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催产素减轻抑郁症状机制的研究进展*

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摘要　抑郁症是临床上常见的精神疾病. 目前缺少治疗抑郁症的有效手段. 催产素（oxytocin，OT）是一种由下丘脑室旁核和视上核神经元分泌的神经肽，参与生理和病理状态下多种复杂神经精神活动. 近年来，许多临床和基础研究显示OT可通过多种机制减轻抑郁症状. 本文就OT的生理作用，抑郁状态下OT分泌水平，OT对抑郁相关激素、脑区、环路和神经可塑性及OT对氧化应激反应的作用等最新研究进展做一综述，探究OT减轻抑郁症状的机制.

关键词　催产素，抑郁症，HPA轴，杏仁核，海马，神经可塑性，氧化应激
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1　概　　述

抑郁症是一种以情绪低落、思维迟钝、兴趣减退、动作语言减少为主要特征，伴有自杀倾向的精神疾病[1]. 根据世界卫生组织（world health organization，WHO）的数据，抑郁症影响3.5亿人，终生患病率超过17%，是第九大致残与死亡的疾病[2]. 在中国深圳，抑郁症患病率高达6.5%[3]. 流行病学研究发现，至少有3%（研究估计范围3%~9%）的青少年人群会患有抑郁症[4]. 在老年人群中，患病率约为5%[5]. 当今抗抑郁药物是治疗抑郁症的首选疗法，但约30%~40%的患者对经典抗抑郁药物，如盐酸氟西汀，无反应[6-9]. 近年来，人们发现催产素（oxytocin，OT）有减轻抑郁症状的作用. 针对OT的种种功能，我们在此探讨OT抗抑郁症的可能作用机制.

2　OT的生理作用

OT是一种在进化过程中高度保守的神经肽，由下丘脑室旁核（paraventricular nucleus，PVN）和视上核（supraoptic nucleus，SON）神经元分泌. OT具有两种调节方式：一是体液调节，即在垂体后叶通过血液被运送至各个靶器官[10]；二是神经调节，室旁核OT神经元末梢直接投射至中枢神经系统其他区域. 机体通过负反馈机制调节OT水平，影响其生理功能[11]. 在中枢神经系统中，哺乳动物中的下丘脑中的OT细胞有两种类型：大细胞（magnocellular OT，magnOT）和副细胞（parvocellular OT，parvOT）. MagnOT细胞调控孕期妇女的应激、恐惧等情绪反应，parvOT主要调控血压、心律、肠道反应和痛觉感受等[12]. OT与神经调节和情绪管理密不可分.

OT受体（oxytocin receptor，OTR）在全脑中均有表达，特别是在涉及精神、情感、情绪和社会行为的关键脑区中表达水平较高，如在自主神经系统、额叶皮层、嗅觉系统、基底神经节、边缘系统、丘脑、下丘脑、脑干和脊髓[13]等. OTR可通过触发肌醇三磷酸盐介导的钙释放，激活机械门控Ca^{2+}通道和电压门控Ca^{2+}通道等下游信号通路[14-15]，产生相关的生理功能，例如增强分娩过程中的子宫收缩及促进泌乳期乳汁排出等[16].

近几年的研究发现，OT还是情绪情感和动机

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的重要调节激素，在多种神经精神疾病中发挥重要调节作用，如OT相关的通路可能参与调控抑郁情绪的发生发展过程[17]. 但目前对OT抗抑郁症的具体机制仍不清楚. 最新研究发现，OT的抗抑郁作用可能涉及调节5-HT释放、下丘脑-垂体-肾上腺（hypothalamic-pituitary-adrenal axis，HPA）轴、精氨酸加压素（arginine vasopressin，AVP）、杏仁核、海马、神经可塑性、抗炎抗氧化和基因多态性等[18-19]，因此本文将针对这几个方面，对其抗抑郁症机制的基础研究进展做一综述.

3　OT水平与抑郁程度密切相关

已有研究报道，催产素的血清水平与抑郁程度有一定的关联. Scantamburlo等[20]发现重度抑郁症患者（汉密尔顿抑郁量表17分以上）血清中催产素与抑郁症状得分呈显著负相关. 另一项对产后抑郁的研究使用爱丁堡产后抑郁量表（Edinburgh postnatal depression scale，EPDS）评估产后抑郁风险，研究结果显示，与产后抑郁症低风险组受试者相比，高风险组（产后EPDS评分为10或更高）的血浆OT浓度较低[21]. 这提示了催产素可能参与抑郁症的发病机制.

3.1　OT的抗抑郁作用可能与5–HT通路活性相关

单胺递质假说是抑郁症发病机制的经典假说之一，经典抗抑郁药多针对单胺递质如5-HT和多巴胺等为药物作用靶点发挥抗抑郁作用. 单胺递质假说认为，抑郁症状由脑内单胺递质失衡导致[22]. 在抑郁症患者中，血小板5-HT结合位点减少[23]，脑脊液5-HT代谢物水平降低. 在正电子发射型计算机断层显像研究中发现，急性抑郁症患者和康复患者大脑中5-HT_{1A}受体广泛减少[24-25]. 与此同时，研究发现健康参与者大脑中5-HT水平也与情绪诱导的抑郁样行为呈负相关[22]. 动物实验证实，在突触间隙增加5-HT可激活其下游与神经可塑性相关的基因转录[26]. 以上种种事实说明5-HT通路的下调和抑郁的易感性之间存在联系.

有研究发现，OT可以调节中枢5-HT的释放. Yoshida等[27-28]发现，通过微透析探针注入OT到OTR敲入小鼠的中缝核（median raphe nucleus，MRN），可诱导MRN中5-HT的释放. 这证明OT可以通过直接激活MRN中5-羟色胺能神经元上的OTR，进而调节5-羟色胺释放.

有意思的是，改变中枢5-HT水平反过来也可影响催产素分泌. 雄性大鼠脑室内输注5-HT溶液5 min后催产素分泌水平为初始浓度的8倍，15 min后缓慢下降. 低剂量5-HT激动剂对催产素分泌无明显效应，高剂量5-HT激动剂显著升高血浆催产素水平至正常水平的3倍，表明脑内5-HT激动剂对催产素的分泌呈浓度依赖性. 用5-HT拮抗剂WAY、LY或RS23等预处理可显著抑制5-HT诱导的催产素分泌比原先减少75%，提示5-HT诱导的催产素分泌涉及5-HT_{1A}、5-HT_{2C}和5-HT_4受体[29]. 这些研究证据提示5-HT通路与OT水平的相关性.

以上研究提示OT分泌与中枢5-HT活性之间可能存在正反馈作用，一方面OT可以上调5-HT释放，另一方面5-HT释放可以影响催产素分泌，提示催产素治疗可能增加单胺类递质靶点药物的抗抑郁效能，或减轻经典抗抑郁药物的脱靶效应.

3.2　OT通过调节HPA轴影响抑郁症状

HPA轴活动受下丘脑中促肾上腺皮质激素释放因子（corticotropinreleasing factor，CRF）支配，通过激活垂体促肾上腺皮质激素（adreno-cortico-tropic-hormone，ACTH）的分泌，最终刺激肾上腺皮质中糖皮质激素的分泌[30-31]. 慢性应激引起的HPA轴过度激活，被认为是抑郁症的发病风险因素之一[32]. HPA轴的过度上调表现为腺体过度增大[33]、海马体积减小[34]、分泌细胞过度激活、血浆或体液中的激素水平增加[35]、激素相关受体及其下游通路过度激活等. 大量临床研究发现抑郁症患者唾液、血浆和尿液中皮质醇水平增加[36-37]，垂体和肾上腺的体积增大，CRF水平上升等. 动物实验证明，给予外源皮质激素足以引发动物出现抑郁样和焦虑样行为，而抑制CRF或皮质醇的水平，可显著缓解多种抑郁症动物模型的抑郁症状[38].

OT可通过减弱HPA轴活动调节应激反应[39]，从而下调应激行为和自主神经系统反应[40]. 动物实验表明，在卵巢切除7 d后的大鼠脑室内通过微型泵输注催产素（100 ng/h）可减少正常和应激刺激30 min后的血浆ACTH浓度以及下丘脑中CRF的pre-mRNA[41]. 对健康男性接受特里尔社会压力测试的一项研究发现，压力测试50 min前接受鼻内催产素（24 IU）可降低被试者的唾液皮质醇水平，这表明给予OT减轻了应激引起的HPA轴功能上调[42]. 因此OT减少可能导致抑郁症患者HPA系统失调，提示OT可能通过影响HPA轴的功能调节抑郁症状. Windle等[43]通过高架十字迷宫实验评价不同剂量催产素对噪声应激处理后大鼠HPA轴的反应. 结果显示，当动物在陌生的环境中受到轻

度压力时，催产素处理可减轻焦虑水平. 因此，催产素可能通过调节HPA轴发挥抗抑郁和焦虑作用.

3.3 OT的抗抑郁作用受AVP和性别影响

OT由下丘脑PVN和SON或边缘系统中的神经元合成并分泌，同时AVP也可由上述核团中的神经内分泌细胞产生. 研究发现，OT发挥抗焦虑和抗抑郁作用，而AVP主要增强焦虑和抑郁相关行为[44]. 外周AVP水平的上升也与自杀风险有关[45]. 越来越多的证据表明，OT和AVP在调节抑郁症状方面存在拮抗效应[46]. 静脉内给予AVP导致ACTH和皮质醇水平上升，增加抑郁症患病风险[47]. AVP V_{1b}受体的某种单核苷酸多态性表型可预防复发性重度抑郁症[48]. 下丘脑PVN和SON中的AVP神经元激活导致抑郁症患者的HPA轴过度上调，并促进下游通路中的ACTH和皮质醇的释放，从而诱发抑郁症状[49]. 因此，Neumann等[50]提出这样的假设：中枢OT和AVP信号通路之间的动态平衡可影响下丘脑和边缘通路，参与调节多种精神病理学情绪行为.

然而有趣的是，OT的抗抑郁效果具有男女性别差异. 女性抑郁症的终生患病率是男性的2倍[51]. 雌性小鼠体内的雌激素可上调PVN内的OT合成，并可通过激活雌激素α和β受体调节杏仁核中的OTR表达. 与OT相反，AVP主要受雄激素，如睾酮影响，但也受雌激素受体介导的信号通路的影响[52]. 但是OT抗抑郁作用的性别差异机制目前尚不清楚.

3.4 OT对杏仁核功能和神经活动的调节作用

杏仁核不是单一的同质结构，而是一组结构和功能相异的核团集合体，不同核团执行边缘系统和皮层处理区域连接的不同模式[53]. 抑郁使杏仁核-前额叶回路内的结构和功能变化偏向应激反应[54]. 杏仁核-前额叶活动耦联的增加对于急性应激诱发抑郁的恢复至关重要[55-56]. Hamilton等[57]发现重度抑郁症与杏仁核体积异常有关. 未经药物治疗的抑郁症患者的杏仁核体积减少，而服药患者的杏仁核体积显著增加，提示杏仁核功能及相关通路受损是抑郁症发病的重要机制.

OTR广泛分布于认知和情绪相关的脑区，研究发现OTR在杏仁核中大量表达，并且在杏仁核中存在大量分泌OT的神经元，例如magnOT细胞和parvOT细胞[12, 58]. 这些证据提示了杏仁核OT通路可能与抑郁症状有关. Eckstein等[59]的实验表明，OT对杏仁核的神经调节功能发挥重要作用. OT增加了杏仁核与背内侧前额叶的连通性. 同时OT改变了不同杏仁核亚核团到上游皮质节点的神经环路，特别是前额叶-顶叶和小脑下游区域与杏仁核亚核团的连通性. 由于浅表杏仁核-前额叶通路的活动水平与亚临床抑郁水平呈负相关，因此OT可能通过改善杏仁核-前额叶投射抑制抑郁症状[59]. 这进一步提示增加脑内OT可能通过杏仁核环路参与情绪调节.

3.5 OT改变神经可塑性和神经再生影响抑郁行为和症状

神经可塑性是突触和神经通路由于行为、环境、神经活动、思维情绪或各种创伤而产生的适应性变化，是神经系统对内外环境变化产生适应的特性[60]. 神经可塑性包括突触重塑（synaptic remodeling）、长时程增强（long-term potentiation，LTP）和长时程抑制（long-term depression，LTD）[61].

海马是参与中枢神经系统可塑性的关键脑区，临床和基础研究也指出抑郁可造成海马神经可塑性损伤[62]. 临床研究表明，抑郁症患者的海马体积和功能都显著下降. 海马通过其对下丘脑的投射负向调控HPA轴[63]. 因此海马功能障碍可能导致应激反应失调，从而加重抑郁症状[61]. 成人神经元的病理改变增加对抑郁的易感性，而成人海马齿状回的神经发生和突触增加对复发性抑郁症有保护作用[64-65].

催产素可直接影响海马脑区的神经可塑性. 有证据显示催产素能够减少海马神经元凋亡并促进成年神经发生[66]. 在动物实验中发现，通过改善成年海马神经可塑性，OT减轻了母婴分离诱导的成年大鼠的抑郁样行为. Ji等[67]研究发现鼻内给药影响了母婴分离诱导的成年大鼠的抑郁样行为和海马神经发生. 母婴分离导致实验动物在新环境中的身体活动和情绪反应减少，与此同时血浆、下丘脑和海马中的OT水平降低. 鼻内给予OT促进了海马神经元再生，减轻了母婴分离后新生小鼠的抑郁样行为，其具体机制可能为OT促进了海马新生神经元的增殖和分化，并提高了树突分支复杂性. 电生理实验表明，OT增强了雄性大鼠海马CA1区的LTP[68]. 鼻内施用的OT通过细胞外信号调节激酶（extracellular regulated protein kinases，ERK）通路增强了应激大鼠海马CA1区LTP，并减少了相应区域的LTD[69]. Lee等[69]的研究结果表明，鼻内给予OT可有效预防应激诱导的海马可塑性改变. 他

们发现提高脑内OT水平可激活抑制性的非锥体神经元，提高其对海马锥体神经元的抑制作用，下调压力相关的ERK通路，进而改善应激诱发的海马突触可塑性和空间记忆损伤.

3.6　OT的抗炎抗氧化作用

炎症反应涉及错综复杂的中枢免疫信号网络.早期研究表明，在生理情况下，外周炎症标志物与抑郁指数之间呈正相关[70].细胞因子IFN-α治疗可导致抑郁症状，甚至导致治疗者出现符合临床诊断标准的抑郁症，有研究报道IFN-α引发抑郁症的几率高达45%[71-72].在神经炎症发生过程中，小胶质细胞的激活是促炎细胞因子分泌的重要途径[73-74].Yuan等[75]发现使用OT预处理显著抑制LPS诱导的BV-2和原代小胶质细胞的活化，减少随后的促炎因子释放.其机制可能为抑制脂多糖诱导的小胶质细胞中ERK和p38的磷酸化，和升高胞内钙离子浓度.在脂多糖诱导的急性炎症模型中，OT预处理显著抑制小鼠脑内小胶质细胞活化，并减弱促炎因子水平.

有研究表明，抑郁症通常伴有线粒体功能障碍和抗氧化系统损伤[76].Maes等[77]报道重度抑郁症状与较低血浆浓度抗氧化剂（如高密度脂蛋白胆固醇、维生素E、辅酶Q10和锌）和较低总抗氧化剂状态相关.线粒体功能障碍与高水平的氧化和亚硝化应激（ROS和NO的过量产生）、抗氧化损伤（GSH水平的降低）和能量代谢受损（ATP产生减少）有关.ROS系统在抑郁症的发病中起重要作用[78-79].由ROS产生的氧化应激被认为是氧化和抗氧化系统之间的不平衡造成的.早期生活压力能够通过影响抗氧化系统和过度生成的自由基，例如活性氧（reactive oxygen species， ROS）改变大脑的正常线粒体功能[80-81].

Amini-Khoei等[82]的实验证明：给予OT可减轻应激小鼠的抑郁样行为，改善线粒体功能和减少炎症因子在海马中的表达.母婴分离后的成年雄性小鼠有明显抑郁样行为，而鼻内给予OT改善其在强迫游泳、旷场实验和蔗糖偏好实验中的抑郁样行为.与生理盐水组相比，母婴分离诱导的抑郁样小鼠海马的ROS水平显著增加，而鼻内给予OT显着降低了其海马中ROS的水平，提示了抑制ROS升高可能是OT抗抑郁症机制的另一个方面.

3.7　OT的基因多态性与抑郁症有关联

Kushner等[83]发现OT受体基因单核苷酸多态性（rs53576）减轻了抑郁程度.Thompson等[84]的研究发现抑郁症女性青少年的抑郁症状水平与OTR基因型显著相关.携带至少一个OTR rs53576的A等位基因的青少年也有早期母婴分离史，并在青春期中也表现出严重抑郁症状.Tost等[85]发现A等位基因减少了下丘脑的体积并且增加了下丘脑与杏仁核和背侧前扣带回皮层的结构和下丘脑的连通性.另一OTR基因单核苷酸多态性（rs2254298）同样能够增加下丘脑和边缘系统的体积，增强其功能和连接性[86].表观遗传学研究表明，OTR外显子1的甲基化水平与抑郁症有关，外显子1甲基化水平下降使OT受体表达水平改变或降低[87]，提示了抑郁可能下调了OT受体水平，抑制了OT信号通路.

但令人遗憾的是，目前尚无关于OT水平对抑郁症风险基因影响的表观遗传水平研究，因此我们无法从基因层面上判断OT水平对抑郁症遗传风险的作用.

4　展　　望

综上所述，OT发挥抗抑郁效果的机制复杂，可能涉及激素水平、神经环路、神经可塑性以及性别差异（图1）.虽然其机制尚不明确，但是OT的抗抑郁效果已经得到了大量临床和动物实验的支持，鼻内OT给药可能提供一种潜在的抑郁症干预途径.OT的生理作用可与高级功能，如社会功能、情感和社交等等相关，提示深入了解OT机制将有助于理解抑郁症，特别是重度抑郁症的高级情感和认知功能损伤的机制，也有助于结合经典抗抑郁药物开发联合治疗，为开发抑郁症治疗的新策略提供依据.

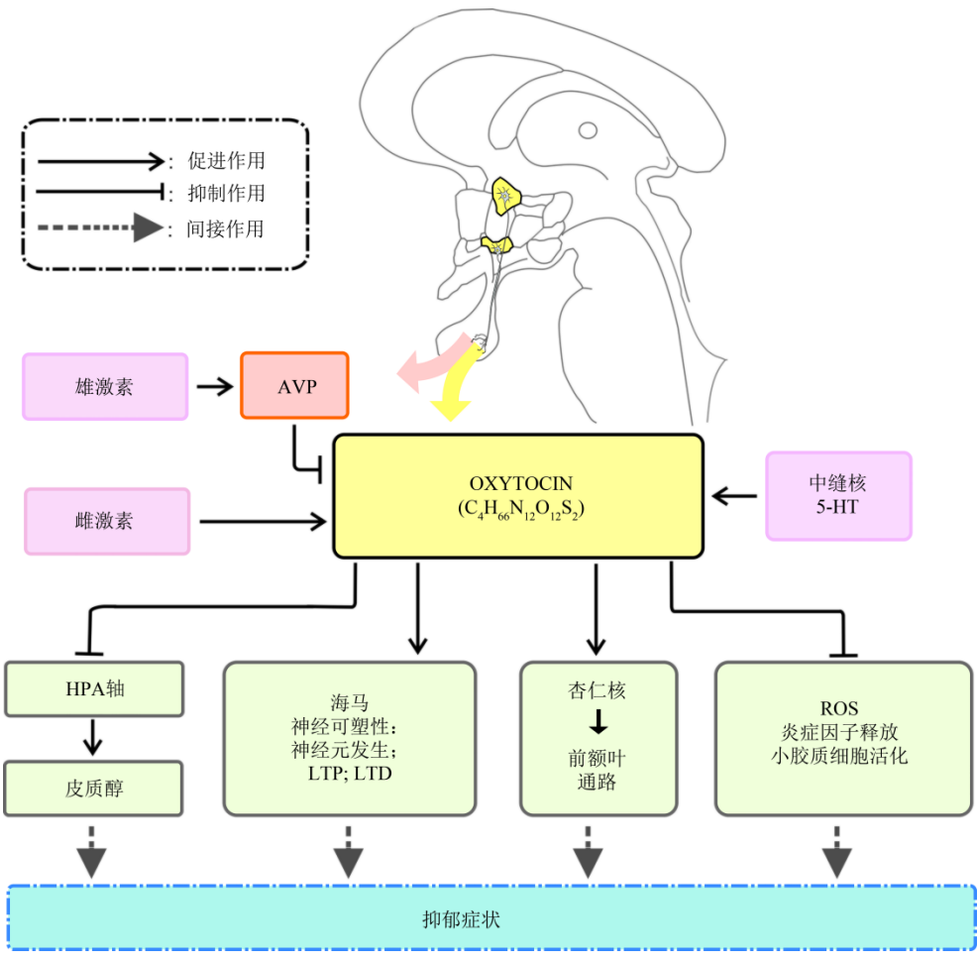

Fig. 1　Anti-depression mechanism of oxytocin

图1　催产素的抗抑郁机制

OT可由下丘脑室上核和室旁核的神经元分泌. OT的血浆浓度受多种因素调节，包括：由中缝核释放的5-HT引起OT的浓度增加；雌激素的作用促进OT水平上升；雄激素对AVP有促进作用，而AVP能够抑制OT功能. OT抗抑郁症作用可通过：抑制HPA轴的上调来降低血浆皮质醇的水平；改善海马可塑性，增强海马CA1区LTP和减弱LTD；增强杏仁核与前额叶通路的连通性；抑制ROS的升高，抑制小胶质细胞的活化，减少炎症因子的释放. OT：催产素；AVP：精氨酸加压素；5-HT：五羟色胺；HPA：下丘脑-垂体-肾上腺轴；LTP：长时程增强；LTD：长时程抑制；ROS：活性氧.

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The Mechanisms of Oxytocin in Alleviating Depressive Symptoms*

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Abstract Depression is a common mental illness. Currently, there is no effective way to treat depression. Oxytocin (OT) is a neuropeptide secreted by the paraventricular nucleus and the supraoptic nucleus neurons in the hypothalamus. OT is involved in a variety of complex neuropsychiatric activities under physiological and pathological conditions. In recent years, many clinical and basic studies have shown that OT can relieve depressive symptoms through multiple mechanisms. This article reviews the research progress of the physiological role of OT, the level of OT secretion in depression, the effect of OT on depression-related hormones, brain regions, neural plasticity and oxidative stress. Our review highlights the potential administration of OT in the treatment of depression.

Key words oxytocin, depression, HPA axis, amygdala, hippocampus, neural plasticity, oxidative stress

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