合后可介导不同的生理功能, 这也反映了食欲素系统在神经精神疾病中的潜在作用机制。

在情绪调节方面, 食欲素受体拮抗剂已被证明在改善抑郁和焦虑症状方面具有巨大潜力。食欲素受体在中枢神经系统和外周组织中的广泛分布及其功能多样性, 使其成为研究神经精神疾病和代谢紊乱的重要靶点。

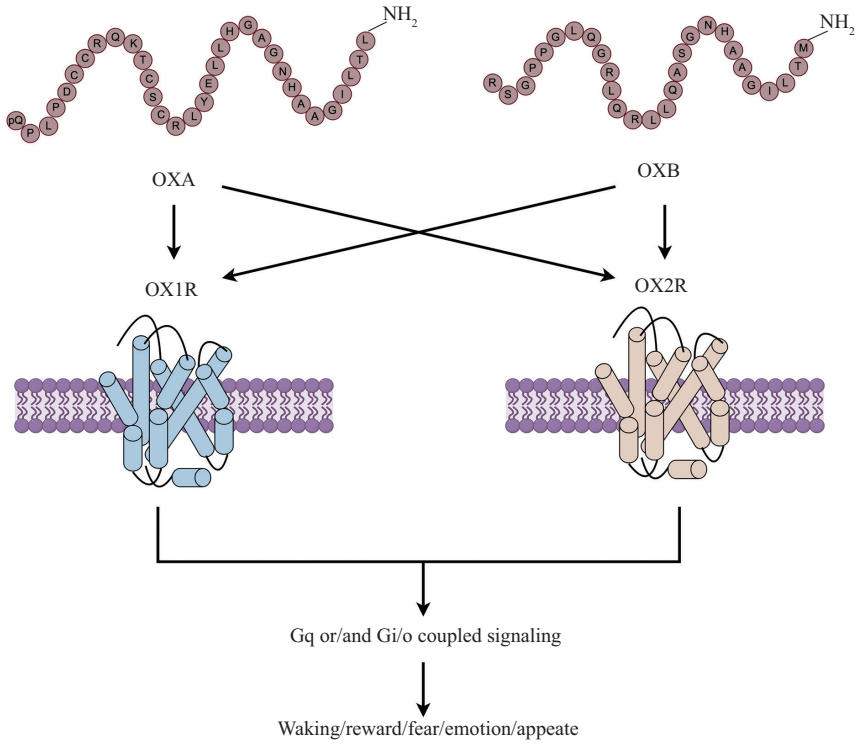
2 食欲素系统与神经精神疾病

2.1 食欲素系统在抑郁症中的作用

抑郁症是一种以情绪低落、快感缺失和认知功能损害为核心特征的精神疾病, 其病理机制复杂, 涉及神经递质失衡、神经可塑性损伤及代谢异常等多方面。近年来, 食欲素系统因其在调节睡眠–觉醒、应激反应和情绪中的关键作用, 逐渐成为抑郁症研究的热点。

2.1.1 *食欲素水平异常与抑郁样行为的关联* 大量临床和动物模型研究表明, 食欲素水平异常可能与抑郁症存在密切关联。在临床研究中, SALOMON等[13]发现, 抑郁症患者脑脊液中食欲素A的水平显著高于健康对照组。进一步针对特定人群的研究中, LU等[14]发现女性抑郁症患者的OX1R系统异常升高, 并且这一现象在经典抑郁模型中得到了验证, 提示食欲素系统的异常可能参与了抑郁症的病理过程。动物模型研究进一步揭示了食欲素系统的

复杂调控机制。FENG等[15]的研究表明, 在年轻大鼠抑郁模型中, 食欲素水平显著降低, 而在成年大鼠模型中则显著升高, 其推测这可能与胺能神经元去抑制功能缺陷相关。在慢性不可预测温和应激模型实验中, 研究人员观察到小鼠海马中的食欲素水平升高, 而通过拮抗OX1R(如SB-334867)可明显改善大

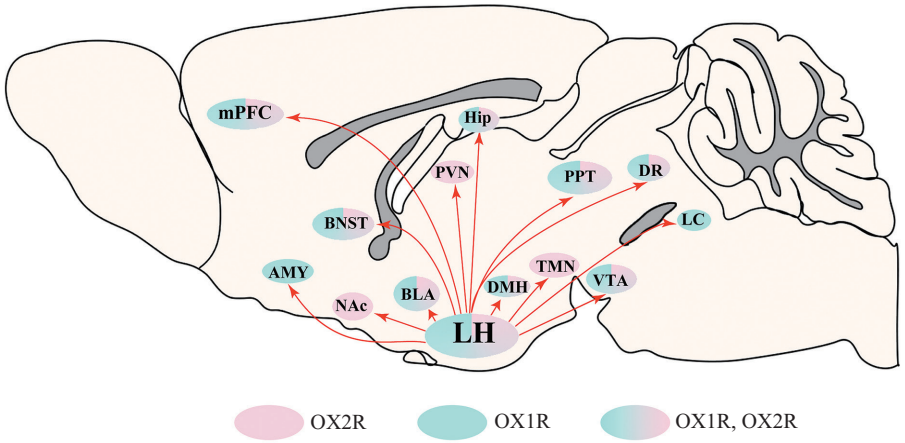


食欲素A和食欲素B是下丘脑分泌和合成的两种神经肽亚型。它们通过Gq和/或Gi/o蛋白偶联的OX1R和OX2R受体介导发挥作用, 在觉醒、奖赏、恐惧、情绪和食欲等诸多生理过程中扮演着重要角色。

Orexin A and orexin B are two subtypes of neuropeptides synthesized and secreted by the hypothalamus. Through OX1R and OX2R receptors linked to Gq and/or Gi/o proteins, they play vital roles in many physiological processes, including awakening, reward, fear, emotion, and appetite.

图1　与OX1R和OX2R激活相关的信号机制

Fig.1　Signaling mechanisms associated with the activation of OX1R and OX2R



LH: 下丘脑外侧区; BLA: 基底外侧杏仁核; NAc: 伏隔核; mPFC: 内侧前额叶皮层; BNST: 终纹床核; PVN: 下丘脑室旁核; TMN: 结节乳头核; PPT: 桥脑脚核; DR: 中缝背侧; VTA: 腹侧被盖区; LC: 蓝斑; DMH: 背内侧下丘脑; Hip: 海马体。

LH: lateral hypothalamus; BLA: basolateral amygdala; NAc: nucleus accumbens; mPFC: prefrontal cortex; BNST: bed nucleus of the stria terminalis; PVN: paraventricular nucleus of the hypothalamus; TMN: tuberomammillary nucleus; PPT: pedunculopontine tegmental nucleus; DR: dorsal raphe; VTA: ventral tegmental area; LC: locus coeruleus; DMH: dorsomedial hypothalamic nucleus; Hip: hippocampus.

图2　食欲素神经元的投射及食欲素受体的分布

Fig.2　Projections of orexin neurons and distribution of orexin receptors

鼠的抑郁样行为和认知功能障碍[16]。此外, 有研究在大鼠抑郁模型中发现, 食欲素神经元数量的减少及大小的变化与抑郁症状相关。然而, 不同研究模型和脑区检测结果存在差异。有研究发现应激诱导的抑郁小鼠下丘脑外侧表达食欲素的神经元数量显著多于年龄匹配的对照组[17]。这提示食欲素水平的变化在不同脑区和不同类型的抑郁模型中可能存在差异。对此其他研究进一步证实了这一点, 抑郁小鼠模型中, 海马体食欲素的低表达与抑郁行为呈负相关, 而杏仁核中食欲素及其受体*OX1R* mRNA的高表达则与抑郁行为呈正相关[18]。这些研究结果提示, 食欲素系统在抑郁症中的作用具有复杂性, 其水平的异常变化可能与抑郁样行为存在密切关联。然而, 不同脑区、发育阶段、模型类型及受体亚型所表现出的差异性甚至矛盾性结果, 凸显了其作用机制的复杂性, 亟需更深入的研究以阐明具体调控机制。

2.1.2 *抑郁症中食欲素与其他神经递质系统的交互作用* 抑郁症是一种复杂的中枢神经精神障碍性疾病, 其发病机制涉及多神经递质系统的协同功能失调及神经环路异常重构。当前研究证实, 食欲素能神经系统不仅能通过其特异性受体OX1R/OX2R介导的神经调控网络, 在情绪调控、应激反应调控及代谢整合过程中发挥重要作用, 还能与多巴胺能、5-羟色胺能及下丘脑垂体肾上腺轴形成复杂的交互网络, 共同参与抑郁症的发生与发展。

在中脑奖赏环路中, 多巴胺能神经传递异常已被证实与抑郁症的快感缺失及动机缺陷密切相关。食欲素神经元通过投射至腹侧被盖区和伏隔核, 激活多巴胺能神经元上的OX1R, 促进多巴胺释放, 增强奖赏效应[19-20]。动物实验表明, 慢性应激模型中OX1R拮抗剂干预可显著抑制多巴胺释放, 改善抑郁样行为[21]。以上结果提示食欲素多巴胺交互在疾病中的关键作用, 其失调可能导致快感缺失等核心症状的出现。

5-羟色胺是经典单胺类神经递质, 其信号转导异常与情感障碍(抑郁症、精神分裂症和焦虑症)的发生发展密切相关。ZHANG等[22]发现抑郁模型组大鼠海马中内源性5-羟色胺1A受体/食欲素1型受体(5-hydroxytryptamine 1A receptor/orexin receptor-1, 5-HT1AR/OX1R)异二聚体的数量显著升高, 5-HT通过激活G蛋白依赖性信号, 如环磷酸腺苷/环磷腺苷反应元件结合蛋白(cyclic AMP/cAMP-response element binding protein, cAMP/CREB)通路调控神经可塑性。脑源性神经营养因子(brain-derived neurotrophic factor, BDNF)是大脑中神经元突触可塑性的关键介质, 与抑郁和抗抑郁作用有关。CREB-BDNF通路的失调已被证实与焦虑和抑郁的病理机制相关[23]。在慢性不可预测轻度应激模型动物中, TM4/TM5肽段干预不仅可逆转海马区5-HT1AR/OX1R二聚化水平, 还能通过增强CREB磷酸化及BDNF表达, 恢复前额叶边缘系统神经环路功能。该研究结果为OX1R参与抑郁症调控的分子机制提供了关键性实验证据。

在分子互作层面, OX1R与κ阿片受体的异源二聚化现象为食欲素系统参与情绪调控提供了新的机制见解。该异二聚体可结合Gα蛋白, 从而导致细胞内cAMP水平的升高以及cAMP反应元件的激活[24]。WANG等[25]通过原代培养的大鼠海马神经元实验发现, OX1R与κ阿片受体在细胞内存在共定位。在抑郁模型小鼠的海马及下丘脑组织中, OX1R和κ阿片受体的表达水平均低于对照小鼠。其中OX1R蛋白表达呈现显著下调, κ阿片受体仅出现轻微降低。这一结果表明, 抑郁症可能导致脑组织中OX1R和κ阿片受体之间的表达失衡[24]。

食欲素系统与下丘脑–垂体–肾上腺(hypothalamic-pituitary-adrenal, HPA)轴之间的交互调控在抑郁症的发生发展中具有重要意义。HPA轴功能失调作为抑郁症的经典病理标志, 其与食欲素系统的相互作用备受关注。下丘脑外侧的食欲素神经元能够向多个脑区投射信号, 这些投射在调控机体应激反应方面发挥着重要作用, 并且与HPA轴的功能紧密相关[26]。YUN等[27]利用给小鼠注射OX2R拮抗剂发现, 实验组的小鼠在应激反应方面表现得较为迟钝, 其HPA轴的激活程度也有所减弱。这表明OX2R参与了HPA轴在下丘脑室旁核中的调控过程, 并且在HPA轴的调控机制中发挥了主导作用。选择性OX2R拮抗剂不仅能有效抑制HPA轴过度激活, 还能通过非神经源性途径改善抑郁样行为。这一结果表明, 食欲素系统对神经内分泌网络的调控具有多靶点协同作用特征, 并在调节机体应激反应和维持神经内分泌平衡方面发挥着关键作用。

综上, 食欲素系统通过OX1R/OX2R介导的多巴胺奖赏环路强化、5-HT神经可塑性调节、HPA轴功能失调及跨受体分子(如κ阿片受体)互作, 形成多

维度的抑郁调控网络。食欲素系统功能失调导致患者快感缺失、神经环路异常和内分泌紊乱，以上均为抑郁症发生发展的关键枢纽。

2.2 食欲素系统在焦虑中的作用

临床研究表明，焦虑障碍患者中枢神经系统内食欲素系统存在显著功能紊乱。25例惊恐障碍患者的脑脊液检测结果显示，患病组OX1R蛋白表达水平较健康对照组呈现显著波动，这一发现提示OX1R可能参与焦虑相关病理机制[28]。该临床观察在啮齿类动物模型中得到验证。研究发现，特异性激活的食欲素受体可显著增强小鼠社交回避行为，而拮抗OX1R则可以减轻大鼠惊恐发作模型中的焦虑样反应[28-29]。上述结果表明，食欲素受体信号的异常增强可能通过负性调控机制诱发焦虑症状。食欲素系统的功能异常与多类神经精神疾病的病理生理机制密切相关，其分子机制涉及GABA能、谷氨酸能及内源性大麻素系统的复杂调控网络。

在神经环路层面，OXA的抗焦虑作用被认为与特定受体亚型介导的突触重塑密切相关。PALOTAI等[30]的研究证实，OXA的抗焦虑作用是通过调节$GABA_A$能、α和β-肾上腺素能神经传递实现的。LUNGWITZ等[31]揭示，终纹床核(the bed nucleus of the stria terminalis, BNST)内OXA诱导的焦虑样行为与谷氨酸能系统之间存在相互作用。研究发现*N*-甲基-*D*-天冬氨酸(*N*-methyl-*D*-aspartic acid receptor, NMDA)受体拮抗剂AP5可完全抑制OXA诱导的焦虑样行为，而α-氨基-3-羟基-5-甲基-4-异恶唑丙酸(α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, AMPA)受体拮抗剂仅产生部分抑制效应。这一结果表明，在BNST中，OXA与NMDA受体的相互作用更为显著，而与AMPA受体的相互作用仍需进一步验证。

分子机制研究进一步揭示了OX1R的调控作用。SHAHSAVARI等[32]在口面部伤害感受模型中发现，喙腹内侧延髓注射OXA可显著提升海马p-ERK1/2表达水平，给予OX1R拮抗剂可完全逆转这一效应[33]。OXA可能通过OX1R和细胞外信号调节激酶1/2(extracellular regulated protein kinases 1/2, ERK1/2)激活促进大鼠海马体中的神经元激活而使患者产生焦虑样行为。此外，OX1R与大麻素受体1(cannabinoid 1 receptor, CB1R)之间的相互作用已被证明能够有效调节伤害性信号转导及焦虑相关行为[34-35]。

从信号转导角度分析，OX1R主要通过Gq蛋白偶联激活磷脂酶C(phospholipase C, PLC)-蛋白激酶C(protein kinase C, PKC)通路，参与情绪及学习记忆的调控[36]。激活PLC可促进二酰甘油(diacylglycerol, DAG)和三磷酸肌醇(inositol triphosphate, IP3)的生成，进而激活PKC并触发内质网钙释放[37]。该通路在杏仁核中可显著增强突触可塑性提升神经兴奋性，这一效应与焦虑和恐惧记忆的形成密切相关。

上述研究提示，食欲素系统在焦虑的发生发展中扮演着关键角色。它可以通过GABA能系统、谷氨酸能系统以及CB1R与OX1R的交互作用，经Gq-PLC-PKC通路激活ERK1/2，进而在BNST等神经环路中对突触重塑过程进行调控，最终参与到焦虑的病理机制当中。这些发现为焦虑障碍的干预提供了全新的潜在靶点。不过，当前相关研究仍处于不断探索和完善的阶段。未来，还需要更多高质量的研究来进一步明确其中的具体作用机制和临床应用价值。

2.3 食欲素系统在创伤后应激障碍(PTSD)中的作用

PTSD是一种与创伤相关的疾病，其病理特征表现侵入性创伤记忆再体验、恐惧条件反射异常增强、持续性回避行为及过度觉醒状态。临床研究发现，PTSD患者普遍存在食欲素系统功能异常，且这种异常与疾病严重程度密切相关。

在记忆调控方面，内源性食欲素扮演着重要角色。有研究表明，内源性食欲素通过OX2R抑制海马突触*N*-甲基-*D*-天冬氨酸受体(*N*-methyl-*D*-aspartic acid receptor, NMDAR)功能，进而影响记忆形成[38]。临床队列研究显示，PTSD患者脑脊液中OX1R蛋白表达水平较健康对照组显著降低，这一现象揭示OX1R信号缺失可能参与疾病严重程度的调控过程[39]。在PTSD患者中，压力诱发的焦虑和夸张的恐惧记忆是其重要特征。TEN-BLANCO等[40]的研究发现，OXA可通过激活内源性大麻素2-花生四烯酰甘油(2-arachidonylglycerol, 2-AG)信号，诱导杏仁核中大麻素受体(cannabinoid receptor 2, CB2R)表达上调，进而影响恐惧记忆消退。神经调控研究进一步揭示了OX1R在恐惧记忆加工中的时序特异性作用。SEARS等[41]通过特异性激活NA^{LC}通路发现食欲素受体与无条件刺激配对可显著增强线索恐惧记忆形成。进一步研

究显示, 脑室内注射SB-334867至蓝斑, 可选择性抑制恐惧记忆巩固, 而对记忆检索过程无显著影响, 这一结果提示OX1R在记忆加工的不同阶段具有差异性调控作用。

在应激反应调控方面, 食欲素系统与HPA轴形成双向调节网络。研究证实, 食欲素能神经元可以调节促肾上腺皮质激素释放因子(corticotropin-releasing factor, CRF)活性, 参与厌恶记忆的巩固过程[42]。食欲素还可以刺激促肾上腺皮质激素释放激素(corticotropin-releasing hormone, CRH)、HPA轴的促肾上腺皮质激素(adrenocorticotropic hormone, ACTH)和中枢杏仁核的CRF分泌加剧应激反应[43-44]。同时, 食欲素拮抗剂在获得恐惧记忆中的有效性也得到了证实。在杏仁核内注射食欲素拮抗剂可阻断食欲素与其受体偶联, 进而抑制食欲素诱导的CRF水平升高及条件性恐惧记忆的形成。但目前OX1R的作用机制及其控制的神经回路仍有待进一步解析。

综上所述, 食欲素在PTSD中发挥着关键的核心调控作用。其不同受体(OX1R、OX2R)在记忆形成、恐惧记忆加工以及应激反应调节等多个环节发挥作用, 并且与其他神经递质系统及神经内分泌轴相互关联, 共同影响PTSD的病理进程。一方面, 内源性食欲素通过OX2R影响突触传递活动相关的受体功能, 影响记忆形成, 且OX1R信号缺失可能参与疾病严重程度的调控过程。另一方面, 食欲素激活2-AG信号, 影响恐惧记忆消退; 食欲素还与HPA轴形成双向调节网络, 通过调节CRF活性影响厌恶记忆巩固及应激反应强度。食欲素受体拮抗剂在恐惧记忆中也显示出有效性。

2.4 食欲素系统在睡眠障碍中的作用

失眠(insomnia disorder)作为一种全球流行的慢性睡眠–觉醒节律紊乱性疾病, 其核心病理特征表现为入睡时间延长、睡眠维持困难及夜间觉醒频发等, 进而导致显著的日间功能障碍, 其中主要包括认知灵活性下降、情绪调节异常及自主神经失调等临床症状[45]。近年研究表明, 食欲素系统在参与调节睡眠–觉醒周期方面起着关键作用[46]。该系统通过激活大脑皮层、丘脑和脑干核团, 调节OX1R和OX2R的活性, 进而双向调控快速动眼期(rapid eye movement, REM)睡眠和非快眼动睡眠(non-rapid eye movement sleep, NREM)的动态平衡。研究表明, OX2R激动剂可显著延长觉醒时间, 而OX1R激动剂主要抑制REM睡眠[47]。

失眠患者常表现为夜间觉醒时间延长以及睡眠碎片化。WANG等[48]的研究提示失眠可能与食欲素信号过度活跃有关。研究发现肠道微生物紊乱导致丁酸盐(一种可能调节食欲素神经元活性的代谢物)减少, 间接增强食欲素神经元的激活, 从而延长觉醒时间。

食欲素能系统与觉醒调控网络之间存在着复杂的双向调控关系。食欲素能神经元不仅通过传出纤维投射至靶神经元, 还构建了与靶神经元之间的双向神经环路, 其中包括接受来自单胺能神经元(如5-羟色胺能、组胺能、多巴胺能和胆碱能神经元)的反向投射。研究发现, 在中缝背核及蓝斑区域, 食欲素与单胺能神经元构建了负反馈通路[49-55]。这种相互作用使得食欲素能神经元的激活, 促进单胺能神经元的电活动, 反之单胺能神经元通过减弱对食欲素能神经元的抑制性调控, 进而维持觉醒状态的稳定性。

电生理学进一步揭示了食欲素对觉醒神经元的作用机制, 其中包括抑制K^+通道或超极化激活和环核苷酸门控阳离子通道、L型Ca^{2+}的活化通道、非选择性阳离子通道或Na-Ca^{2+}交换器等[56-63]。上述机制协同作用, 使食欲素能神经元持续释放神经递质, 维持大脑皮层的觉醒状态。

综上, 食欲素系统可激活大脑多部位的OX1R和OX2R, 双向调控REM和NREM睡眠平衡。食欲素与单胺能神经元形成双向负反馈环路, 相互作用维持觉醒状态稳定。食欲素还能通过多种分子机制对唤醒神经元兴奋产生影响。这些多层次的分子机制共同构成食欲素系统驱动觉醒的生物学基础, 为开发新型失眠治疗策略提供关键靶点。

2.5 食欲素系统在神经退行性疾病中的作用

大量研究表明, 食欲神经系统功能障碍与许多神经退行性疾病有关, 其调控异常可加剧阿尔茨海默病(Alzheimer's disease, AD)及帕金森病(Parkinson's disease, PD)等疾病的神经炎症与突触损伤[64-68]。因此深入探究其作用机制对于理解神经退行性疾病的发生发展及寻找潜在治疗靶点具有重要意义。

2.5.1 *阿尔茨海默病与食欲素系统* 阿尔茨海默病也是世界上代价最高的进行性疾病之一, 其典型症状包括记忆丧失、抑郁、睡眠障碍、痴呆等, 特征性病理表现为淀粉样蛋白β肽(amyloid β-protein,

Aβ)的异常积累。临床病理学研究显示, AD患者脑脊液中OXA浓度随疾病进展呈动态变化。与轻度AD或健康对照相比, 中度至重度AD患者的食欲素水平升高[69]。进一步研究表明, 食欲素会干扰小胶质细胞对Aβ的正常降解过程, 从而加剧Aβ在脑内的堆积[70]。一项研究发现, OXA能够加重APP/PS1小鼠的Aβ积累、认知缺陷以及线粒体损伤。OXA可促进Aβ处理的SH-SY5Y细胞发生细胞死亡以及线粒体损伤[71]。此外, 调查AD患者血浆中2-AG浓度的研究显示, 与年龄匹配的对照相比, AD患者血浆中2-AG浓度显著增加[72]。大量数据支持OXA可诱导2-AG生成, 而其代谢产物2-花生四烯酰溶血磷脂酸(2-arachidonoyl lysophosphatidic acid, 2-AGP)可以调节突触可塑性、Tau磷酸化和认知功能[73-81]。睡眠障碍和失眠等情况会激活食欲素神经元兴奋性, 进而进一步促进觉醒状态以及2-AGP的产生, 形成恶性循环, 加快AD的病理进程[82]。

2.5.2 *帕金森病与食欲素系统* 帕金森病是一种以运动迟缓、强直和静止性震颤为特征的神经退行性疾病, 其主要病理机制与黑质致密部多巴胺能神经元的进行性退变紧密相关。许多PD患者患有胃肠道(gastrointestinal, GI)功能障碍, 具体表现为胃轻瘫(胃排空延迟)、早饱、腹胀、便秘和吞咽困难等症状[83-85]。在动物实验研究中, 向LH给予OXA可显著增加胃动力, 而通过预先给药SB-334867可完全阻断这一效应[86]。大量研究表明, 食欲素在PD的体外和体内动物模型中均表现出神经保护特性。在脑缺血再灌注损伤模型中, OXA通过抑制自噬生物标志物的表达发挥神经保护作用, 并通过激活OX1R介导的丝裂原活化蛋白激酶/细胞外信号调节激酶/哺乳动物靶蛋白(mitogen activated protein kinase/extracellular signal-regulated kinase/mammalian target of rapamycin, MAPK/ERK/mTOR)信号通路抑制过度自噬的发生[87]。进一步研究表明, OXA的神经保护作用与BDNF调控网络密切相关。在1-甲基-4-苯基-1,2,3,6-四氢吡啶(1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, MPTP)诱导的PD模型中, OXA干预可通过OX1R介导的磷脂酰肌醇-3-激酶(phosphoinositide 3-kinase, PI3K)和PKC信号通路, 促进BDNF水平的恢复[88-90]。

综上所述, 食欲素系统与神经退行性疾病关联密切。在阿尔茨海默病中, OXA升高干扰小胶质细胞降解Aβ, 加剧其堆积与线粒体损伤, 还可诱导2-AG生成进一步促进觉醒状态, 从而导致睡眠障碍和失眠; 在帕金森病中, OXA通过OX1R介导的MAPK/ERK/mTOR及PI3K/PKC信号通路和神经营养因子发挥保护作用, 对研究神经退行性疾病机制及治疗靶点意义重大。尽管现有研究已初步阐明食欲素能系统在神经退行性疾病中的多靶点调控机制, 但其神经保护效应的特异性通路网络仍待解析。

2.6 食欲素系统在药物成瘾中的作用

药物成瘾(drug addiction)是一种以强迫性觅药行为和奖赏系统功能重塑为特征的慢性复发性脑疾病。近年来研究发现, 食欲素系统及其受体OX1R和OX2R在多种物质(如酒精、尼古丁、可卡因)成瘾进程中扮演关键角色[91-93]。以往研究认为, OX2R主要负责调控觉醒功能。但最新研究发现, 该信号通路也是介导药物寻求行为的重要介质[94-96]。研究表明, 全身给予OX1R或OX2R拮抗剂能有效抑制酒精和蔗糖的过度摄入行为[91,96]。此外, 将OXA注射到后室旁核中, 可诱导可卡因寻找行为的恢复, 并延长可卡因自我给药行为的持续时间[97]。

腹侧被盖区(ventral tegmental area, VTA)作为奖赏环路的枢纽, 其多巴胺能神经元的突触重塑是成瘾的关键环节。BORGLAND等[98]利用全细胞膜片钳技术揭示, OXA通过激活PLC/PKC信号通路, 特异性增强VTA多巴胺神经元中NMDA受体介导的兴奋性突触后电流。进一步研究发现, 可卡因暴露可诱导突触后适应性改变, 增加食欲素神经元中的AMPA/NMDA受体比率[99]。在VTA内注射SB-334867可抑制可卡因诱导的复吸行为, 而AMPA受体正向变构调节剂PEPA可完全逆转这一效应[100]。这一结果表明, 可卡因寻求行为的恢复依赖于VTA中OX1R和AMPA受体之间的相互作用。此外, TUNG等[101]的研究阐明了食欲素系统在压力诱导复吸中的作用。VTA多巴胺神经元上突触后Gq偶联的食欲素受体的激活, 可增强突触前GABA能输入处的逆行内源性大麻素信号转导, 从而抑制GABA释放改变VTA多巴胺神经元的兴奋性平衡。

分子机制研究进一步揭示了食欲素受体不同亚型在信号转导中的特异性调控作用。食欲素能信号通过PLC-PKC级联反应, 介导NMDA受体GluN2B亚基向突触后膜的动态易位, 从而增强VTA多巴胺能神经元的突触后兴奋性, 在成瘾相关奖赏效应中

发挥核心调控作用[102-103]。一方面, OXA激活突触后的OX1R, 加快NMDAR介导的神经传递过程, 增加AMPAR介导的电流强度。另一方面, OXB通过突触前作用促进谷氨酸释放, 同时激活突触后OX2R, 选择性地增强NMDAR介导的兴奋性突触后电流[104]。

综上所述, 食欲素在药物成瘾中具有关键作用。它通过OX1R和OX2R受体, 激活PLC/PKC信号通路, 增强VTA多巴胺神经元兴奋性, 强化成瘾行为。OX1R与AMPA受体相互作用, 是药物寻求恢复的重要机制。分子层面, 食欲素信号调节NMDA受体亚基易位, 增强突触后兴奋性, 这种受体亚型的特异性调控为成瘾治疗提供了潜在靶点。

3 结语与展望

食欲素系统是调控多种神经精神疾病的关键枢纽。其功能紊乱与抑郁、焦虑、PTSD、睡眠障碍、神经退行性疾病及药物成瘾等多种神经精神疾病密切相关。研究揭示, 食欲素受体OX1R和OX2R通过调控HPA轴活性、突触可塑性及神经炎症等多种通路, 在不同疾病中呈现“时空动态调控”特征。在抑郁症中食欲素系统驱动相关脑区过度兴奋, 打破情绪调节平衡; 在PTSD中OXA损害恐惧记忆消退, 导致病理性记忆固化; 在AD中食欲素加剧Aβ沉积, 加速神经退行性变; 在药物成瘾中食欲素系统可以增强VTA多巴胺能信号, 强化奖赏效应。上述发现为食欲素受体拮抗剂的治疗应用提供了理论基础。深入探究食欲素系统的调控机制, 不仅为开发神经精神疾病创新疗法提供关键理论依据, 还将有力推动相关靶向药物的研发及其临床转化应用。

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