药物成瘾与抑郁症共病机制的研究进展

李宗辉[1,2] 曹通[1,2] 陆永利[1,2] 李自成[1,2]*

([1]三峡大学医学院机能学系, 宜昌 443002; [2]三峡大学国家中药管理局药理科研三级实验室, 宜昌 443002)

摘要 药物成瘾和抑郁症的共患率日益提高, 已发展成为常见的精神共病状态, 但这两种疾病之间的联系及潜在的机制仍不明确, 开发针对药物成瘾共病抑郁症的有效治疗手段仍是一项重大挑战。大量的文献表明, 药物成瘾和抑郁症存在着共同的发生脑区及分子机制。该文阐述了伏隔核、外侧缰核和中脑腹侧被盖区等脑区在这种共病中的重要性, 还介绍了κ阿片受体、促肾上腺激素释放因子和脑源性神经营养因子等分子在这种共病中的作用及机制。这些发现为研究药物成瘾与抑郁症共病的机制提供了新的思路, 并为药物成瘾共病抑郁症患者的治疗提供了新的靶点。

关键词 药物成瘾; 抑郁症; 共病

Research Progress on the Mechanism of Comorbidity between Drug Addiction and Depression

LI Zonghui[1,2], CAO Tong[1,2], LU Yongli[1,2], LI Zicheng[1,2]*

([1]*Department of Functional Sciences, Medical College of China Three Gorges University, Yichang 443002, China*; [2]*Third-Grade Pharmacological Laboratory on Traditional Chinese Medicine, State Administration of Traditional Chinese Medicine, China Three Gorges University, Yichang 443002, China*)

Abstract The comorbidity rate of drug addiction and depression is increasing gradually, and it has developed into a common mental comorbidity. But the relationship between the two diseases and the underlying mechanism are still unclear, and it is a major challenge to develop effective interventions for comorbidity of drug addiction with depression. A large amount of literatures shows that there are common brain regions and molecular mechanism underlying drug addiction with depression. In this review, the importance of brain regions such as the nucleus accumbens, the lateral habenula and the ventral tegmental area in this comorbidity is described. On the other hand, the role and mechanism of kappa opioid receptors, adrenocorticotropin-releasing factors and brain-derived neurotrophic factors in this comorbid disease are also described. These findings provide new ideas for the underlying mechanism of drug addiction comorbid depression, as well as new targets for the treatment of patients with drug addiction comorbid depression.

Keywords drug addiction; depression; comorbidity

药物成瘾是一种慢性复发性脑疾病, 其特征是强迫性的药物寻求, 无限度的药物使用, 以及在停止使用药物后会出现一系列包括抑郁相关症状在内的负性行为[1]。抑郁症是一种以持续性情绪低下和快感缺失为特征的精神疾病。一项全美酒精及相关疾病流行病学调查显示, 美国有32%的药物成瘾患者

收稿日期: 2022-10-28 接受日期: 2022-12-07
国家自然科学基金面上项目(批准号: 81971248)资助的课题
*通讯作者。Tel: 13872471482, E-mail: zichengli@ctgu.edu.cn
Received: October 28, 2022 Accepted: December 7, 2022
This work was supported by the National Natural Science Foundation of China (Grant No.81971248)
*Corresponding author. Tel: +86-13872471482, E-mail: zichengli@ctgu.edu.cn

同样也患有严重抑郁障碍, 而药物成瘾者患严重抑郁障碍的风险也是正常人的3.8倍[2]。药物成瘾患者往往因为不能够持续保持药物使用, 导致比普通人更高的抑郁风险; 而抑郁症患者, 需要经常服用抗抑郁药物进行治疗, 也比普通人更易患药物成瘾[3]。鉴于类似于这两种疾病高度共患的现象,《精神疾病诊断和统计手册》(第3版)首次用“共病”一词来规范化描述这种现象, 以表示同时存在两种或两种以上不同的精神疾病的情况[4]。药物成瘾和抑郁症的共病, 往往导致患者社交、职业和娱乐活动等功能受损, 造成巨大的社会危害。在临床上, 诊断和筛查共病对治疗方案的制定十分重要。因此, 找到这两种疾病背后的共同联系, 对于药物成瘾共病抑郁症的治疗至关重要。

1 药物成瘾与抑郁症共病的脑区机制

1.1 伏隔核在药物成瘾与抑郁症共病中的作用

伏隔核(nucleus accumben, NAc)是中脑边缘奖赏系统的重要组成部分, 主要接受来自中脑腹侧被盖区的多巴胺能投射、基底外侧杏仁核的谷氨酸能投射以及中缝核的5-羟色胺能投射[5]。研究发现抑制NAc多巴胺能神经元投射可以减少小鼠海洛因的自我给药[6], 敲除NAc内的多巴胺转运体可以改善成年小鼠的抑郁样行为[7], 提示多巴胺在NAc中的传递促进了药物成瘾与抑郁症的发生。NAc中负责信息输出的神经元主要是γ-氨基丁酸(gamma aminobutyric acid, GABA)能神经元, 这类神经元主要投射到中脑腹侧被盖区、腹侧苍白球和基底杏仁核[8]。抑制NAc内GABA能神经元的活动可以同时促进大鼠的抑郁样行为及可卡因的自我给药[9]。MARGARITA等[10]发现, NAc内P11蛋白可以调节小鼠的成瘾和抑郁行为, NAc的GABA能神经元中P11缺失会诱导可卡因成瘾, 而胆碱能神经元中P11缺失则会诱导抑郁行为。最近有研究报道, NAc的侵入性深部脑刺激疗法在治疗成瘾和抑郁方面均取得了一定的成效[11-12], 由于这两种疾病都可以通过靶向NAc来进行治疗, 因此NAc可能是药物成瘾和抑郁症共病的关键区域。

1.2 外侧缰核在药物成瘾与抑郁症共病中的作用

外侧缰核(lateral habenula, LHb)为大脑的“抗奖赏中心”, 参与调节前脑和中脑区域的对话, 与奖赏回路失调相关的多种神经疾病包括药物成瘾[13]和抑郁症[14]密切相关。LHb主要接收的谷氨酸能投射来自外侧下丘脑, 其活性与奖惩刺激有关, 使用光遗传手段激活该通路会导致实时条件位置厌恶, 并且可介导小鼠对厌恶刺激的逃避行为[15]。LHb也接受腹侧苍白球的谷氨酸能投射, 抑制腹侧苍白球谷氨酸能神经元可增强奖赏反应, 提高小鼠对蔗糖的偏好, 改善抑郁样症状[16]。LHb还接受来自边缘系统结构包括内侧隔区、外侧视前区的强烈GABA能输入[17], 激活外侧视前区至LHb的GABA能投射, 可以驱动大鼠的厌恶动机行为[18]。除此之外, LHb还接受来自黑质致密部和中脑腹侧被盖区多巴胺能投射[19], 研究发现LHb多巴胺D2受体参与了大脑对厌恶情绪的编码, 在双侧LHb输注多巴胺D2受体拮抗剂可以显著减少可卡因诱导的负性情绪[20]。LHb中的输出性神经元主要包括谷氨酸能神经元, 且LHb的谷氨酸能神经元投射到中脑腹侧被盖区可形成外侧缰核–腹侧被盖区回路, 调节奖赏和厌恶行为[21]。在小鼠可卡因成瘾模型中发现, 可卡因驱动LHb谷氨酸能神经元输入到中脑腹侧被盖区, 并且谷氨酸能神经元进一步投射到前额叶皮层、伏隔核和外侧下丘脑[22]。LHb神经元还可以通过被盖内侧核直接或间接投射到中缝5-羟色胺能神经元[19], 并且LHb通过激活GABA能神经元, 可以导致中脑腹侧被盖区多巴胺能神经元和中缝5-羟色胺能神经元受到抑制, 从而介导抑郁症状[23-24]。

靶向LHb来治疗共病抑郁障碍的酒精成瘾已被证明是有效的, 抑制LHb中钙调蛋白依赖性激酶α的活性可抑制大鼠的抑郁样行为和酒精摄入[25]。此外, SEUNGWOO等[26]的研究发现抑制LHb中谷氨酸的运输, 可以显著缩短酒精成瘾大鼠在强迫游泳实验中静止不动的时间, 改善共病酒精成瘾大鼠的抑郁症状。药物成瘾与抑郁症引起的奖赏失衡, 导致LHb对正反馈和负反馈失去正常的判断与预期, 最终使大脑偏向消极的奖赏预期以及奖赏阈值偏离正常的范围[27-28], 这可能是LHb介导药物成瘾与抑郁症共病的潜在机制[29]。

1.3 中脑腹侧被盖区在药物成瘾与抑郁症共病中的作用

中脑腹侧被盖区(ventral tegmental area, VTA)是大脑调节应激奖惩的一个重要区域, 应激及其诱导的情绪障碍和药物成瘾的发生都与VTA的失调密切相关[30-31]。VTA神经元主要由多巴胺能、GABA

能和谷氨酸能神经元组成，这些神经元中60%~65%是多巴胺能神经元，35%是GABA能神经元，只有少量的谷氨酸能神经元[32]。VTA的多巴胺能神经元可投射到前额叶皮质和伏隔核，以及下丘脑、杏仁核、外侧缰核、苍白球和终纹床核[33]，在奖赏、动机、认知、厌恶中起着重要的作用[34-35]。研究发现，刺激VTA的多巴胺能神经元可促进可卡因成瘾大鼠的复吸行为[36]；而KAY等[37]的研究发现VTA多巴胺能神经元也参与调节了抑郁相关行为，刺激VTA的多巴胺能神经元可逆转应激诱导的抑郁相关行为，提示VTA多巴胺能神经元在调节药物成瘾和抑郁症中发挥着重要作用，但VTA多巴胺能神经元调节药物成瘾与抑郁症共病的机制仍需进一步研究。尽管VTA的多巴胺神经元一直备受关注，近年来人们发现VTA的GABA能神经元在应激与奖惩中同样扮演着重要角色[38]。VTA内的GABA能神经元主要由VTA局部中间神经元和VTA尾部即被盖头内侧核神经元构成[39-40]，并可向中脑多巴胺神经元发送密集的抑制性投射，通过调节多巴胺的水平间接参与大脑奖赏系统的调控[41]。VTA的GABA能神经元通过干扰奖赏寻求的间隔时间，从而调控奖赏信息的寻求[42]。抑制VTA的GABA能神经元改善了应激诱导的奖赏寻求缺失[38,43]，而这种奖赏寻求缺失是抑郁症的核心症状，也使得大脑奖赏系统失调，致使抑郁症更容易与药物成瘾共病。VTA的谷氨酸能神经元相对较少，相关研究报道了VTA谷氨酸能神经元投射到NAc介导了小鼠的动机行为[44]，而ROOT等[45]发现在VTA中表达囊泡谷氨酸转运体2的谷氨酸能神经元亚群，其放电频率随受到的奖赏或厌恶刺激而改变，提示VTA的谷氨酸能神经元可能也参与了奖惩信号的调节。

2 药物成瘾与抑郁症共病的分子机制

2.1 κ阿片受体在药物成瘾与抑郁症共病中的作用

阿片受体系统在情绪、奖赏和疼痛的调节中发挥重要作用，因此成为治疗许多神经病理性疾病的有力靶点[46-49]。在阿片受体系统中，κ阿片受体(kappa opioid receptor, KOR)与奖惩失调相关疾病的关系尤为密切，是调节应激反应、情绪和强化学习的重要参与者，已成为治疗疼痛、成瘾以及情绪障碍的分子靶标[50-52]。在临床和动物实验中发现，KOR的激活会使人类和动物产生厌恶和抑郁样行为，而拮抗KOR可以抑制压力诱导的寻药行为的恢复，逆转应激对啮齿类动物的多种负性情绪影响，发挥与抗抑郁药物相似的作用[53-54]。此外，反复暴露于酒精、阿片和可卡因等各种药物会导致KOR的过度激活，BLEVINS等[55]使用正电子发射断层扫描技术发现，KOR和可卡因自我给药之间存在显著相关性，KOR结合水平较高的可卡因成瘾个体更容易发生可卡因的复吸。目前已有相关研究考虑将KOR作为靶点来治疗严重抑郁障碍共病可卡因及阿片类等药物成瘾[48,56-57]。

KOR属于G蛋白偶联受体，被激活后会促进抑制性G蛋白门控内向整流钾通道的开放，使神经元超极化，抑制电压门控钙通道的开放及兴奋性突触囊泡的释放，最终降低神经元兴奋性[58]。KOR广泛分布于大脑多个区域，表达于不同类型的神经元中，但主要表达于多巴胺能神经元中[50,59]。研究发现酒精成瘾患者体内KOR的上调，导致了多巴胺受体1的下调，进而导致了多巴胺系统信号转导的失衡，从而引起了酗酒者的负性情绪状态[60]。LIU等[61]发现，敲除小鼠多巴胺神经元上表达KOR的基因，阻止了疼痛诱导的条件性位置厌恶，这证明抑制KOR可恢复慢性疼痛诱发的多巴胺释放和奖赏相关行为。此外，KOR通过激活VTA多巴胺能神经元介导厌恶情绪[62]，而阻断KOR从伏隔核投射到VTA多巴胺能投射逆转了疼痛损伤诱导的厌恶和快感缺失[63]。然而，最近关于KOR介导的厌恶情绪是由多巴胺能神经元所驱动的假说受到了挑战，相关研究认为KOR介导的厌恶情绪不是通过抑制多巴胺能神经元的输出而是由于KOR在多巴胺能神经元上对p38丝裂原活化激酶信号的激活而发挥作用的，KOR通过激活p38丝裂原活化激酶信号通路，调节神经元的增殖、分化，抑制神经信号的传导[58,64-65]。进一步的研究p38丝裂原活化酶对多巴胺的生理作用，可帮助我们加深对KOR系统介导药物成瘾及抑郁共病的理解。

2.2 促肾上腺皮质激素释放因子在药物成瘾与抑郁症共病中的作用

促肾上腺皮质激素释放因子(corticotropin-releasing factor, CRF)是一种在下丘脑室旁核中产生的应激相关神经肽，广泛表达于整个中枢神经系统，但主要分布在下丘脑室旁核和延伸的杏仁核区域，分别与CRF1受体和CRF2受体结合而发挥作用[66]。最

近的啮齿动物研究表明, CRF-CRF1受体系统在调节觅药行为以及药物成瘾诱导的相关负性情绪方面扮演重要角色[67]。下丘脑室旁核中表达的CRF1受体调节创伤后应激障碍、抑郁和成瘾等精神疾病, 这些异常病理活动会激活下丘脑室旁核中的CRF神经元并使其释放CRF, 从而促进附近的CRF1受体与之结合, 导致CRF神经元接受的抑制性GABA能突触信号强度异常增加[68]。此外, CRF信号已被证明在各种酒精成瘾模型中发挥调节作用, 并且与酒精戒断带来的负性情绪密切相关[69-70]。酒精成瘾患者体内基础CRF信号的升高会诱导过度饮酒, 而过度饮酒又会进一步导致CRF水平升高[71]。研究发现, 在酒精成瘾模型中, 中央杏仁核CRF神经元比其他非CRF神经元更活跃, 且CRF神经元表现出更高的放电频率和更多的爆发式放电[72]。GUGLIELMO等[73]发现在慢性酒精暴露模型中, 中央杏仁核神经元中约有80%为CRF神经元, 使用光遗传技术抑制这些神经元减少了大鼠的饮酒行为及戒酒后的负面症状, 且抑制中央杏仁核CRF神经元向终纹床核投射后, 同样可观察到成瘾样行为的逆转。ASOK等[74]同样使用光遗传手段沉默该通路, 从而阻止了应激恐惧记忆的形成。这些研究提示, 杏仁核CRF通路在调节酒精成瘾以及应激奖惩后的负性情绪中具有重要作用。最近的几项荟萃分析显示, 靶向CRF的相关药物能有效缓解患者的负性情绪如抑郁, 发挥出与抗抑郁药相似的作用, *CRF1*基因与抑郁症易感性和抑郁症相关的认知功能障碍高度相关[75-77]。这些研究表明, 过量的大脑CRF信号可能参与抑郁症等负面情绪的产生及药物成瘾的复发, 未来需通过进一步的研究来确定CRF在药物成瘾及抑郁症共病中的作用。

2.3 脑源性神经营养因子在药物成瘾与抑郁症共病中的作用

近年来, 脑源性神经营养因子(brain-derived neurotrophic factor, BDNF)受到越来越多的关注。研究发现BDNF不仅广泛参与突触活动、神经细胞发育以及学习记忆形成等生理过程[78], 而且在药物成瘾、焦虑抑郁等病理性过程中扮演重要角色[79-80]。BDNF是人体内含量最多的神经营养因子, 它通过与酪氨酸激酶B(tyrosine kinase B, TrkB)的结合而发挥作用。BDNF及其受体TrkB被发现在中脑边缘奖赏环路中表达, 中脑边缘前额叶皮层中的BDNF下调介导了应激诱导的抑郁样行为, 而激活VTA多巴胺能神经元, 可以促进BDNF向前额叶皮层的释放及其与TrkB的结合, 从而减轻抑郁症状[81-82]。除此之外, 伏隔核中BDNF浓度升高也已被证明会加重抑郁症状和促进可卡因成瘾[80,83]。BDNF通过与TrkB结合, 促进ERK-MAP激酶级联反应, 并降低中脑边缘系统谷氨酸及多巴胺的水平, 进而导致觅药行为及戒断后的负性情绪的产生[84-85]。此外, 在海洛因成瘾大鼠海马区发现BDNF水平的异常升高, 而这种异常升高通过抑制多巴胺转运体(dopamine transporter, DAT)的活性进而影响多巴胺系统的调节[86], 并且在海洛因成瘾者中, DAT的活性和汉密尔顿抑郁评分之间存在显著相关性[87], 这些结果说明BDNF诱导的DAT下降及多巴胺水平的失调可能是导致海洛因成瘾者共病抑郁症的潜在原因。

3 总结与展望

不论是药物成瘾还是抑郁症, 目前都已成为全球面临的重大公共卫生问题, 并且这两种疾病的共患率日益提高, 单独治疗其中一种疾病的效果并不理想。因此, 找到这两种疾病的共同治疗靶点至关重要。这里我们阐述了伏隔核、外侧缰核和中脑腹侧被盖区等脑区在这种共病中的重要作用, 还介绍了κ阿片受体、促肾上腺激素释放因子和脑源性神经营养因子等分子在这种共病中的作用及机制(图1), 从而揭示了药物成瘾与抑郁症之间的共病关系。这些信息的累积对我们以后揭示共病的潜在机制以及为共病患者选择正确的治疗方法至关重要。然而, 还需要更多有效的动物及临床共病证据来充分阐明其具体的机制。尽管目前的研究有些许局限, 未来如果能够进一步将这些脑区机制与分子机制联系起来, 探索其背后可能存在的交叉机制, 将有助于指导临床药物成瘾与抑郁症共病的预防以及寻找新的共病治疗靶点。

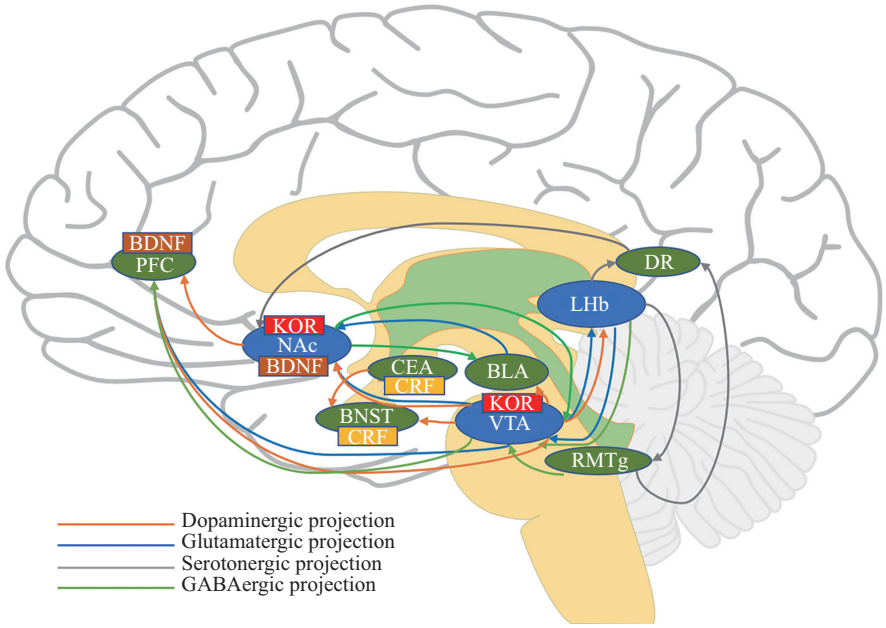
参考文献 (References)

[1] KOOB G F. Negative reinforcement in drug addiction: the darkness within [J]. Curr Opin Neurobiol, 2013, 23(4): 559-63.

[2] CAREY T L. Use of antidepressants in patients with co-occurring depression and substance use disorders [J]. Handb Exp Pharmacol, 2019, 250: 359-70.

[3] DAVIS L, UEZATO A, NEWELL J M, et al. Major depression and comorbid substance use disorders [J]. Curr Opin Psychiatry, 2008, 21(1): 14-8.

[4] ANKER J J, KUSHNER M G. Co-occurring alcohol use disorder



药物成瘾与抑郁症的共病与前额叶皮层、伏隔核、中央杏仁核、终纹床核、基底外侧杏仁核、腹侧被盖区、外侧缰核、尾状被盖核及中缝背核等脑区形成的神经回路密切相关, κ阿片受体、促肾上腺素激素释放因子和脑源性神经营养因子在这些脑区的活动也参与了药物成瘾与抑郁症的共病。

The comorbidities of drug addiction and depression are closely related to the prefrontal cortex, nucleus accumbens, central amygdaloid nucleus, bed nucleus of stria terminalis, basolateral amygdaloid nucleus, ventral tegmental area, lateral habenular nucleus, caudate tegmental nucleus and dorsal raphe nucleus. The activities of κ opioid receptor, corticotropin-releasing factor and brain-derived neurotrophic factor in these brain regions are also involved in the comorbidities of drug addiction and depression.

图1　药物成瘾与抑郁症共病的神经环路机制图

Fig.1　Neural circuit mechanism of comorbidity between drug addiction and depression

and anxiety: bridging psychiatric, psychological, and neurobiological perspectives [J]. Alcohol Res, 2019, 40(1): arcr.v40.1.03.

[5] LEGATES T A, KVARTA M D, TOOLEY J R, et al. Reward behaviour is regulated by the strength of hippocampus-nucleus accumbens synapses [J]. Nature, 2018, 564(7735): 258-62.

[6] CORRE J, VAN ZESSEN R, LOUREIRO M, et al. Dopamine neurons projecting to medial shell of the nucleus accumbens drive heroin reinforcement [J]. eLife, 2018, 7: e39945.

[7] BAHI A, DREYER J L. Dopamine transporter (DAT) knockdown in the nucleus accumbens improves anxiety- and depression-related behaviors in adult mice [J]. Behav Brain Res, 2019, 359: 104-15.

[8] CASTRO D C, BRUCHAS M R. A motivational and neuropeptidergic hub: anatomical and functional diversity within the nucleus accumbens shell [J]. Neuron, 2019, 102(3): 529-52.

[9] CROFTON E J, NENOV M N, ZHANG Y, et al. Glycogen synthase kinase 3 beta alters anxiety-, depression-, and addiction-related behaviors and neuronal activity in the nucleus accumbens shell [J]. Neuropharmacology, 2017, 117: 49-60.

[10] ARANGO-LIEVANO M, KAPLITT M G. Comorbidité entre la dépression et l'addiction [J]. Médecine/sciences, 2015, 31(5): 546-50.

[11] QU L, GE S, LI N, et al. Clinical evaluation of deep brain stimulation of nucleus accumbens/anterior limb of internal capsule for opioid relapse prevention: protocol of a multicentre, prospective and double-blinded study [J]. BMJ Open, 2019, 9(2): e23516.

[12] DANDEKAR M P, FENOY A J, CARVALHO A F, et al. Deep brain stimulation for treatment-resistant depression: an integrative review of preclinical and clinical findings and translational implications [J]. Mol Psychiatry, 2018, 23(5): 1094-112.

[13] NAIR S G, SMIRNOV D S, ESTABROOK M M, et al. Effect of chemogenetic inhibition of lateral habenula neuronal activity on cocaine- and food-seeking behaviors in the rat [J]. Addiction Biology, 2021, 26(1): e12865.

[14] AIZAWA H, ZHU M. Toward an understanding of the habenula's various roles in human depression [J]. Psychiat Clin Neuros, 2019, 73(10): 607-12.

[15] STAMATAKIS A M, VAN SWIETEN M, BASIRI M L, et al. Lateral hypothalamic area glutamatergic neurons and their projections to the lateral habenula regulate feeding and reward [J]. J Neurosci, 2016, 36(2): 302-11

[16] TOOLEY J, MARCONI L, ALIPIO J B, et al. Glutamatergic ventral pallidal neurons modulate activity of the habenula-tegmental circuitry and constrain reward seeking [J]. Biol Psychiatry, 2018, 83(12): 1012-23.

[17] FAKHOURY M. The dorsal diencephalic conduction system in reward processing: spotlight on the anatomy and functions of the habenular complex [J]. Behav Brain Res, 2018, 348: 115-26.

[18] BARKER D J, MIRANDA-BARRIENTOS J, ZHANG S, et al. Lateral preoptic control of the lateral habenula through convergent glutamate and GABA transmission [J]. Cell Rep, 2017, 21(7): 1757-69.

[19] METZGER M, SOUZA R, LIMA L B, et al. Habenular connections with the dopaminergic and serotonergic system and their role in stress-related psychiatric disorders [J]. Eur J Neurosci, 2021, 53(1): 65-88.

[20] SHELTON K, BOGYO K, SCHICK T, et al. Pharmacological modulation of lateral habenular dopamine D2 receptors alters the anxiogenic response to cocaine in a runway model of drug self-administration [J]. Behav Brain Res, 2016, 310: 42-50.

[21] LAZARIDIS I, TZORTZI O, WEGLAGE M, et al. A hypothalamus-habenula circuit controls aversion [J]. Mol Psychiatry, 2019, 24(9): 1351-68.

[22] CLERKE J, PRESTON-FERRER P, ZOURIDIS I S, et al. Output-specific adaptation of habenula-midbrain excitatory synapses during cocaine withdrawal [J]. Front Synaptic Neurosci, 2021, 13: 643138.

[23] XU C, SUN Y, CAI X, et al. Medial habenula-interpeduncular nucleus circuit contributes to anhedonia-like behavior in a rat model of depression [J]. Front Behav Neurosci, 2018, doi: 10.3389/fnbeh.2018.00238.

[24] METZGER M, SOUZA R, LIMA L B, et al. Habenular connections with the dopaminergic and serotonergic system and their role in stress-related psychiatric disorders [J]. Eur J Neurosci, 2021, 53(1): 65-88.

[25] LI J, KANG S, FU R, et al. Inhibition of AMPA receptor and CaMKII activity in the lateral habenula reduces depressive-like behavior and alcohol intake in rats [J]. Neuropharmacology, 2017, 126: 108-20.

[26] KANG S, LI J, BEKKER A, et al. Rescue of glutamate transport in the lateral habenula alleviates depression- and anxiety-like behaviors in ethanol-withdrawn rats [J]. Neuropharmacology, 2018, 129: 47-56.

[27] SHABEL S J, WANG C, MONK B, et al. Stress transforms lateral habenula reward responses into punishment signals [J]. Proc Natl Acad Sci USA, 2019, 116(25): 12488-93.

[28] HU H, CUI Y, YANG Y. Circuits and functions of the lateral habenula in health and in disease [J]. Nat Rev Neurosci, 2020, 21(5): 277-95.

[29] SHOR C, ZUO W, ELOY J D, et al. The emerging role of LHb CaMKII in the comorbidity of depressive and alcohol use disorders [J]. Int J Mol Sci, 2020, 21(21): 8123.

[30] POLTER A M, KAUER J A. Stress and VTA synapses: implications for addiction and depression [J]. Eur J Neurosci, 2014, 39(7): 1179-88.

[31] SHEPARD R D, NUGENT F S. Early life stress- and drug-induced histone modifications within the ventral tegmental area [J]. Front Cell Dev Biol, 2020, 8: 588476.

[32] BOUARAB C, THOMPSON B, POLTER A M. VTA GABA neurons at the interface of stress and reward [J]. Front Neural Circuits, 2019, 13: 78.

[33] GALAJ E, RANALDI R. The strength of reward-related learning depends on the degree of activation of ventral tegmental area dopamine neurons [J]. Behav Brain Res, 2018, 348: 65-73.

[34] KAUFLING J. Alterations and adaptation of ventral tegmental area dopaminergic neurons in animal models of depression [J]. Cell Tissue Res, 2019, 377(1): 59-71.

[35] DOUMA E H, DE KLOET E R. Stress-induced plasticity and functioning of ventral tegmental dopamine neurons [J]. Neurosci Biobehav Rev, 2020, 108: 48-77.

[36] MAHLER S V, BRODNIK Z D, COX B M, et al. Chemogenetic manipulations of ventral tegmental area dopamine neurons reveal multifaceted roles in cocaine abuse [J]. J Neurosci, 2019, 39(3): 503-18.

[37] TYE K M, MIRZABEKOV J J, WARDEN M R, et al. Dopamine neurons modulate neural encoding and expression of depression-related behaviour [J]. Nature, 2013, 493(7433): 537-41.

[38] LOWES D C, CHAMBERLIN L A, KRETSGE L N, et al. Ventral tegmental area GABA neurons mediate stress-induced blunted reward-seeking in mice [J]. Nat Commun, 2021, 12(1): 3539.

[39] POLTER A M, BARCOMB K, TSUDA A C, et al. Synaptic function and plasticity in identified inhibitory inputs onto VTA dopamine neurons [J]. Eur J Neurosci, 2018, 47(10): 1208-18.

[40] SMITH R J, VENTO P J, CHAO Y S, et al. Gene expression and neurochemical characterization of the rostromedial tegmental nucleus (RMTg) in rats and mice [J]. Brain Struct Funct, 2019, 224(1): 219-38.

[41] FAKHOURY M. The tail of the ventral tegmental area in behavioral processes and in the effect of psychostimulants and drugs of abuse [J]. Prog Neuropsychopharmacol Biol Psychiatry, 2018, 84: 30-8.

[42] SHIELDS A K, SUAREZ M, WAKABAYASHI K T, et al. Activation of VTA GABA neurons disrupts reward seeking by altering temporal processing [J]. Behav Brain Res, 2021, 410: 113292.

[43] LOWES D C, CHAMBERLIN L A, KRETSGE L N, et al. Ventral tegmental area GABA neurons mediate stress-induced blunted reward-seeking in mice [J]. Nature Communications, 2021, 12(1): 3539.

[44] YU J, ISHIKAWA M, WANG J, et al. Ventral tegmental area projection regulates glutamatergic transmission in nucleus accumbens [J]. Sci Rep, 2019, 9: 18451.

[45] ROOT D H, ESTRIN D J, MORALES M. Aversion or salience signaling by ventral tegmental area glutamate neurons [J]. iScience, 2018, 2: 51-62.

[46] MCHUGH K L, KELLY J P. Modulation of the central opioid system as an antidepressant target in rodent models [J]. Prog Brain Res, 2018, 239: 49-87.

[47] DARCQ E, KIEFFER B L. Opioid receptors: drivers to addiction [J]? Nat Rev Neurosci, 2018, 19(8): 499-14.

[48] BROWNE C A, JACOBSON M L, LUCKI I. Novel targets to treat depression: opioid-based therapeutics [J]. Harv Rev Psychiatry, 2020, 28(1): 40-59.

[49] WANG S. Historical review: opiate addiction and opioid receptors [J]. Cell Transplantation, 2019, 28(3): 233-8.

[50] JI M, YANG J, GAO Z, et al. The role of the kappa opioid system in comorbid pain and psychiatric disorders: function and implications [J]. Front Neurosci, 2021, 15: 642493.

[51] JACOBSON M L, BROWNE C A, LUCKI I. Kappa opioid receptor antagonists as potential therapeutics for stress-related disorders [J]. Annu Rev Pharmacol Toxicol, 2020, 60(1): 615-36.

[52] KO M C, HUSBANDS S M. Pleiotropic effects of kappa opioid receptor-related ligands in non-human primates [J]. Handb Exp

Pharmacol, 2022, 271: 435-52.
[53] REED B, BUTELMAN E R, KREEK M J. Kappa opioid receptor antagonists as potential therapeutics for mood and substance use disorders [J]. Handb Exp Pharmacol, 2022, 271: 473-91.
[54] JACOBSON M L, WULF H A, BROWNE C A, et al. The kappa opioid receptor antagonist aticaprant reverses behavioral effects from unpredictable chronic mild stress in male mice [J]. Psychopharmacology, 2020, 237(12): 3715-28.
[55] BLEVINS D, MARTINEZ D. Role for kappa-opioid system in stress-induced cocaine use uncovered with PET [J]. Neuropsychopharmacology, 2020, 45(1): 233-4.
[56] ANGARITA G A, HADIZADEH H, CERDENA I, et al. Can pharmacotherapy improve treatment outcomes in people with co-occurring major depressive and cocaine use disorders [J]? Expert Opin Pharmacother, 2021, 22(13): 1669-83.
[57] BROWNE C A, LUCKI I. Targeting opioid dysregulation in depression for the development of novel therapeutics [J]. Pharmacol Ther, 2019, 201: 51-76.
[58] TEJEDA H A, BONCI A. Dynorphin/kappa-opioid receptor control of dopamine dynamics: implications for negative affective states and psychiatric disorders [J]. Brain Res, 2019, 1713: 91-101.
[59] ESTAVE P M, SPODNICK M B, KARKHANIS A N. KOR control over addiction processing: an exploration of the mesolimbic dopamine pathway [J]. Handb Exp Pharmacol, 2022, 271: 351-77.
[60] BAZOV I, SARKISYAN D, KONONENKO O, et al. Dynorphin and κ-opioid receptor dysregulation in the dopaminergic reward system of human alcoholics [J]. Mol Neurobiol, 2018, 55(8): 7049-61.
[61] LIU S S, PICKENS S, BURMA N E, et al. Kappa opioid receptors drive a tonic aversive component of chronic pain [J]. J Neurosci, 2019, 39(21): 4162-78.
[62] DE GUGLIELMO G, KALLUPI M, POMRENZE M B, et al. Inactivation of a CRF-dependent amygdalofugal pathway reverses addiction-like behaviors in alcohol-dependent rats [J]. Nat Commun, 2019, 10(1): 1238.
[63] MASSALY N, COPITS B A, WILSON-POE A R, et al. Pain-induced negative affect is mediated via recruitment of the nucleus accumbens kappa opioid system [J]. Neuron, 2019, 102(3): 564-73.
[64] WANG F, MEI F. Kappa opioid receptor and oligodendrocyte remyelination [J]. Vitam Horm, 2019, 111: 281-97.
[65] EHRICH J M, MESSINGER D I, KNAKAL C R, et al. Kappa opioid receptor-induced aversion requires p38 MAPK activation in VTA dopamine neurons [J]. J Neuroscience, 2015, 35(37): 12917-31.
[66] SIMPSON S, SHANKAR K, KIMBROUGH A, et al. Role of corticotropin-releasing factor in alcohol and nicotine addiction [J]. Brain Res, 2020, 1740: 146850.
[67] WELSCH L, BAILLY J, DARCQ E, et al. The negative affect of protracted opioid abstinence: progress and perspectives from rodent models [J]. Biol Psychiatry, 2020, 87(1): 54-63.
[68] JIANG Z, RAJAMANICKAM S, JUSTICE N J. CRF signaling between neurons in the paraventricular nucleus of the hypothalamus (PVN) coordinates stress responses [J]. Neurobiol Stress, 2019, 11: 100192.
[69] SCHREIBER A L, GILPIN N W. Corticotropin-releasing factor (CRF) neurocircuitry and neuropharmacology in alcohol drinking [J]. Handb Exp Pharmacol, 2018, 248: 435-71.
[70] AGOGLIA A E, HERMAN M A. The center of the emotional universe: alcohol, stress, and CRF1 amygdala circuitry [J]. Alcohol, 2018, 72: 61-73.
[71] PLEIL K E, SKELLY M J. CRF modulation of central monoaminergic function: implications for sex differences in alcohol drinking and anxiety [J]. Alcohol, 2018, 72: 33-47.
[72] ARONI S, MARINO R A M, GIRVEN K S, et al. Repeated binge ethanol drinking enhances electrical activity of central amygdala corticotropin releasing factor neurons *in vivo* [J]. Neuropharmacology, 2021, 189: 108527.
[73] DE GUGLIELMO G, KALLUPI M, POMRENZE M B, et al. Inactivation of a CRF-dependent amygdalofugal pathway reverses addiction-like behaviors in alcohol-dependent rats [J]. Nat Commun, 2019, 10(1): 1238.
[74] ASOK A, DRAPER A, HOFFMAN A F, et al. Optogenetic silencing of a corticotropin-releasing factor pathway from the central amygdala to the bed nucleus of the stria terminalis disrupts sustained fear [J]. Mol Psychiatry, 2018, 23(4): 914-22.
[75] DING Y, WEI Z, YAN H, et al. Efficacy of treatments targeting hypothalamic-pituitary-adrenal systems for major depressive disorder: a meta-analysis [J]. Front Pharmacol, 2021, 12: 732157.
[76] RAMOZ N, HOERTEL N, NOBILE B, et al. Corticotropin releasing hormone receptor CRHR1 gene is associated with tianeptine antidepressant response in a large sample of outpatients from real-life settings [J]. Transl Psychiatry, 2020, 10: 378.
[77] DAVIS E G, KELLER J, HALLMAYER J, et al. Corticotropin-releasing factor 1 receptor haplotype and cognitive features of major depression [J]. Transl Psychiatry 2018, 8: 5.
[78] KOWIAŃSKI P, LIETZAU G, CZUBA E, et al. BDNF: a key factor with multipotent impact on brain signaling and synaptic plasticity [J]. Cell Mol Neurobiol, 2018, 38(3): 579-93.
[79] ANDREATTA M, NEUEDER D, GENHEIMER H, et al. Human BDNF rs6265 polymorphism as a mediator for the generalization of contextual anxiety [J]. J Neurosci Res, 2019, 97(3): 300-12.
[80] XU L, NAN J, LAN Y. The nucleus accumbens: a common target in the comorbidity of depression and addiction [J]. Front Neural Circuits, 2020, 14: 37.
[81] LIU D, TANG Q, YIN C, et al. Brain-derived neurotrophic factor-mediated projection-specific regulation of depressive-like and nociceptive behaviors in the mesolimbic reward circuitry [J]. Pain, 2018, 159(1): 175.
[82] KOO J W, CHAUDHURY D, HAN M, et al. Role of mesolimbic brain-derived neurotrophic factor in depression [J]. Biol Psychiatry, 2019, 86(10): 738-48.
[83] GUEYE A B, ALLAIN F, SAMAHA A. Intermittent intake of rapid cocaine injections promotes the risk of relapse and increases mesocorticolimbic BDNF levels during abstinence [J]. Neuropsychopharmacology, 2019, 44(6): 1027-35.
[84] MORELLA I, HALLUM H, BRAMBILLA R. Dopamine D1 and glutamate receptors co-operate with brain-derived neurotrophic factor (BDNF) and TrkB to modulate ERK signaling in adult striatal slices [J]. Front Cell Neurosci, 2020, 14.

[85] MCGINTY J F, WHITFIELD T W, BERGLIND W J. Brain-derived neurotrophic factor and cocaine addiction [J]. Brain Res, 2010, 1314: 183-93.

[86] LI Y, XIA B, LI R, et al. Changes in expression of dopamine, its receptor, and transporter in nucleus accumbens of heroin-addicted rats with brain-derived neurotrophic factor (BDNF) overexpression [J]. Med Sci Monit, 2017, 23: 2805-15.

[87] LIU Y, HAN M, LIU X, et al. Dopamine transporter availability in heroin-dependent subjects and controls: longitudinal changes during abstinence and the effects of Jitai tablets treatment [J]. Psychopharmacology, 2013, 230(2): 235-44.