[综述]

物质成瘾与昼夜节律相互关系的研究进展*

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摘要 药物成瘾是一个突出的社会问题,给家庭和社会带来了巨大损失。然而其发生机制尚不完全清楚,近年来,在众多机制假说中生物节律机制的研究越来越受到关注。本文将以可卡因为例,从其体内代谢过程、对人体危害、作用机制,到昼夜节律系统、以及物质成瘾和昼夜节律两者相互关系的研究进展,做一详细综述。

关键词 药物成瘾;可卡因;昼夜节律;钟基因

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Research progress on the relationship between substance addiction and circadian rhythm

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Abstract Drug addiction is a prominent social problem, which has brought great losses to families and society. However, the mechanism is not completely clear. In recent years, the research on the biological rhythm mechanism of drug addiction has attracted more and more attention among many mechanism hypotheses. This paper will take cocaine as an example to make a detailed review from its physiological effects, internal metabolic processes, harm to human body and mechanism of action, to the circadian rhythm system, as well as the research progress of the relationship between substance addiction and circadian rhythm.

Keywords substance addiction; cocaine; circadian rhythm; clock gene

物质成瘾是一个突出的社会问题,给家庭和社会带来了巨大损失。可卡因是一种广泛使用的成瘾药物。每年有1400多万人使用可卡因。在发达国家,大约2%的人在他们的一生中使用过可卡因[1]。在1990年,可卡因直接导致2400人死亡。在2013年,可卡因直接导致的死亡人数明显增加至4300人[2]。近年来物质成瘾与昼夜节律之间的联系关注度逐渐增加,本文将以可卡因为例,从其体内代谢过程、对人体危害、作用机制,到昼夜节律系统、以及物质成瘾和昼夜节律两者相互作用的研究进展,做一详细综述。

1 可卡因

1.1 生理作用

可卡因是一种生物碱,属于莨菪烷型,它是一种强兴奋剂,也是消遣性药物。人在使用后会出现心率增加、出汗、瞳孔散大等躯体症状。症状在使用后

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数秒就可以出现,持续时间一般在 5 - 90 min 之间。可卡因作用的持续时间取决于服用量和给药途径。可卡因使人达到欣快感效果最快的摄入方式是像吸烟一样吸入(只需要 3 - 5 s) ,而鼻吸的方式因为可卡因收缩鼻粘膜血管而被延迟(5 min) 。像吸烟一样吸入可卡因,效果持续时间是 5 - 15 min,而以鼻吸的方式吸入可卡因,持续时间最长可达 60 - 90 min。重复多次使用同样剂量的可卡因后,感受到快乐的能力可能会下降,同时身体也会感觉疲惫。可卡因的使用还会提高警觉性、增强幸福感,增加精力和活动,增强能力感和性欲[3]。大剂量使用可卡因还可以使血压和体温升高[4]。可卡因局部用药可以作为麻醉剂缓解疼痛[5]。

可卡因具有成瘾性,因为它可以抑制大脑奖赏通路(中脑边缘通路) 多巴胺的再摄取而容易在使用后对其形成依赖。1961 年联合国《麻醉品单一公约》旨在消除大麻、可卡因和阿片类药物的非法生产和非医疗用途。

1.2 可卡因的代谢及不良反应

可卡因在血浆中的半衰期较短,从 0.5 - 1.5 h 不等,其浓度最高的部位是大脑、脾脏、肾脏和肺[6]。其主要代谢物苯甲酰芽子碱(BE) 的半衰期大约为 6 h[7]。可卡因及 BE 可在尿液、血液、唾液、毛发和汗液中检测到,还可以在胎粪和羊水中检测到[8]。鼻吸方式使用可卡因 100 mg,2 - 3 d 内可在尿液中检测出 BE[9],12 h 内可在血液中检测出可卡因[1]。单次静脉注射 20 mg 可卡因,1 - 2 d 内可在尿液中检测出 BE[10]。若长期大量每日使用可卡因,唾液样本 10 d 内可检测到 BE[11],血液样本 5.1 d 内可检测到 BE[12],尿液样本可在 22 d 内检测到 BE[13]。

可卡因及其代谢产物可以损伤心血管系统[14]、呼吸系统[15]、肌肉骨骼系统[16]、消化系统[17]、泌尿系统[18]。可卡因能阻断多巴胺、去甲肾上腺素和血清素的再摄取[19]。可卡因还会导致内皮细胞产生的内皮素(一种强效血管收缩剂) 和一氧化氮(一种强效血管舒张剂) 减少[20]。可卡因以上特性可引起心率、血压增加、血管收缩、心肌耗氧量增加等,最终引起胸痛、心肌梗死、主动脉夹层、脓毒性栓子、心肌缺血、间歇性冠状动脉痉挛、心肌病、心脏原因导致的猝死、心肌炎、心律失常、脑出血等心血管相关问题[8]。可卡因也可引起纵隔气肿、气胸、非心源性肺水肿[21]、支气管收缩[22]、横纹肌溶解症、肠缺血、肠梗死、肠穿孔、缺血性结肠炎、间质性肾炎和肾小球肾炎等其他问题[23]。可卡因具有高亲水和亲脂的特性,所以可卡因可以轻易地通过血脑屏障,并破坏大脑屏障从而产生神经毒性[24]。可卡因在脑内阻止神经突触中神经递质的再摄取,可卡因的奖赏效应以及成瘾性都与此有关[25],几乎可卡因所有的中枢神经系统效应都可以归因于这一机制[26]。可卡因还可以引起昼夜节律的紊乱[27]。

2 物质成瘾机制

2.1 奖赏系统

奖赏系统是大脑结构和神经通路一个集合,它可奖励相关的认知,包括联想学习、激励显著性(如,动机和“想要”、渴望或渴望奖励) 和积极情绪[28]。奖赏系统通常用来描述与奖赏的“渴求”或欲望成分,包括欲望行为、趋向行为、准备行为、工具行为、预期行为和寻求的行为[29]。奖赏系统的大脑结构主要包含在皮质 - 基底神经节 - 丘脑环路,基底神经节区可驱动奖赏系统环路内的活动[30]。奖赏系统路径的主要连接结构是谷氨酸能中间神经元,γ - 氨基酸能棘突神经元(MSNs) 和多巴胺能投射神经元[31],同时也有其它投射的神经元,例如: 食欲肽能投射神经元[32]。奖赏系统包含了腹侧被盖区(VTA) 、腹侧纹状体(伏隔核(NAc) 和嗅结节) 、背侧纹状体(尾状核和壳核) 、黑质、前额叶皮层(PFC) 、扣带回皮层、岛叶皮层、海马、下丘脑、苍白球(包括外白球和内白球) 、腹侧苍白球、臂旁核、杏仁核和延伸杏仁核的其余部分[33 - 34]。中脑边缘多巴胺通道与奖赏系统密切相关[35]。中脑边缘多巴胺通道是从腹侧被盖区投射到伏隔核[36]。出现奖赏相关刺激时,VTA 释放多巴胺到伏隔核、杏仁核、前额叶皮层(PFC) 和海马[36]。谷氨酸能信号起源于 PFC、杏仁核和海马,最终传递到 NAc[37]。此外,外侧下丘脑和缰核向 VTA 发送谷氨酸信号[38]。

2.2 可卡因成瘾

可卡因对奖赏通路内多巴胺再摄取的阻断作用是其具有成瘾性的重要因素[39]。可卡因的使用,首先导致突触间多巴胺水平升高。增加的多巴胺结合多巴胺受体,然后通过 cAMP 依赖通路,最终导致 CREB 磷酸化[40]。CREB 磷酸化增加促使 ΔFosB 水平增加,ΔFosB 与 JunD 抑制 c - Fos 基因[41]。c -

Fos 被抑制又反过来使 ΔFosB 在神经元内积累[42]。而磷酸化的 ΔFosB 高度稳定,可以在神经元内存在 1 到 2 个月,它通过重复接触可卡因慢慢积累得更多[43]。ΔFosB 作为"主控制蛋白质之一"导致大脑结构发生变化,当积累的量足够时,再借助其下游目标(如 NF-κB),最终诱导出上瘾的状态[44]。伏隔核 D_1 型棘突神经元内 ΔfosB 的过表达对药物成瘾的形成至关重要[45]。伏隔核 D_1 型棘突神经元表达的 ΔfosB 能直接调节自身给药和奖赏敏化作用,同时减弱厌恶的敏感性[46]。人们即使短时间使用,也可能对可卡因产生依赖[39]。

3 昼夜节律系统

3.1 时钟基因

昼夜节律系统代表了一个复杂的多振荡的时间网络,这个网络,包括被光/黑暗周期调制的下丘脑视交叉上核中的主要昼夜节律起搏器,随后将同步信号传递给外周节律振荡器[47]。昼夜节律是一个遵循 24 小时循环的生物过程。24 小时的节律是由生物钟驱动的[48]。Per_1,Per_2,Per_3,Cry_1,Cry_2,*Rev-erbα*,*CKIε*,*Timeless*,$Npas_2$,*Clock*,$Bmal_1$ 是核心的生物时钟基因[49]。节律性的基因表达需要依靠内在的转录/翻译反馈环(TIFL)才能完成[50]。在分子水平上,生物钟由核心反馈环和辅助反馈环组成[51]。反馈环的活动创造了一种基因表达的自我延续的震荡模式,该模式的周期接近 24 小时[52]。哺乳动物体内核心反馈环的组成:(1)由 CLOCK 和 $BMAL_1$ 两者形成异质二聚体的转录激活剂结合并激活 E-boxes 引发 Per_1 和 *Cry* 等基因的转录[50]。(2)PER 和 CRY 蛋白被翻译并在细胞中积累,然后它们的异二聚体被转移到细胞核内从而抑制 CLOCK/$BMAL_1$ 的活性,导致自身转录的抑制[50]。哺乳动物体内辅助反馈环的组成:CLOCK/$BMAL_1$ 异质二聚体引发 REV-ERBα/β 和 RORα/β 的表达,REV-ERBα/β 和 RORα/β 绑定到 RORE 调节 $BMAL_1$ 的节律性表达[51]。CRY 分为 CRY_1 和 CRY_2。PER 分为了 PER_1、PER_2、PER_3,三者都在分子时钟内发挥着各自独立的作用[53]。例如,PER_3 在大脑内发挥的作用微不足道[53],却扮演了调节外周组织节律的角色[54]。

3.2 昼夜节律起搏器

哺乳动物体内最主要的生物钟位于下丘脑的一对视交叉上核。有科学研究将含有昼夜节律基因突变的供体动物的下丘脑视交叉上核(SCN)组织移植到 SCN 损伤的野生型宿主中赋予宿主突变的昼夜节律表型,实验结果表明 SCN 为昼夜节律起搏器[55-56]。在人类和其他哺乳动物中,光调制昼夜节律系统依赖于包含了视网膜视锥细胞、视杆细胞还有视网膜神经节细胞的视网膜光感受器[57-58]。内在感光视网膜神经节细胞包含了视黑素这种感光色素[59],通过视网膜下丘脑束投射到 SCN,其末梢释放的神经递质为谷氨酸和垂体腺苷酸环化酶活性多肽[60]。每个 SCN 大约包含 8000-10000 个神经元[61]。每个 SCN 神经元与 SCN 组织分离后都能独立产生自我维持的昼夜节律[62-63]。然而,完整 SCN 内的神经元相互耦合形成一个整体可形成自发电活动[64]、钙振荡[65]、体液输出[66]、代谢活动和基因表达[67]的同步昼夜节律[49]。光信息进入 SCN 被转换成神经和体液输出信号,这些信号影响身体的各种节律,包括温度、活动水平和激素分泌[68]。SCN 通过下丘脑内的投射还具有调节睡眠-觉醒周期的能力[69]。

3.3 外周节律振荡器

研究表明昼夜节律振荡器在哺乳动物全身都有分布,除了视交叉上核,在其它脑区、外周器官、甚至培养的细胞株中都存在[70]。内在的感光视网膜神经节细胞对光调制外周时钟是必需的。外周独立的时钟系统对外周组织很重要[52]。基因的相位表达驱使有机体在生理和行为上都表现出昼夜节律[52]。来自 SCN 的信号使整个身体的独立生物钟同步到适当的相位[71]。昼夜节律钟系统是一个具有鲜明等级的多震荡器网络,其中视交叉上核是中枢起搏点。视交叉上核时钟在对抗遗传和环境干扰方面比外周时钟更强[72]。中枢节律起搏器调节外周器官的时相,但是中枢起搏器和外周振荡器是来自同一个网络,整个网络受光线调制,并且受食物、运动、甲基苯丙胺等调节[73]。SCN 的同步对于行为的节律性很重要[74]。同时,中枢时钟和外周时钟共同组成生理定时系统,帮助生物更好地适应外部环境[75]。

4 物质成瘾和昼夜节律

可卡因抑制奖赏相关通路内多巴胺的再摄取是可卡因成瘾的重要因素。而早期和近几年文献都证明脑内多巴胺水平具有 24 小时节律变化[76]。多巴胺转运体(DAT)和酪氨酸羟化酶(TH)以及多巴胺

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受体在不同脑区也呈节律性表达[77]。钟基因是一调节蛋白家族,通过位于目的基因(如钟控基因)启动子区被称作"E - box"的 DNA 结合域,刺激或抑制基因表达;这些被钟基因调节的目的基因,称作钟控基因。钟控基因也存在近日节律或每日变化模式[78]。多巴胺能系统中 TH(多巴胺合成的限速酶)和 DAT(将多巴胺从突触转运至细胞外),在小鼠、大鼠和人编码这两个蛋白的基因启动子区包含供 CLOCK/$BMAL_1$ 复合体结合的"E - box"序列,CLOCK/$BMAL_1$ 是转录因子钟基因家族成员。多巴胺受体如 D_1 和 D_2 受体,在它们启动子区也包含公认的 E - box 序列[79]。因此这些基因都属于钟控基因。这样,TH 和 DAT 水平按照光照:黑暗循环相位被调节,相应的细胞外多巴胺水平也具有近日节律变化。作为转录因子的钟基因以 24 小时周期节律性表达[80],在多巴胺能系统每日变化中充当调节器。例如,与觅药行为有关的几个脑区钟基因的表达被 SCN 昼夜节律起博点同步化[81]。这些脑区包括腹侧被盖区、伏隔核、纹状体和前额叶[82]。这些脑区都包含在奖赏系统内,也包含在与奖赏相关的多巴胺通路内。由此可知,可卡因成瘾与昼夜节律系统相关。

也有研究证明物质成瘾和昼夜节律不仅关系密切,而且成瘾和昼夜节律紊乱两者存在双向作用[83]。反复暴露甲基苯丙胺诱导了小鼠自发活动和尾状核/壳 $mPer_1$ 表达的敏化作用[84]。慢性给予甲基苯丙胺的大鼠,视交叉上核 $rPer_1$ mRNA 表达与生理盐水组基本上完全相同,然而,尾壳核和顶叶皮层部位的 $rPer_1$,$rPer_2$ 和 $Bmal_1$ mRNA 表达与生理盐水组相比位相完全相反[85]。反复的可卡因暴露导致 Per_2、$Bmal_1$、Cry_1 和 $Npas_2$ 在纹状体中的表达降低,但增加了 Per_1 和 *Clock* 在纹状体中的表达,也增强了 Per_1 和 Per_2 在海马中的表达[86]。我们的研究发现,可卡因稽延性戒断会导致大鼠大脑奖赏相关脑区磷酸化的糖原合酶激酶 3β 的节律性表达紊乱[87],而中脑腹侧被盖区可能是可卡因条件性位置偏爱昼夜变化的关键脑区[88]。吗啡依赖大鼠在急性戒断期 $rPer_1$ 和 $rPer_2$ mRNA 表达在视交叉上核与盐水组表达基本完全相同,而在伏隔核核心部、杏仁核核心部均完全丧失节律,在其它脑区如腹侧背盖区仅是位相不同,伏隔核壳部、杏仁核背外侧部则与盐水组表达基本相同[89],而大鼠阿片类物质的稽延性戒断扰乱 $rPer_1$、$rPer_2$ 和 $rPer_3$ 在奖赏相关脑区中的节律性表达至少持续 60 天[90]。昼夜节律的紊乱可以增加成瘾的易感性[91]。时钟基因 *Per* 能影响小鼠对可卡因的行为反应,且 Per_1 和 Per_2 基因产生的影响相反[92]。通过脱氧核酶降低小鼠 Per_1 表达则可阻断吗啡诱导的条件性位置偏爱[93]。此外,$Clock\Delta_{19}$ 突变的小鼠表现出 VTA 多巴胺能活性增强,同时也表现出可卡因偏爱和奖赏的强化[94]。

人的临床研究显示,海洛因使用者自然戒断后外周血单核细胞中 $hPer_1$ 和 $hPer_2$ mRNA 的节律性表达紊乱至少持续 30 天[95]。酒依赖患者和适度饮酒者血液样本中 $Bmal_1$ 的表达都显著降低[96]。也有研究证明失眠是酒精成瘾者停止饮酒后经常会出现的症状[97]。昼夜节律系统调节基因表达的昼夜节律,基因表达昼夜节律的变化常常对药物吸收、分布、代谢和消除有影响[98]。药物的功效和耐受性会受到昼夜节律药动学和药效学的严重影响[99]。有研究指出:在身体的大部分细胞中,细胞自主的生物钟与代谢途径密切相关,生理时钟适应意义的一个新观点是它们的基本作用为协调新陈代谢[100]。

5 总结和展望

可卡因是一种成瘾物质,很早就在古柯叶中被发现。可卡因摄入方式多样,可对全身各个系统造成损害,最严重的可导致死亡。可卡因也具有麻醉、镇痛等医疗作用。可卡因抑制奖赏相关通路内多巴胺的再摄取是可卡因成瘾的重要因素。研究证明多巴胺水平具有 24 小时节律变化。多巴胺转运体、酪氨酸羟化酶、多巴胺受体的基因都属于钟控基因,被时钟基因调节。已有研究显示了物质成瘾与昼夜节律之间存在相互作用,但现有研究仍较少,尚不足以阐明药物依赖发生机制中昼夜节律的确切作用,还有待于未来进一步深入研究。从基因调节角度来看,参与药物成瘾机制的多巴胺系统,无论是合成酶、还是多巴胺受体或转运体的基因,在启动子区均有节律基因调节的"E - box"序列,这样推测从昼夜节律系统深入研究成瘾机制或许可以成为治疗物质成瘾一个新的突破口。

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