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二乙酰吗啡成瘾及神经毒性作用机制研究进展

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【摘要】 二乙酰吗啡(diacetylmorphine,DAM)是一种具有极强依赖性的中枢性兴奋剂,长期滥用会产生严重的神经毒性症状。DAM 是我国滥用人数最多的毒品,已成为危害社会稳定的严重公共卫生问题。DAM 可以诱导神经细胞发生凋亡,对人体健康产生极大的影响。本文对 DAM 成瘾和戒断机制以及对神经因子的影响作一综述,为 DAM 对神经细胞毒性作用机制研究提供理论依据。

【关键词】 二乙酰吗啡;成瘾;神经毒性作用
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Research progress of diacetylmorphine in addiction and neurotoxic mechanisms

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【Abstract】 Diacetylmorphine (DAM) is a highly dependent central stimulant that produces severe neurotoxic effects over a long period. DAM is the most abused drug in our country and has become a serious public health issue endangering social stability. DAM induces nerve cell apoptosis, which has a great influence on human health. In this article, the mechanism of DAM addiction and withdrawal as well as its effects on neural factors are reviewed, providing a theoretical basis to study the mechanism of DAM toxicity in nerve cells.

【Keywords】 diacetylmorphine; addiction; neurotoxic effect
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二乙酰吗啡(diacetylmorphine,DAM)已成为当今世界滥用最为广泛的毒品,被联合国认定为一级管制毒品,也是中国监控、查禁的最主要的毒品之一。DAM 对人类的身心健康危害极大,长期吸食、注射 DAM 可出现精神障碍、心理变态和寿命缩减,尤其对神经系统伤害最为明显。DAM 分子式为 $C_{21}H_{23}NO_5$, 分子量为 369。DAM 在体内迅速代谢为单乙酰吗啡(半衰期 5 min),进而代谢为吗啡(半衰期 30 min),再生成葡萄糖醛酸吗啡从尿液中排出。因此常以血、尿中检出单乙酰吗啡来证明短期

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内曾摄入 DAM,为禁毒、戒毒提供参考。DAM 过量滥用可引起一系列的中毒症状,包括呼吸深度抑制、心率减慢、瞳孔缩小、脉搏细弱、血压下降、皮肤湿冷、体温降低、全身性紫癜、昏迷、尿少或尿潴留等。DAM 在引起神经中枢应激反应[1]、损伤神经细胞[2-5]的同时促进神经元合成释放儿茶酚胺类激素[6],诱发成瘾和戒断症状,甚至导致死亡[7]。

1 DAM 成瘾和戒断机制

在正常生理状态下,大脑中含有作用与吗啡相似的“内啡肽”。当吸食 DAM 后,替代并抑制“内啡肽”的合成和释放,使吸食者体内产生强烈的刺激作用[8],形成对 DAM 的强烈渴求记忆(心理性成瘾)。当停止吸食 DAM,吸食者感觉浑身疼痛难忍,出现毒瘾发作症状,即“戒断症状”。只有再次吸食 DAM 方能减轻戒断症状。大脑额叶皮质(prefrontal cortex, PFC)、腹侧被盖区(ventral tegmental area, VTA)、尾状核(caudate nucleus, CN)、伏隔核(nucleus accumbens, NAc)等[9]脑组织参与 DAM 成瘾过程。在 DAM 作用下,VTA 合成释放多巴胺(DA),将信息传递到 NAc[10]、CN[11]和 PFC[11]产生犒赏效应。2022 年,King 等[12]采用磁共振成像(magnetic resonance imaging, MRI)技术,首次在 DAM 成瘾患者大脑中观察到 PFC 和缰核(habenula, HB)之间有明显的纤维通路,该通路在 DAM 成瘾和戒断过程中起关键作用。

动物实验发现,按剂量递增法给予 Wistar 大鼠 DAM 建立成瘾模型,放射免疫法检测 VTA、PFC、NAc、海马(hippocampus, Hipp)[13]、蓝斑核(locus coeruleus, LC)[14]等脑组织中儿茶酚胺类激素水平比对照组明显升高。肾上腺素(radrenaline, A)、去甲肾上腺素(noradrenaline, NA)、DA 能引起人情绪激动、心血管和骨骼肌收缩[15-16]。先给予利血平作为干预措施,使脑组织中儿茶酚胺类激素耗竭,再给予 DAM,动物戒断症状明显减轻,脑组织中儿茶酚胺类激素水平比 DAM 组明显降低[17]。研究结果显示,DAM 通过促进儿茶酚胺类激素系统[18]合成释放 A、NA、DA 引起兴奋、成瘾[19-20]。DAM(“第一信使”)与 NAc[21]、VTA、HB 受体结合,激活腺苷酸环化酶、鸟苷酸环化酶产生 cAMP、cGMP(“第二信使”),促进 A、DA、NA 合成和释放并作用于靶器官出现成瘾、戒断症状。研究结果表明,去甲肾上腺素通路、多巴胺通路与 DAM 成瘾机制有关[22]。

2 DAM 对神经组织损伤因子表达的影响

各种刺激都可引起神经系统即刻早期基因应激蛋白(c-Fos)的表达。c-Fos 通过影响下游靶基因,引起神经细胞因子表达,使神经元损伤。免疫组化检测,DAM 成瘾大鼠小脑细胞中 c-Fos 阳性细胞数明显多于对照组[23],c-Fos 一旦表达,标志着神经元进入凋亡程序[24]。DAM 也能通过诱导促凋亡基因 Bax 表达,引起神经元损伤和凋亡[25-26]。在稳态过程中,Bax 主要作为潜在单体存在于胞浆中,在逆境胁迫下转化为低聚蛋白,使线粒体通透增加,凋亡诱导因子、细胞色素 c(cytochrome c, Cytc)、凋亡蛋白激活因子等进入细胞质,激活 caspase-9、caspase-3,诱导细胞凋亡[27]。苏丽萍等[28]研究表明,给予大鼠小脑颗粒神经元不同浓度 DAM,随着给药浓度的增加,神经元网状结构不同程度的消失、细胞形态改变、碎裂的数量明显增多($P < 0.01$),C-jun、Cytc、caspase-9 水平呈高表达,凋亡率显著增高($P < 0.01$)。DAM 成瘾大鼠小脑细胞出现明显的形态学改变,细胞 Bax、caspase-9 蛋白呈高表达趋势[29]。DAM 和甲基苯丙胺联合用药较单独用药更具有神经毒性。甲基苯丙胺又称“冰毒”,小剂量时有短暂的兴奋抗疲劳作用,表现出精神振奋、清醒、机敏、话多、兴致勃勃、思维活跃、情绪高涨、注意力集中、工作能力(特别是技巧性工作能力)提高,而且长时间工作或学习无疲劳感、无饥饿感。过量使用甲基苯丙胺可导致急性中毒,严重者出现精神混乱、性欲亢进、焦虑、烦躁、幻觉、昏迷甚至死亡。Bax 表达增加,Caspase-3 和 Caspase-9 活性升高,通过线粒体凋亡途径诱导神经细胞凋亡[30]。给予孕鼠不同剂量的 DAM,胚胎子鼠大脑组织中 Bax 表达水平比对照组显著增加($P < 0.05$, $P < 0.01$)[31]。

3 DAM 对神经元保护因子表达的影响

脑源性神经营养因子(brain derived neurotrophic factor, BDNF),在神经元存活、增殖[32]、分化、修复[33]等方面起着重要的作用[34]。BDNF 与酪氨酸激酶受体 B(tyrosine kinase receptor B, TrkB)结合,起到保护神经元免受损伤死亡、促进受损伤神经元修复、再生等重要作用[35]。李莎等[36]报道,

给予 SD 大鼠 DAM 后,大鼠脑边缘前区和下边缘皮层 BDNF 表达显著高于对照组。黄静等[37]连续 6 d 给予大鼠吗啡 10 mg/kg,大鼠海马内 BDNF 阳性细胞数、BDNF 水平显著高于对照组。Xiao 等[38]对 120 名 DAM 成瘾者和 113 名对照人员检测发现,BDNF 甲基化水平明显高于对照组。结果显示,BDNF 参与 DAM 成瘾和戒断过程[39]。神经元受到伤害性刺激时,热休克蛋白-70(heat shock protein-70,HSP-70)合成加快。HSP-70 是一种分子伴侣蛋白,在分子伴侣网络中处于核心位置,在其他多肽进行正常折叠、组装、转运、降解过程中起到重要的协助作用[40-41]。神经元应激损伤时,由于翻译过程中的缺陷,或者是压力因素改变蛋白质的天然构象,使蛋白质错误折叠和聚集,导致蛋白质稳态改变[42]。HSP-70 通过识别错误折叠蛋白的分子伴侣,并将其重新折叠到功能构象和/或靶向降解来维持蛋白质稳态[43-44]。在应激反应中,神经元内 HSP-70 水平上调[45],凋亡蛋白酶(caspases)和应激蛋白激酶(c-Jun N-terminal kinase,JNK)活性降低,促进神经元增生[46],发挥应激保护作用[47-48]。给予成瘾大鼠 HSP-70 抑制剂 PES 和 KNK437 后,NAc 内 HSP-70 表达下调[49]。表明 HSP-70 在 DAM 成瘾过程中起重要促进作用,参与 DAM 依赖的发生发展。

4　神经细胞因子在 DAM 损伤过程中动态调节作用

DAM 在引起神经细胞促凋亡因子(c-Fos、Bax、caspase-9)表达的同时,诱导保护因子(HSP-70、BDNF、TrkB)的表达,从而减轻 DAM 对神经元的损伤程度。然而,动物实验发现,DAM 成瘾大鼠杏仁核(amygdaloid nucleus,ADN)、NAc 中 BDNF 表达水平下调[50-52],胶质细胞源性神经营养因子(glial cell derived neurotrophic factor,GDNF)和神经营养因子受体 p75(neurotrophic factor receptor p75,p75NTR)阳性细胞免疫反应明显减弱,平均吸光度明显降低,GDNF、p75NTR 水平显著降低[53]。结果表明,DAM 通过下调保护因子表达,降低对受损神经元的修复能力,导致神经元损伤、凋亡。Patel 等[54]敲除小鼠 BDNF 或 *Bax* 基因后发现,缺乏 BDNF 的小鼠膝状神经节神经元的数量和神经节体积减少了一半,缺乏 Bax 的小鼠神经元数量和神经节的体积增加了一倍。这些发现表明,神经元凋亡和死亡受 Bax 促凋亡蛋白调控,BDNF 通过防止细胞凋亡和死亡而不是促进细胞增殖来调节神经元数量。由此看出,DAM 对神经组织细胞损伤程度受神经组织细胞促凋亡因子和抗凋亡因子的调控[55]。

5　结语

DAM 成瘾是中枢神经系统内相关神经元受外来药物强化作用而出现的应激性变化过程[56]。由于中枢神经系统结构和功能的复杂性,影响 DAM 成瘾机制的确定[57]。VTA[9]、NAc[10]、CN[58]、Hipp[59]、PFC[60]、HB[61]、LC[62]等脑组织参与 DAM 成瘾和戒断过程。A[15]、NA[63]、DA[64]是导致 DAM 成瘾和戒断症状的体内主要因素。DAM 对神经组织细胞的损伤主要通过上调促凋亡因子(c-Fos、Bax、Caspase-9)水平、下调神经保护因子(HSP-70、BDNF、TrkB)水平的途径导致神经元凋亡和死亡。

DAM 对神经组织细胞损伤机制错综复杂,文中只例举了不同家族中的一员为代表进行表述。除上述因子外还有很多因子参与 DAM 对神经组织细胞的损伤过程,如谷氨酸(Glu)和 γ-氨基丁酸(γ-aminobutylic acid,GABA)[65]、肿瘤坏死因子(TNF-α)[66]、5-羟色胺(5-HT)[67]、激活转录因子-3(activating transcription factor-3,ATF-3)[68]等均为二乙酰吗啡诱导神经元损伤和凋亡的关键因子。

DAM 成瘾性强、戒断难度大,成瘾后个体易出现严重的心理依赖性,导致成瘾者戒断治疗后容易复吸[69]。因此,对 DAM 成瘾者在对症治疗的同时,开展心理疏导尤为必要[70]。

参　考　文　献(References)

[1] Lefevre EM, Gauthier EA, Bystrom LL, et al. Differential patterns of synaptic plasticity in the nucleus accumbens caused by continuous and interrupted morphine exposure [J]. J Neurosci, 2023, 43(2): 308-318.

[2] 乐凯, 文若剑. 阿片成瘾中的神经免疫机制 [J]. 江汉大学学报(自然科学版), 2017, 45(3): 241-246.
Le K, Wen RJ. Neuroimmune mechanism of opiates addiction [J]. J Jianghan Univ (Nat Sci Ed), 2017, 45(3): 241-246.

[3] 胡夏韵, 苏天园, 刘丽, 等. c-Jun 和 Bcl-2 在海洛因所致大鼠小脑颗粒细胞凋亡中的作用 [J]. 新疆医科大学学报, 2017, 40(12): 1549-1554.
Hu XY, Su TY, Liu L, et al. Effects of c-Jun and Bcl-2 in diacetylmorphine-induced apoptosis in rat cerebellar granule cells [J]. J Xinjiang Med Univ, 2017, 40(12): 1549-1554.

[4] 张浩林, 王学伟, 崔彩莲. 阿片类物质对成体神经发生的影响 [J]. 中国药物依赖性杂志, 2015, 24(3): 187-192.
Zhang HL, Wang XW, Cui CL. Effects of opioids on adult

neurogenesis [J]. Chin J Drug Dependence, 2015, 24(3): 187-192.

[5] 张朋, 徐星, 毛紫娟, 等. microRNAs 在甲基苯丙胺滥用诱导神经退行性疾病中的研究进展 [J]. 中国药物依赖性杂志, 2017, 26(6): 411-417.
Zhang P, Xu X, Mao ZJ, et al. Research progress of microRNAs in neurodegenerative diseases induced by methamphetamine abuse [J]. Chin J Drug Depend, 2017, 26(6): 411-417.

[6] Shahzadi A, Yunusoglu O, Karabulut E, et al. Influence of selective dopamine agonist ropinirole on conditioned place preference and somatic signs of morphine withdrawal in rats [J]. Front Behav Neurosci, 2022, 16: 855241.

[7] Lynn E, Doyle A, Keane M, et al. Drug poisoning deaths among women: a scoping review [J]. J Stud Alcohol Drugs, 2020, 81(5): 543-555.

[8] Van den Brink W, Hendriks VM, Blanken P, et al. Beneficial effect of heroin in heroin addicts [J]. Eur Neuropsychopharmacol, 2002, 12: 120.

[9] Lu L, Yang W, Zhao D, et al. Brain recovery of the NAc fibers and prediction of craving changes in person with heroin addiction: a longitudinal study [J]. Drug Alcohol Depend, 2023, 243: 109749.

[10] Kruyer A, Kalivas PW. Astrocytes as cellular mediators of cue reactivity in addiction [J]. Curr Opin Pharmacol, 2021, 56: 1-6.

[11] Haleem DJ, Nawaz S, Salman T. Dopamine and serotonin metabolism associated with morphine reward and its inhibition with buspirone: a study in the rat striatum [J]. Pharmacol Biochem Behav, 2018, 170: 71-78.

[12] King SG, Gaudreault PO, Malaker P, et al. Prefrontal-habenular microstructural impairments in human cocaine and heroin addiction [J]. Neuron, 2022, 110(22): 3820-3832.

[13] 俞发荣, 连秀珍, 张红梅, 等. 儿茶酚胺类激素在海洛因成瘾中的作用 [J]. 中国应用生理学杂志, 2014, 30(2): 124-126, 131.
Yu FR, Lian XZ, Zhang HM, et al. Role of catecholamine hormone in heroin addicts [J]. Chin J Appl Physiol, 2014, 30(2): 124-126, 131.

[14] Chandler DJ. Evidence for a specialized role of the locus coeruleus noradrenergic system in cortical circuitries and behavioral operations [J]. Brain Res, 2016, 1641: 197-206.

[15] 羊毅, 李萍. 海洛因中毒性周围神经病变肌电图观察 [J]. 中国现代医学杂志, 2000, 10(6): 59-61.
Yang Y, Li P. Electromyographic observation of heroin-induced peripheral neuropathy [J]. Chin J Mod Med, 2000, 10(6): 59-61.

[16] 范明霞, 陈一燕. 多巴胺系统与药物依赖 [J]. 海峡药学, 2003, 15(5): 131-133.
Fan MX, Chen YY. Dopamine system and drug dependence [J]. Strait Pharm J, 2003, 15(5): 131-133.

[17] 俞发荣, 李建军, 俞鑫, 等. 干预措施对精神依赖药物成瘾生理生化机制的影响 [J]. 中国实验动物学报, 2018, 26(6): 799-803.
Yu FR, Li JJ, Yu X, et al. Effects of intervention on the physiological and biochemical mechanisms of psycho-dependent drug addiction [J]. Acta Lab Anim Sci Sin, 2018, 26(6): 799-803.

[18] 张栋梁, 沈泽虹, 陈德兴, 等. 多巴胺系统与药物成瘾的关系 [J]. 神经解剖学杂志, 2010, 26(5): 564-568.
Zhang DL, Shen ZH, Chen DX, et al. The relationship between dopamine system and drug addiction [J]. Chin J Neuroanat, 2010, 26(5): 564-568.

[19] Büttner A, Mall G, Penning R, et al. The neuropathology of heroin abuse [J]. Forensic Sci Int, 2000, 113(1-3): 435-442.

[20] 郑希耕, 隋南. 吗啡作用的中枢机制及相关的基因调控 [J]. 中国神经科学杂志, 2001, 17(4): 343-346, 361.
Zheng XG, Sui N. Brain mechanisms of morphine abuse and related gene expression [J]. Chin J Neurosci, 2001, 17(4): 343-346, 361.

[21] 陈晗晖, 郝伟, 赵敏. 物质成瘾中重要神经核团的作用 [J]. 中国药物滥用防治杂志, 2006, 12(6): 338-340.
Chen HH, Hao W, Zhao M. The role of important nerve nuclei in substance addiction [J]. Chin J Drug Abuse Prev Treat, 2006, 12(6): 338-340.

[22] 李锦, 曹丹旎, 吴宁. 抗阿片成瘾药物研究历史与现状 [J]. 中国药理学与毒理学杂志, 2012, 26(3): 255-262.
Li J, Cao DN, Wu N. History and current status of research on anti-opioid addiction drugs [J]. Chin J Pharmacol Toxicol, 2012, 26(3): 255-262.

[23] 连秀珍, 谢明仁, 朱喜春, 等. 海洛因对小脑皮质 C-FOS 表达的影响 [J]. 甘肃科学学报, 2012, 24(3): 95-97.
Lian XZ, Xie MR, Zhu XC, et al. Effect of heroin on C-FOS expression of cerebellar cortex of rat [J]. J Gansu Sci, 2012, 24(3): 95-97.

[24] Tsai SF, Liu YW, Kuo YM. Acute and long-term treadmill running differentially induce c-Fos expression in region- and time-dependent manners in mouse brain [J]. Brain Struct Funct, 2019, 224(8): 2677-2689.

[25] 俞发荣, 连秀珍, 谢明仁, 等. 海洛因成瘾模型建立及中脑腹侧被盖区 Bax 的表达 [J]. 中国实验动物学报, 2012, 20(6): 82-84, 103.
Yu FR, Lian XZ, Xie MR, et al. Effect of heroin on Bax expression in the brain ventral tegmental area and establishment of a rat model of heroin addiction [J]. Acta Lab Anim Sci Sin, 2012, 20(6): 82-84, 103.

[26] 谢明仁, 李作平, 俞发荣, 等. 海洛因对小脑皮质 Bax 表达的影响 [J]. 实验动物科学, 2013, 30(5): 6-8.
Xie MR, Li ZP, Yu FR, et al. Effect of heroin on bax expression in cerebellar cortex in rat [J]. Lab Anim Sci, 2013, 30(5): 6-8.

[27] Bloch NB, Wales TE, Prew MS, et al. The conformational stability of pro-apoptotic BAX is dictated by discrete residues of the protein core [J]. Nat Commun, 2021, 12(1): 4932.

[28] 苏丽萍, 路子扬, 刘丽, 等. 二乙酰吗啡致大鼠小脑颗粒神

经元细胞凋亡过程中 C-Jun、Cytc 和 Caspase-9 的作用 [J]. 中国组织工程研究, 2021, 25(25): 3943-3948.
Su LP, Lu ZY, Liu L, et al. C-Jun, Cytc and Caspase-9 in the apoptosis of cerebellar granule neurons induced by diacetylmorphine in rats [J]. Chin J Tissue Eng Res, 2021, 25(25): 3943-3948.

[29] Pu HW, Su LP, Miao N, et al. Involvement of Bax and caspase-9 in heroin-induced apoptosis in cerebellar granule neurons via C-Jun pathway activation [J]. Int J Clin Exp Pathol, 2016, 9(2): 773-788.

[30] Tian X, Ru Q, Xiong Q, et al. Neurotoxicity induced by methamphetamine-heroin combination in PC12 cells [J]. Neurosci Lett, 2017, 647: 1-7.

[31] 俞发荣, 李建军, 连秀珍, 等. 精神依赖物海洛因对大鼠胚胎发育和脑组织 Bax 表达的影响 [J]. 中国实验动物学报, 2019, 27(4): 527-531.
Yu FR, Li JJ, Lian XZ, et al. Effects of heroin on embryonic development and Bax expression in embryonic rat brain tissue [J]. Acta Lab Anim Sci Sin, 2019, 27(4): 527-531.

[32] 杨恩璐, 孙秉贵. BDNF 及其下游通路与 GABA 能神经元发育相关性的研究进展 [J]. 生命科学, 2020, 32(6): 544-550.
Yang EL, Sun BG. Role of BDNF and its related pathways in GABA ergic neuron development [J]. Chin Bull Life Sci, 2020, 32(6): 544-550.

[33] 姚欣怡, 王玉玲, 郭彦谷, 等. BDNF 在脊髓损伤修复中的双重作用及其表观遗传调节因素 [J]. 神经解剖学杂志, 2018, 34(6): 757-760.
Yao XY, Wang YL, Guo YG, et al. The dual role of BDNF in spinal cord injury repair and its epigenetic regulatory factors [J]. Chin J Neuroanat, 2018, 34(6): 757-760.

[34] Keeler JL, Patsalos O, Chung R, et al. Short communication: Serum levels of brain-derived neurotrophic factor and association with pro-inflammatory cytokines in acute and recovered anorexia nervosa [J]. J Psychiatr Res, 2022, 150: 34-39.

[35] Holt LM, Hernandez RD, Pacheco NL, et al. Astrocyte morphogenesis is dependent on BDNF signaling via astrocytic TrkB.T1 [J]. Elife, 2019, 8: 44667.

[36] 李莎, 王颖, 朱再满, 等. BDNF 和 GDNF 在海洛因诱导条件性位置偏爱大鼠 mPFC 的表达 [J]. 神经解剖学杂志, 2022, 38(1): 8-14.
Li S, Wang Y, Zhu ZM, et al. Expressions of BDNF and GDNF in mPFC region of heroin-induced CPP rats [J]. Chin J Neuroanat, 2022, 38(1): 8-14.

[37] 黄静, 方琴, 王季石, 等. 吗啡依赖大鼠海马内脑源性神经营养因子的表达 [J]. 贵州医药, 2009, 33(1): 8-10.
Huang J, Fang Q, Wang JS, et al. Expression of brain-crived neurotrophic factor (BDNF) in hippocampus in rats after chronic morphine treatment [J]. Guizhou Med J, 2009, 33(1): 8-10.

[38] Xiao Y, Zhu Y, Li Y. Elevation of DNA methylation in the promoter regions of the brain-derived neurotrophic factor gene is associated with heroin addiction [J]. J Mol Neurosci, 2021, 71(9): 1752-1760.

[39] 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: 2805-2815.

[40] 张翔, 王祖峰. 分子伴侣 Hsp70 变构机制及其在水生动物中的应用研究进展 [J]. 大连海洋大学学报, 2022, 37(4): 707-718.
Zhang X, Wang ZF. Advances in allosteric mechanism and potential application of Hsp70 molecular chaperones in aquaculture animals: a review [J]. J Dalian Ocean Univ, 2022, 37(4): 707-718.

[41] 唐宇琦, 叶松涛, 刘嘉, 等. 分子伴侣作用下的蛋白质稳定与进化 [J]. 合成生物学, 2022, 3(3): 445-464.
Tang YQ, Ye ST, Liu J, et al. Molecular chaperones promote protein stability and evolution [J]. Synth Biol J, 2022, 3(3): 445-464.

[42] Tedesco B, Ferrari V, Cozzi M, et al. The role of small heat shock proteins in protein misfolding associated motoneuron diseases [J]. Int J Mol Sci, 2022, 23(19): 11759.

[43] Jacob-Tomas S, Alagar Boopathy LR, Vera M. Using single-molecule fluorescence microscopy to uncover neuronal vulnerability to protein damage [J]. Methods Mol Biol, 2022, 2515: 237-254.

[44] 陈智暹, 戴斌, 王利强, 等. Hsp70 在神经退行性疾病中的作用机制研究进展 [J]. 生命科学, 2021, 33(8): 931-938.
Chen ZX, Dai B, Wang LQ, et al. Research progress on the mechanism of Hsp70 in neurodegenerative diseases [J]. Chin Bull Life Sci, 2021, 33(8): 931-938.

[45] Petrović A, Kaur J, Tomljanović I, et al. Pharmacological induction of heat shock protein 70 by celastrol protects motoneurons from excitotoxicity in rat spinal cord *in vitro* [J]. Eur J Neurosci, 2019, 49(2): 215-231.

[46] 陈皓, 王隆, 张莉. 谷氨酰胺对小鼠脑损伤中热休克蛋白 70 表达的影响 [J]. 河南大学学报(自然科学版), 2022, 52(4): 441-448.
Chen H, Wang L, Zhang L. Effects of glutamine on the expression of heat shock protein 70 in mice with brain injury [J]. J Henan Univ Nat Sci, 2022, 52(4): 441-448.

[47] 赵光强. 细胞凋亡过程中热休克蛋白的调节 [J]. 潍坊学院学报, 2006, 6(2): 77-81.
Zhao GQ. The regulation of heat shock proteins in apoptosis [J]. J Weifang Univ, 2006, 6(2): 77-81.

[48] 朱熊兆, 亓晓丽, 姚树桥, 等. 热休克蛋白 70 对小鼠海马 CA3 区神经元损伤的保护作用 [J]. 中国心理卫生杂志, 2006, 20(7): 425-429.
Zhu XZ, Qi XL, Yao SQ, et al. The protective role of the Hsp70 in hippocampal CA3 neurons against chronic psychological stress [J]. Chin Ment Health J, 2006, 20(7): 425-429.

[49] Wei S, Li YL, Gong Q, et al. Molecular chaperone heat shock protein 70 inhibitors suppress conditioned place preference induced by morphine exposure in male rats [J]. Addict Biol,

2022, 27(3): e13163.

[50] Fatahi Z, Zeinaddini-Meymand A, Karimi-Haghighi S, et al. Naloxone-precipitated withdrawal ameliorates impairment of cost-benefit decision making in morphine-treated rats: involvement of BDNF, p-GSK3-β, and p-CREB in the amygdala [J]. Neurobiol Learn Mem, 2020, 167: 107138.

[51] Fatahi Z, Zeinaddini-Meymand A, Karimi S, et al. Impairment of cost-benefit decision making in morphine-dependent rats is partly mediated via the alteration of BDNF and p-CREB levels in the nucleus accumbens [J]. Pharmacol Biochem Behav, 2020, 194: 172952.

[52] Li Y, Xia B, Li R, et al. Expression of brain-derived neurotrophic factors, neurotrophin-3, and neurotrophin-4 in the nucleus accumbens during heroin dependency and withdrawal [J]. Neuroreport, 2017, 28(11): 654-660.

[53] 李杰, 李一欣, 夏白娟, 等. 海洛因成瘾、戒断、脱毒对大鼠前额叶皮质 GDNF 和 p75NTR 表达的影响 [J]. 神经解剖学杂志, 2019, 35(3): 271-276.
Li J, Li YX, Xia BJ, et al. Effects of heroin addiction, withdrawal and detoxification on the expression of GDNF and p7NTR in prefrontal cortex regions of rat brain [J]. Chin J Neuroanat, 2019, 35(3): 271-276.

[54] Patel AV, Krimm RF. BDNF is required for the survival of differentiated geniculate ganglion neurons [J]. Dev Biol, 2010, 340(2): 419-429.

[55] 刘松松, 项阳, 王剑. 热休克蛋白 70 在细胞凋亡途径中的作用研究进展 [J]. 中国畜牧杂志, 2020, 56(8): 45-49.
Liu SS, Xiang Y, Wang J. Effect of heat shock protein 70 on the process of cellular apoptosis [J]. Chin J Anim Sci, 2020, 56(8): 45-49.

[56] Zhang J, Fan Y, Zhou J, et al. Methylation quantitative trait locus rs5326 is associated with susceptibility and effective dosage of methadone maintenance treatment for heroin use disorder [J]. Psychopharmacology, 2021, 238(12): 3511-3518.

[57] Wang K, Zhang H, Ji J, et al. Expression quantitative trait locus rs6356 is associated with susceptibility to heroin addiction by potentially influencing TH gene expression in the hippocampus and nucleus accumbens [J]. J Mol Neurosci, 2022, 72(5): 1108-1115.

[58] De Pirro S, Galati G, Pizzamiglio L, et al. The affective and neural correlates of heroin versus cocaine use in addiction are influenced by environmental setting but in opposite directions [J]. J Neurosci, 2018, 38(22): 5182-5195.

[59] Wei X, Li W, Chen J, et al. Assessing drug cue-induced brain response in heroin dependents treated by methadone maintenance and protracted abstinence measures [J]. Brain Imaging Behav, 2020, 14(4): 1221-1229.

[60] King SG, Gaudreault PO, Malaker P, et al. Prefrontal-habenular microstructural impairments in human cocaine and heroin addiction [J]. Neuron, 2022, 110(22): 3820-3832.

[61] Müller UJ, Ahrens M, Vasilevska V, et al. Reduced habenular volumes and neuron numbers in male heroin addicts: a post-mortem study [J]. Eur Arch Psychiatry Clin Neurosci, 2021, 271(5): 835-845.

[62] Aston-Jones G, Waterhouse B. Locus coeruleus: from global projection system to adaptive regulation of behavior [J]. Brain Res, 2016, 1645: 75-78.

[63] Snyder AE, Silberman Y. Corticotropin releasing factor and norepinephrine related circuitry changes in the bed nucleus of the stria terminalis in stress and alcohol and substance use disorders [J]. Neuropharmacology, 2021, 201: 108814.

[64] George BE, Dawes MH, Peck EG, et al. Altered accumbal dopamine terminal dynamics following chronic heroin self-administration[J]. Int J Mol Sci, 2022, 23(15): 8106.

[65] 潘际刚, 潘贵书, 徐国强, 等. 海洛因使大鼠背侧海马功能和 Glu/GABA 递质系统紊乱 [J]. 中国药理学通报, 2009, 25(5): 646-649.
Pan JG, Pan GS, Xu GQ, et al. Heroin interferes with dorsal hippocampal function and Glu/GABA transmitter system in rats [J]. Chin Pharmacol Bull, 2009, 25(5): 646-649.

[66] 李卫峰, 苏丽萍, 胡夏韵, 等. TNF-α、Rho、C-AbI 蛋白表达对海洛因致大鼠小脑颗粒神经元细胞凋亡的作用和意义 [J]. 新疆医科大学学报, 2019, 42(4): 472-478, 483.
Li WF, Su LP, Hu XY, et al. The role and significance of TNF-α, Rho and C-AbI protein in apoptosis of rat cerebellar granule neurons induced by heroin [J]. J Xinjiang Med Univ, 2019, 42(4): 472-478, 483.

[67] 洪艳, 梁文妹, 夏白娟, 等. 5-HT、SP 在海洛因戒断、脱毒、复吸大鼠直肠组织中的表达 [J]. 世界华人消化杂志, 2011, 19(5):477-482.
Hong Y, Liang WM, Xia BJ, et al. Expression of 5-HT and SP in the rectum of rats during heroin abstinence, detoxification or relapse [J]. World Chin J Dig, 2011, 19(5): 477-482.

[68] Zhang J. Heroin activates ATF3 and CytC via c-Jun N-terminal kinase pathways to mediate neuronal apoptosis [J]. Med Sci Monit Basic Res, 2015, 21: 53-62.

[69] 刘菁菁, 王丽楠, 周雪莹, 等. 基于路径分析模型的新型毒品成瘾者心理健康状况影响因素研究 [J]. 中国全科医学, 2022, 25(30): 3775-3782.
Liu JJ, Wang LN, Zhou XY, et al. Factors associated with mental health status in people addicted to new synthetic drugs: a path analysis [J]. Chin Gen Pract, 2022, 25(30): 3775-3782.

[70] Jones S, Jack B, Kirby J, et al. Methadone-assisted opiate withdrawal and subsequent heroin abstinence: the importance of psychological preparedness [J]. Am J Addict, 2021, 30(1): 11-20.

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