

· 综述 ·

多巴胺奖赏系统传入调节参与抑郁机制的研究进展

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【摘要】 快感缺失是抑郁症的核心症状之一,而多巴胺能系统在快感缺失中发挥关键作用。多巴胺能活动十分复杂,受多种大脑结构调节,包括海马体的腹侧下神经带、伏隔核、腹侧苍白球和基底外侧杏仁核等。基础研究和临床研究表明抑郁症中多巴胺能系统缺陷,而这些缺陷可能源于传入回路的失调。本文从抑郁症与多巴胺能系统的联系入手,总结腹侧被盖区多巴胺能神经元的上游通路,包括腹侧海马下托至伏隔核到腹侧苍白球的激活通路和基底外侧杏仁核至腹侧苍白球的抑制通路,并利用基础实验及临床研究客观阐明抑郁样行为及抑郁症中脑多巴胺能系统传入调节的异常,概述了抗抑郁治疗与中脑多巴胺能神经系统的相关性,以期对抑郁症的诊疗和机制的研究提供思路。

【关键词】 多巴胺; 抑郁症; 腹侧被盖区; 传入调节; 综述

Research progress on the involvement of dopamine reward system input regulation in the mechanism of depressive disorder

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【Abstract】 Anhedonia is one of the core symptoms of depressive disorder, and the dopaminergic system plays a crucial role in the occurrence of anhedonia. Dopaminergic activity is highly complex and regulated by various brain structures, including the ventral subiculum, nucleus accumbens, ventral pallidum, and basolateral amygdala. Basic and clinical studies have shown that dopaminergic system defects in depressive disorder can be attributed to dysregulation of the input circuit. This paper starts with the correlation between depressive disorder and dopaminergic system, and summarizes the upstream pathways of dopaminergic neurons in the ventral tegmental area, including the activation pathway from the ventral subiculum to the nucleus accumbens to the ventral pallidum, and the inhibition pathway from the basolateral amygdala to the ventral pallidum. Moreover, this paper objectively elucidates depressive-like behavior and abnormal input regulation of the midbrain dopaminergic system in depressive disorder through basic experiments and clinical studies, and outlines the correlation between antidepressant treatment and midbrain dopaminergic nervous system, so as to provide directions for the diagnosis, treatment, and mechanism research of depressive disorder.

【Key words】 Dopamine; Depressive disorder; Ventral tegmental area; Input regulation; Review

抑郁症是全球最普遍的精神障碍之一^[1]。2019年WHO对冲突环境下精神障碍患病率进行统计分析,发现抑郁症和其他精神障碍性疾病在任何时间点的总患病率均为22.1%^[2]。我国成人抑郁症的终生患病率高达6.8%,而得到充分治疗的患者不足1%^[3]。抑郁症病理生理机制十分复杂,其发病机制尚未完全阐明,目前相当一部分患者的治疗效果并不理想^[4]。此外,抑郁症的不同症状群如情感症状群、认知行为症状群、自主神经症状群等可能涉及多条神经回路^[5],进一步增加了治疗难度。

目前,抑郁症的药物治疗主要针对单胺能

机制发挥作用。传统抗抑郁药如三环类抗抑郁药可通过减少突触前膜的5-HT和去甲肾上腺素(Norepinephrine, NE)再摄取,同时阻断突触后组胺受体、5-HT受体、毒蕈碱型乙酰胆碱受体、肾上腺素能受体等发挥作用,因其明显的抗胆碱能不良反应及心脏毒性而逐渐被取代^[6]。SSRIs可高度选择性抑制突触前膜的5-HT再摄取,而对NE和组胺几乎没有激动或抑制效应,抗胆碱能效应也较小,是目前抑郁症临床一线治疗用药^[7]。虽然新型抗抑郁药物较传统抗抑郁药物不良反应少,但其需要数周才能达到治疗效果,且容易产生耐受性^[8]。因此,对于

许多存在急性自杀风险的抑郁症患者,迫切需要开发新的、快速有效的、不易耐受的药物以治疗抑郁症。

腹侧被盖区(ventral tegmental area, VTA)富集多巴胺能神经元,其投射至伏隔核、前额叶皮质等区域,是奖赏系统的重要组成部分,其中任何一个关键环节异常或中断都可能导致动机、决策、学习、完全快感等奖励缺失,这些均与抑郁症的一大核心症状快感缺失密切相关^[5,9]。因此,多巴胺奖赏系统参与抑郁症核心症状快感缺失的发生发展^[10]。本文对VTA多巴胺能神经元的传入调节进行综述,探讨其上游神经环路与抑郁症的联系,并总结抗抑郁药物作用于多巴胺能系统的机制。

一、抑郁症中的多巴胺能缺陷

重度抑郁症患者存在的快感缺失可以理解为对未来的期望降低、对获得的回报低估、对积极事物的认可和回忆较少、为获得回报而愿意付诸行动的意愿降低等共同作用的结果,患者经治疗后抑郁情绪好转,但这些因素仍然存在,易造成抑郁症状复发^[11]。因此,快感缺失不仅是对快乐的体验能力缺乏,还包括预期、动机、决策等奖励相关过程的中断。快感缺失作为抑郁症的核心症状之一,可预测抑郁症患者的病程、预后、不良结局及耐药的发生。由于该症状治疗困难,因此确定相关的中断神经回路至关重要,而中脑多巴胺奖赏系统与快感缺失的相关性研究是探索抑郁症患者多巴胺能缺陷的关键切入点^[12-13]。

研究表明,腹侧纹状体多巴胺参与调节奖励的预测和预期^[14],从VTA到腹侧纹状体的多巴胺能神经元投射异常是快感缺失发生的神经生物学基础的一部分,抑郁症快感缺失已被证明与纹状体的奖励减少有关^[15-16]。在神经影像领域,单光子发射计算机断层(SPECT)成像显示重度和非重度抑郁症患者的纹状体亚区多巴胺转运蛋白结合的纹理特征均高于健康对照组,且左侧纹状体边缘区域忙碌程度与抑郁严重程度相关^[17]。抗抑郁药治疗可改变重度抑郁症患者纹状体多巴胺转运体的可用性^[18],既往研究表明苯丙胺及其相关化合物通过促进多巴胺释放、阻断多巴胺再摄取发挥精神兴奋作用,改善抑郁症状^[19-20]。

研究表明,抑郁症模型动物中脑边缘多巴胺能系统功能存在异常,例如慢性轻度应激(chronic mild stress, CMS)小鼠体内VTA多巴胺能神经元自发性活动较健康对照组小鼠减少^[21]。边缘下前额叶皮层(infralimbic prefrontal cortex, iLPFC)的激活可选择

性地抑制内侧VTA多巴胺能神经元活动,这些多巴胺神经元与CMS有关;而直接刺激外侧缰核可选择性地抑制VTA外侧的多巴胺能神经元,其与CMS无关^[23]。大鼠黑质致密部和VTA多巴胺能神经元损伤都会导致大鼠抑郁行为的发生^[24]。习得性无助抑郁模型小鼠外侧缰核的神经元突触增强,调节富含多巴胺能神经元的VTA,进而控制寻求奖励的行为,参与抑郁样行为的发生^[25],该研究中外侧缰核可能也投射到VTA外侧,其与上述研究可能因抑郁动物模型不同导致外侧缰核至VTA的抑制性投射与动物抑郁样行为的联系不同。

综上所述,基础研究和临床影像学研究均表明抑郁样行为的模型动物或抑郁患者多巴胺奖赏系统,尤其是纹状体、VTA多巴胺能神经元及其上游通路存在功能异常,提示多巴胺奖赏系统可能是抑郁症发生的重要机制,在改善抑郁行为方面具有广阔的应用前景。

二、VTA多巴胺能神经元与奖励相关的传入调节

中脑边缘多巴胺系统是大脑中与奖励相关的主要部分,涉及VTA、伏隔核、前额叶皮质、杏仁核、海马等多个脑区^[27]。

已知动物体内多巴胺能神经元存在3种主要的活动模式,分别为不活跃的超极化状态、缓慢单棘不规则的紧张性放电模式和爆发脉冲式的时相性放电模式^[28]。脑桥被盖核谷氨酸神经元直接刺激VTA多巴胺能神经元,使其发生时相性放电^[29];后嗅被盖核的紧张性输入对谷氨酸诱导的麻醉大鼠VTA多巴胺能神经元的爆发式时相放电至关重要,即使体外直接应用谷氨酸刺激VTA,在没有后嗅被盖核输入的情况下,VTA多巴胺能神经元也不能产生时相性放电^[30-31]。简而言之,后嗅被盖核的紧张性输入对维持VTA多巴胺神经元的时相性放电是必需的,而脑桥被盖核主要调节从单棘紧张性放电到突发时相性放电的转变^[31]。来自腹侧苍白球(ventral pallidum, VP)抑制性GABA能神经元的输入能保持VTA中部分多巴胺能神经元的超极化状态^[32]。刺激腹侧海马下托(ventral subiculum, vSub)到伏隔核谷氨酸能输入,使伏隔核GABA能神经元作用于VP^[34],导致VP抑制性神经活动减少,进而兴奋VTA多巴胺能神经元的电活动^[35]。在VTA中局部输注谷氨酸受体拮抗剂(CNQX+AP5)可显著降低由vSub诱发的VTA多巴胺能神经元的兴奋性反应^[36]。抑制iLPFC神经元活动增加了VTA多巴胺能神经元自发放电的比例,这种作用结果也取决于vSub神经

元的活动^[37-38]。抑郁症患者VP中功能异常的5-HT_{1B}受体可能通过与多巴胺、GABA或谷氨酸系统的相互作用引起纹状体(包括伏隔核)内奖励信号功能失调,这也揭示了vSub-伏隔核-VP是调节奖励相关回路的一部分^[39]。

iPFC通过vSub和基底外侧杏仁核(basolateral amygdala, BLA)对VTA多巴胺能神经元施加双向控制^[40]。研究表明,BLA可能参与重度抑郁症中VTA多巴胺能神经元反应的减弱^[41-42],动物实验证实CMS小鼠多巴胺能神经元群体活性的降低可以通过谷氨酸受体拮抗剂犬尿酸阻断BLA-VP谷氨酸能神经元的传入而恢复^[43],使用N-甲基-D-天冬氨酸(NMDA)激活非应激大鼠BLA可降低多巴胺能神经元群体活性,阻断BLA-VP这一途径可逆转VTA多巴胺能神经元的低活性^[44]。此外,有研究发现,BLA对CMS后VTA多巴胺能神经元活性的影响可以通过VP失活抑制^[45],表明BLA-VP可能作为多巴胺能神经元活性的一种抑制通路存在。

综上所述,多巴胺能神经元的群体电活动由两条不同的通路调节,一条是激活通路,vSub到伏隔核再到VP的神经通路,该通路激活可以导致VTA自发放电的多巴胺能神经元比例增大;另一条通路是BLA到VP的投射通路,该通路抑制VTA多巴胺能神经元的紧张性活动。iPFC神经元的激活可选择性抑制VTA中与奖赏相关的多巴胺能神经元^[23],这是通过抑制vSub-伏隔核-VP这一多巴胺能神经元激活通路,激活BLA-VP这一抑制通路而实现的^[37-38]。

三、抑郁症中VTA多巴胺能神经元的传入失调

VTA多巴胺能神经元的传入调节在抑郁症发病机制中发挥重要作用。MRI研究发现,重度抑郁症患者皮质边缘功能连接降低,如内侧前额叶皮质(medial prefrontal cortex, mPFC)-杏仁核功能连接降低^[46];同时,重度抑郁症患者全脑功能连接异常主要集中在腹内侧前额叶皮层(ventromedial prefrontal cortex, vmPFC)^[47]。在大鼠中,mPFC分为边缘下皮层和边缘前皮层,iPFC位于大鼠mPFC的腹侧区域,与灵长类(人和猴子)vmPFC的特定亚区域(区域25)同源^[48]。抑郁症患者vmPFC特定亚区的异常与抑郁模型大鼠中VTA多巴胺能神经元传入调节中的iPFC异常类似。常用的vmPFC两种刺激模式为低强度的高频刺激和高强度的低频刺激,可能有共同的抗抑郁机制^[49]。在抑郁症患者脑MRI结构异常的研究中发现,抑郁症患者的海马体、丘脑和

vmPFC等区域在发病时灰质体积已发生改变,之后向其他大脑区域扩展^[50]。

腹侧海马向伏隔核的谷氨酸能传入可特异地调节小鼠对慢性社会失败压力的易感性,光遗传学方法长期抑制腹侧海马-伏隔核的输入导致小鼠抑郁非易感,而急性增强这一连接则会增加抑郁易感性,这是抑郁症中一种重要且新颖的回路特异性机制^[51]。采用机器学习,有研究发现了一个起源于mPFC和腹侧纹状体的时空动态网络,经杏仁核和VTA传递后汇聚在腹侧海马,可以预测遭受慢性社会失败压力小鼠社会行为功能的障碍^[52]。vmPFC和海马中 β 和 γ 波频局部场电位振荡同步性的增强可能有助于改善大鼠的抑郁样行为^[49]。

VP接收来自伏隔核的密集投射,是中脑边缘奖赏回路的重要组成部分,VP也控制着多巴胺能神经元的活动状态,其中小白蛋白神经元的不同投射介导抑郁症的不同症状^[53]。研究发现,与正常青少年相比,抑郁焦虑青少年在接受奖励后,其伏隔核体积和激活减少。随着时间的推移,伏隔核结构的改变可预测患者抑郁症状的严重程度^[54]。伏隔核侧壳中表达速激肽前体1的神经元投射到VP,影响腹侧中脑多巴胺神经元的活动,导致应激小鼠更易表现出快感缺失样行为^[55-56]。同时,有研究发现,抑制BLA-VP这一抑制通路中的谷氨酸能投射可改善CMS雄性小鼠的抑郁样行为^[57]。

目前,相关研究证实了VTA多巴胺能神经元激活通路及抑制通路参与抑郁症或抑郁样行为的发生,然而腹侧海马中调节抑郁相关行为的区域是否为vSub尚未完全阐明,传入调节中不同神经递质的参与仍需细化,这可能是未来的一个研究方向。

四、基于多巴胺奖赏相关回路的抗抑郁药

传统及新型抗抑郁药大多作用于5-HT和NE系统,虽然这些药物可立即作用于多巴胺能神经元的上游通路,影响单胺传递,但临床研究表明其发挥作用通常需要数周时间^[58]。研究发现,多巴胺能系统在抗抑郁治疗中发挥重要作用^[59]。长期给予氟西汀会增加抑郁患者齿状回中成熟颗粒细胞多巴胺D1受体的表达,增加的D1受体信号传导反过来有助于氟西汀治疗作用的发挥,包括抑制急性应激反应中5-HT的释放、神经的发生和改善抑郁样行为^[60]。全身注射曲唑酮(拮抗5-HT_{2C}受体的抗抑郁药)恢复了Ro60-0175(一种5-HT_{2C}受体激动剂)所抑制的VTA多巴胺能神经元的电活动^[61]。也有研究发现,抗抑郁药去甲替林与果蝇的多巴胺转运蛋白可

发生结合^[62]。此外,腹侧纹状体的奖励系统功能指数调节舍曲林与安慰剂的差异反应,该指数反映多巴胺功能的缺陷^[63],瑞波西汀与米氮平协同作用于mPFC,增强mPFC中的多巴胺和NE功能^[64]。

此外,还有一些非传统意义上的抗抑郁药物通过影响多巴胺奖赏相关系统而产生抗抑郁效果。氯胺酮因其特异的抗抑郁作用成为目前的研究热点,氯胺酮作用于腹侧海马谷氨酸能神经元而发挥抗抑郁作用^[65]。氯胺酮可恢复应激诱发减少的VTA多巴胺能神经元的电活动,并增加mPFC细胞外多巴胺水平,加强mPFC与VTA之间的联系,从而使得抗抑郁作用持续更久^[66-67]。瑞替加滨可激活谷氨酸神经元的下游调节因子Kcnq2基因辅助氯胺酮的抗抑郁效果^[65]。抗精神病药物氨磺必利是多巴胺D2、D3受体拮抗剂,通过阻断突触前多巴胺自身受体从而增强多巴胺的信号传导,服用氨磺必利的抑郁受试者纹状体激活增加、伏隔核和中扣带皮层之间的皮质功能连接增强,若持续服用可显著改善患者抑郁症状^[68]。

综上所述,不论是临床中常用的抗抑郁药还是目前的研究热点氯胺酮以及部分抗精神病药物都可通过影响多巴胺奖赏相关系统产生或增强抗抑郁的效果。然而,部分药物的作用机制尚未完全阐明,其对VTA多巴胺能的传入调节有哪些影响尚不清楚。未来新型抗抑郁药物的研究或许可从多巴胺能传入调节机制着手。

五、总结与展望

不同抑郁症患者的症状不尽相同,只有1/3的抑郁患者对抗抑郁药物完全反应^[71],因新型抗抑郁药治疗的起效时长和耐药的局限性,促使研究者探索血清素和NE之外的单胺类神经递质,而多巴胺奖赏相关回路是一个很好的切入点,特别是VTA多巴胺能神经元的传入调节至关重要。本文对VTA多巴胺能传入通路相关研究进行综述,发现在应激状态下,机体通过vSub-伏隔核-VP激活通路和BLA-VP抑制通路对多巴胺能系统进行调控,从而调节抑郁相关症状。抗抑郁药物的研究以及氯胺酮相关试验也说明了多巴胺能系统与抗抑郁治疗的联系。抑郁症与中脑多巴胺能奖赏系统上游通路的研究仍有待细化,抗抑郁治疗虽与多巴胺奖赏系统存在联系,但作用于其上游通路的机制并未完全阐明,多巴胺奖赏相关神经回路的调节在未来研究中仍值得深入探讨,以期对抑郁症的个性化治疗和新药的开发提供理论方向。

利益冲突 文章所有作者共同认可文章无相关利益冲突

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