What is the biological basis of addiction?

脑内 LTCCs 在药物成瘾形成过程中的调控机制

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摘要 药物成瘾伴随中枢神经系统内钙离子通道数目及开放状态的适应性改变。大量证据表明, L型电压依赖性钙通道(LTCCs)可通过调节神经递质的释放、神经兴奋性、基因的转录及突触可塑性等过程调控成瘾行为。最新的研究还表明, LTCCs的不同亚型 $\text{Ca}_v1.2$ 和 $\text{Ca}_v1.3$ 对药物成瘾的调控分别依赖于D1及D2受体, 且具有脑区及分子机制特异性。并且, $\text{Ca}_v1.3$ 的 α 亚基能够与内质网钙通道蛋白(RyR2)的N末端氨基酸相互结合, 促进胞内钙库 Ca^{2+} 的释放。此外, 骨架蛋白激酶A锚定蛋白79/150(AKAP79/150)可将LTCCs锚定在突触膜上, 从而调控成瘾药物诱导的突触可塑性改变。本文将重点讨论LTCCs在药物成瘾中发挥的调控作用及其潜在的细胞及分子机制。

关键词 LTCCs, 成瘾记忆, 突触可塑性, $\text{Ca}_v1.2$, $\text{Ca}_v1.3$

细胞内游离 Ca^{2+} 浓度的改变是细胞生理功能的重要物质基础, 如神经递质的释放、荷尔蒙的分泌^[1], 也是多种胞内信号传导以及基因表达过程的关键环节^[2]。近年来, 除了N-甲基-D-天冬氨酸受体(N-methyl-D-aspartic acid receptor, NMDAR)这种配体门控的钙离子通道, 电压门控型钙通道(voltage dependent calcium channels, VDCCs)与药物成瘾间的关系正受到日益广泛的关注。与NMDAR引起 Ca^{2+} 内流的机制不同, VDCCs是通过细胞膜的去极化激活从而介导 Ca^{2+} 的内流^[3]。VDCCs根据电生理学特性、药理学属性以及氨基酸组成可以分为高电压激活的(high voltage activated, HVA)VDCCs和低电压激活的(low voltage activated, LVA)VDCCs。HVA通道包括L, N, P/Q和R型VDCCs, LVA通道包括T型VDCCs^[4,5]。一般来讲, HVA通道在膜电位比静息电位高时打开; 而LVA通

道则在膜电位比静息电位低时开放。从构成上讲, VDCCs是由5种亚基构成的异物聚合体: (i) 造孔 α_1 亚基, 其功能是包含钙离子通道调节剂的绑定位点、电压感受器以及选择性过滤器; (ii) 一种由 α_2 和 δ 亚基共同构成的跨膜二硫聚合物; (iii) 细胞内的 β 亚基以及(iv) 跨膜的 γ 亚基^[6]。分子生物学研究已经发现10种不同的基因能够编码不同的 α_1 亚基, 因此研究者根据 α_1 亚基序列的相似性将VDCCs分为不同的家族—— Ca_v1 , Ca_v2 以及 Ca_v3 。 Ca_v1 亚型相当于L型VDCCs(L-type voltage dependent calcium channels, LTCCs), Ca_v2 构成R型、N型及P/Q型VDCCs, 而 Ca_v3 组成T型通道^[6]。所有类型的VDCCs在中枢神经系统中均有表达, 但是他们在生理过程中的角色却各不相同。T型、P/Q型、R型及N型VDCCs一般广泛分布于平滑肌、神经内分泌细胞以及突触前膜, 可以调节

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突触前膜中突触小泡的移动从而调控神经递质的释放^[3,5]。而LTCCs则主要位于突触后膜,当突触后膜去极化时LTCCs被激活并开放,从而调控Ca²⁺内流及胞内相关的信号转导,并且,LTCCs可依据单通道的传导性及对于Ca²⁺拮抗剂和激动剂的敏感性进一步地分为Ca_v1.1~Ca_v1.4共4种亚型,其中Ca_v1.2和Ca_v1.3这两种LTCCs亚型在中枢系统神经元中大量表达^[3,5-8]。

据报道,在吗啡慢性给药过程中,伴随LTCCs通道数目和开放状态的改变,成瘾相关脑区如海马胞内Ca²⁺的浓度也相应改变,且Ca_v1.3的 α 亚基能够通过内质网钙通道蛋白(ryanodine receptor 2, RyR2)受体N末端连接促进胞内钙库进一步释放Ca²⁺,从而形成对成瘾药物的依赖和耐受^[7,9,10]。近期研究还发现,成瘾药物敏化行为中,Ca_v1.2和Ca_v1.3发挥的作用具有脑区及分子机制特异性,例如,Ca_v1.3特异性调节可卡因和安非他明诱导行为敏化的获得,而Ca_v1.2选择性参与敏化行为的表达;伏隔核(nucleus accumbens, NAc)内Ca_v1.2的通道开放依赖于D1受体,开放后的钙通道使Ca²⁺内流同时激活钙/钙调素依赖性蛋白激酶(calcium/calmodulin-dependent protein kinase, CaMK),最终磷酸化GluA1的Ser831位点并诱导GluA1的插膜,而背侧纹状体(dorsal striatum, DS)内Ca_v1.3通道的开放则依赖于D2受体^[11-14]。另外,骨架蛋白激酶A锚定蛋白79/150(A-kinase anchor proteins, AKAP79/150)可将LTCCs锚定于突触膜上,这种LTCCs功能区域的改变直接影响了可卡因觅药行为的重建^[10,15]。此外,LTCCs依赖的突触可塑性,即神经元长时程增强(long-term potentiation, LTP)和长时程抑制(long-term depression, LTD)的诱导和维持也是成瘾记忆形成和发展的必要条件之一。因此,本文将概述LTCCs在药物成瘾形成和发展过程中的作用,及其参与调控成瘾记忆的内在分子基础,为进一步探索成瘾记忆的神经生物学机制拓展视角。

1 药物依赖与耐受

成瘾药物使用的最初阶段会使人产生欢愉感且能够缓解沮丧情绪。而继续使用则会导致中枢神经系统发生适应性改变,进而导致药物耐受、身体依赖、敏化及戒断后的渴求与复吸等现象。其中,药物耐受和依赖反映了药物使用后的生理适应性改变,这也是界定成瘾药物滥用的标准之一^[16]。药物依赖

又可分为身体依赖和精神依赖。身体依赖是反复使用药物后的一种适应状态,其特点是用药者一旦断药,将产生一系列令人难以忍受的戒断症状;而精神依赖则是想要再次体验成瘾药物所带来的愉悦效应的强烈愿望^[16]。

阿片类成瘾药物,如吗啡的反复使用能引起强烈的身体依赖。最近研究表明,这种身体依赖性的产生和吗啡诱导的胞内钙离子变化密切相关。吗啡急性给药时,阿片类受体的激动可抑制LTCCs从而使Ca²⁺内流减少;而长期慢性给予吗啡不仅能够显著提高突触囊泡内的Ca²⁺浓度水平,同时也能够增加突触后LTCCs的通道密度^[17]。而LTCCs诱导的胞内Ca²⁺浓度的增加是吗啡身体依赖形成的关键^[17]。同时,吗啡依赖动物戒断症状的维持时间和LTCCs通道数目的上调在时间上具有同步性。此外,系统注射LTCCs拮抗剂能减弱吗啡依赖大鼠(*Rattus norvegicus*)的戒断症状^[18]。上述结果提示,LTCCs是吗啡依赖和撤药后戒断症状形成的关键因素之一。

另外,LTCCs也参与其他成瘾性药物的非躯体依赖及耐受过程。研究表明,大鼠腹腔注射LTCCs拮抗剂能够减弱可卡因、酒精等成瘾物质所引起的兴奋作用,如降低运动性^[19];鞘内注射LTCCs拮抗剂能显著减弱尼古丁的镇痛作用^[20]。腹腔注射LTCCs拮抗剂不仅减弱了大鼠由尼古丁引起的焦虑,并且增加了大鼠对尼古丁的耐受^[21]。2014年,Biala等人^[22]发现腹腔注射LTCCs拮抗剂能够减弱尼古丁依赖大鼠的非躯体戒断症状,如焦虑、记忆力减退及痛觉过敏等。此外,LTCCs拮抗剂可以阻断尼古丁诱导的大鼠纹状体中多巴胺(dopamine, DA)的释放,从而减弱尼古丁的奖赏效应^[23]。提示,LTCCs可能通过调节神经递质的释放从而调控尼古丁的依赖。最近的研究表明,皮下注射LTCCs拮抗剂硝苯吡啶能够减弱可卡因、安非他明和吗啡引起的奖赏效应。另外,在可卡因、安非他明、吗啡依赖大鼠的额叶皮层(frontal cortex)和边缘前脑(limbic forebrain)中均发现Ca_v1.2和Ca_v1.3蛋白表达水平明显升高^[24]。最近的研究还表明,尼古丁可以增加环磷腺苷效应元件结合蛋白(cAMP-response element binding protein, CREB)的表达并同时上调RyR2,进而开放内质网上的LTCCs通道并释放大量Ca²⁺,诱导细胞内长时间持续Ca²⁺的增加,这可能是尼古丁产生相关药物依赖和耐受的神经基础^[9,25]。并且,有研究表明,酒精依赖与NAc及额叶

皮层的内质网膜上RyR1和RyR2的上调密切相关,并且这一过程依赖于D1受体的激活^[26]。

目前,对于成瘾药物所产生耐受、依赖的LTCCs相关神经机制并不十分清楚,且LTCCs的2种亚型Ca_v1.2和Ca_v1.3在成瘾耐受和依赖中发挥的作用及机制还有待进一步研究。

2 精神运动敏化

成瘾药物诱导的精神运动敏化被认为是诱发药物渴求和复吸的重要因素之一,也是衡量药物成瘾过程中行为可塑性的一个重要模型^[27]。精神运动敏化模型可分为2个阶段:发展阶段和表达阶段。在精神运动敏化的发展阶段,连续多次、多天成瘾药物处理后导致的精神运动性逐渐增加,这一过程和腹侧被盖区(ventral tegmental area, VTA)内相关分子的激活尤其是D1受体密切相关^[28];在精神运动敏化的表达阶段,药物处理戒断后再次给予小剂量成瘾药物会诱发精神运动兴奋性,并且大量证据表明,NAc内神经元的适应性改变参与调节这一过程^[29]。据报道,在吗啡敏化过程中,腹腔注射LTCCs的拮抗剂尼莫地平、尼非地平和维拉帕米能够阻断敏化的形成但不能阻断敏化的表达^[30]。而对于可卡因的敏化过程,VTA内微量注射尼非地平可阻断敏化的形成^[31];NAc内微量注射尼非地平则减弱敏化的表达^[32]。LTCCs对吗啡和可卡因敏化过程调节作用的不同可能是由于成瘾性药物(吗啡vs.可卡因)、模型的戒断时长(3 d vs. 21 d)及LTCCs拮抗剂的给药方式(腹腔注射 vs. VTA/NAc)存在较大差异所造成。最新研究还表明,在可卡因敏化的表达阶段,Ca_v1.2和Ca_v1.3分别在腹侧纹状体(ventral striatum, VS)和DS发挥作用^[13]。这些结果提示,LTCCs调节可卡因敏化行为的形成和表达具有脑区差异性。

此外,可卡因敏化行为的形成与NAc内 α -氨基-3-羟基-5-甲基-4-异恶唑丙酸受体AMPA受体(α -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor, AMPAR)的可塑性改变密切相关^[33,34]。这种可塑性改变的主要表现为AMPA的GluA1亚基磷酸化,该亚基的C末端有多个磷酸化结合位点,其中包括被钙/钙调素依赖性蛋白II型激酶(Ca²⁺/calmodulin-dependent protein kinase II, CaMK II)结合从而被磷酸化的Ser831位点^[35]以及被蛋白激酶A(protein kinase A, PKA)结合从而被磷酸化的Ser845位点^[35],而

NAc内的LTCCs很可能是通过磷酸化AMPA受体GluR1亚基的Ser831位点,从而使AMPA发生适应性改变,并最终调控可卡因的行为敏化过程^[14]。

进一步研究表明,LTCCs的2个亚型Ca_v1.2和Ca_v1.3调控敏化的分子机制也具有差异。在空间分布上,VTA区主要为Ca_v1.3 α_1 mRNA的表达;而NAc内Ca_v1.2和Ca_v1.3的表达水平相当^[24,36]。利用基因敲除及siRNA干扰等技术研究发现,VTA区的Ca_v1.3对可卡因行为敏化的形成具有关键作用;而NAc区的Ca_v1.2则为可卡因行为敏化表达过程所必需^[37]。另外,针对敏化的不同阶段检测Ca_v1.3和Ca_v1.2的mRNA水平发现:Ca_v1.3更多地参与尼古丁暴露的早期阶段,而Ca_v1.2则在尼古丁长期暴露后的适应性改变中发挥关键作用^[12]。Schierberl等人^[14]的研究更进一步揭示,Ca_v1.2和Ca_v1.3在精神行为敏化过程中的不同机制:在可卡因和安非他明敏化形成过程中,VTA区的Ca_v1.3通过激活下游的细胞外调节蛋白II型激酶(extracellular regulated protein kinases 2, ERK2)通路来参与敏化的形成^[37];而在可卡因和安非他明敏化的表达过程中,NAc内D1受体通过调节Ca_v1.2并激活其下游的CaMK II及ERK2,从而磷酸化AMPA受体GluA1亚基的Ser831位点并同时促进GluA1的插膜,并最终参与调控敏化过程。并且,该过程中一系列分子事件的发生需要VTA区Ca_v1.3通道的开放^[14,37]。而在DS中,对于可卡因敏化表达过程的调节主要是由Ca_v1.3所介导,Ca_v1.3先激活D2受体从而抑制其下游分子的活性,其中包括CREB, DARPP-32, Akt和GSK-3 β ,进而降低GluA1^{Ser845}的磷酸化及膜表面GluA1的表达水平^[13]。

上述结果提示,Ca_v1.2和Ca_v1.3不仅在成瘾药物敏化过程中发挥的作用机制不同,且参与调控敏化不同阶段所发挥作用的脑区也各异。

3 成瘾记忆

成瘾记忆是使用成瘾药物过程中形成的异常学习记忆。成瘾相关脑区如VTA, NAc和海马等脑区内神经元的LTP和LTD被认为是成瘾记忆的重要机制^[38,39]。

大量研究表明,LTP的形成需要胞内钙离子的参与,LTCCs作为细胞内钙离子的重要来源之一对于LTP的产生也是必要的^[39]。LTCCs诱导的LTP是通过LTCCs通道开放后内流的Ca²⁺激活酪氨酸激酶实现

的,并且这种LTP是不可逆的^[40].

此外,成瘾药物通过直接或间接作用于DA受体,从而引起细胞内一系列的生化反应,其中与DA受体偶联的G蛋白可以通过PKA调节转录因子CREB的表达,并最终控制神经元生存及可塑性等相关基因的转录.并且,细胞膜去极化后上述相关基因的转录依赖于LTCCs的活化^[41].研究还表明,LTCCs拮抗剂能够阻断神经细胞膜电位去极化诱发的CREB磷酸化的增加,而其他类型VDCCs的拮抗剂则不能阻断这一现象^[42].另外, Ca^{2+} 依赖的信号传导机制如CaMK II、蛋白激酶C(protein kinase C, PKC),也可以被LTCCs通道开放后内流的 Ca^{2+} 激活^[43].此外,尼古丁可以通过激活烟碱乙酰胆碱受体,打开 Ca^{2+} 通道并且引导 Ca^{2+} 通过这些受体,增加 Ca^{2+} 的内流,这种效应足够激活CaMK II,导致LTP的产生^[36].

以上研究结果提示,LTCCs对神经元可塑性的发生具有调控作用,而神经细胞可塑性的变化正是成瘾记忆形成和发展的基础.

3.1 成瘾记忆获取、表达、消退和重建

成瘾记忆的获取是成瘾记忆形成的最初阶段,为成瘾记忆的后续阶段奠定基础.条件位置偏爱模型(conditioned place preference, CPP)和自身给药模型(self-administration, SA)是研究成瘾记忆中最常用的2种动物模型.研究表明,大鼠CPP训练前皮下和腹腔注射LTCCs拮抗剂尼莫地平、伊拉地平能够阻断安非他明、可卡因CPP的获取^[44-46],并且这种阻断效应与LTCCs拮抗剂的剂量密切相关,剂量越大对CPP获取的阻断效果越显著^[24].此外,腹腔注射LTCCs拮抗剂也可以阻断可卡因和吗啡SA的获得^[19,47].

此外,LTCCs也参与调控成瘾记忆的消退过程.有证据表明,大鼠可卡因CPP表达测试前腹腔或VTA内注射LTCCs拮抗剂伊拉地平,并不影响CPP的表达.但在后期的表达测试中,这两组大鼠的CPP评分却明显低于对照组.提示,LTCCs可能在可卡因CPP的消退过程中发挥关键作用.

成瘾记忆消退后,由小剂量药物、药物相关线索或应激因素等诱发的成瘾记忆的重建是长时间戒断后产生复吸的重要原因之一.据报道,LTCCs在调节消退后觅药行为的重建过程中发挥关键作用.大鼠腹腔注射LTCCs拮抗剂尼莫地平能够阻断小剂量尼古丁或吗啡诱导的CPP的重建^[21].此外,大鼠腹腔注

射尼莫地平也可以阻断WIN55,212-2(一种大麻素受体激动剂)和酒精诱导的尼古丁CPP的重建^[48].提示,LTCCs参与调控成瘾记忆的重建过程.

3.2 LTCCs参与成瘾记忆的神经机制

突触可塑性的改变是成瘾记忆中重要的神经基础.有研究表明,成瘾药物的使用能够改变LTCCs诱导的突触可塑性变化.长期低浓度尼古丁暴露能够增加大脑皮层神经元上LTCCs对 Ca^{2+} 的通透性^[49],并且,腹腔注射LTCCs拮抗剂氟苯桂嗪和维拉帕米能够减弱尼古丁诱导的海马脑区产生的LTP^[50].另外,吗啡依赖大鼠海马CA1区诱导的LTP能够被NMDAR拮抗剂APV或LTCCs拮抗剂维拉帕米完全阻断,而未经吗啡处理大鼠的海马CA1区诱导的LTP,必需同时使用APV和维拉帕米才能够将其阻断^[51].上述结果提示,吗啡依赖大鼠海马CA1区内LTCCs依赖的和NMDAR依赖的LTP发生了重合,说明在药物成瘾过程中,海马CA1区LTCCs依赖LTP的功能发生了适应性改变.但是,在成瘾记忆中海马CA1区LTCCs依赖LTP的作用还需要进一步探索.最新研究表明,LTCCs依赖的爆发式电位发放(burst firing)在VTA区也同样存在,使用LTCCs激动剂FPL 64176能够导致多巴胺能神经元的活化并同时产生爆发式电位^[4].

而对VTA内LTCCs亚型的研究表明, $\text{Ca}_v1.3$ 对于VTA内神经元基本电位的发放是不可或缺的,使用转基因技术配合LTCCs激动剂或拮抗剂特异性激活 $\text{Ca}_v1.2$ 或 $\text{Ca}_v1.3$ 能增加VTA内的神经元的放电频率^[8,41,52].使用安非他明慢性处理的大鼠VTA区的多巴胺能神经元 $\text{Ca}_v1.2$ mRNA及其蛋白的表达均增加,而 $\text{Ca}_v1.3$ mRNA及其蛋白表达并无变化^[36].提示,成瘾药物的长期使用可能通过激活VTA内的 $\text{Ca}_v1.2$ 从而增加多巴胺能神经元动作电位的发放频率,而这种神经元放电频率的改变有可能在成瘾记忆过程中发挥关键作用.此外,Degoulet等人^[46]的研究发现,VTA内注射LTCCs拮抗剂能够减弱NMDAR依赖的LTP从而阻断吗啡CPP的获得.不仅如此,LTCCs在NAc中的生物电活动改变对研究成瘾记忆也至关重要.有研究表明,LTCCs拮抗剂地尔硫卓能够减弱NAc内谷氨酸能神经元的动作电位^[53],而成瘾记忆能够引起脑神经元放电模式的改变,这种神经元放电需要谷氨酸神经递质系统的激活,这一发现初步

解释了LTCCs可能是通过参与成瘾记忆中谷氨酸系统动作电位的产生和保持从而参与调控成瘾记忆。

此外, 近期研究表明, LTCCs参与调控成瘾记忆不同阶段的分子机制也不尽相同。吗啡CPP的形成和表达过程中, 大鼠NAc内的RyR2含量明显增加^[54], 且RyR2能够与内质网膜上的LTCCs产生相互作用, 从而导致胞内Ca²⁺水平的上调并最终调控成瘾记忆。而在成瘾记忆的重建中, LTCCs的可塑性改变导致成瘾动物对成瘾药物具有强烈的渴求, 且这种可塑性的变化是通过骨架蛋白AKAP79/150将LTCCs锚定于突触膜上实现的, LTCCs功能区域的改变直接影响了

药物成瘾记忆的重建^[15]。

4 结语

LTCCs在药物成瘾中的作用及其神经机制是近年来成瘾领域的研究热点, 主要是由于神经细胞内LTCCs介导的Ca²⁺内流调控了一系列成瘾相关的信号分子的转导, 而这些信号通路在成瘾药物的依赖、耐受、敏化及成瘾记忆等过程中发挥关键作用。因此, 未来的研究应进一步探索LTCCs参与调控成瘾的神经生物学机制, 为药物成瘾的干预和治疗提供新的思路。

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The mechanism of intracerebral L-type voltage dependent calcium channels in drug addiction

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Changes of intracellular calcium are the fundament of cell physiological function and the key factor in intracellular signal transduction and gene expression. Recently more studies have been focusing on the relationship between voltage dependent calcium channels (VDCCs) and drug addiction. A great deal of evidence suggests that L-type VDCCs (LTCCs), which are activated by membrane depolarization, play an important role in drug addiction by affecting the release of neurotransmitters, excitability of neurons, gene transcription and synaptic plasticity. LTCCs are divided into four subtypes: $\text{Ca}_v1.1$, $\text{Ca}_v1.2$, $\text{Ca}_v1.3$ and $\text{Ca}_v1.4$, according to the conduction of single channel and sensitivity to calcium antagonists and agonists. Among them $\text{Ca}_v1.2$ and $\text{Ca}_v1.3$ are mainly expressed in the central nervous system. It is reported that the increasing of intracellular calcium induced by LTCCs is crucial in physical dependence and withdrawal symptoms of addictive drugs such as morphine. In addition, the enhancement of cAMP-response element binding protein (CREB) and ryanodine receptor 2 (RyR2) induced by LTCCs on endoplasmic reticulum (ER) stimulate the release of calcium in cytoplasm, leading to a long-term increase in intracellular calcium. This relation might underlie the dependence and tolerance of nicotine. Moreover, it is reported that LTCCs also take part in nonsomatic signs of drug withdrawal. For example, intraperitoneal injection of LTCCs antagonists can reduce nonsomatic withdrawal symptoms in chronic nicotine-dependent rats, like anxiety, memory impairment and depression-like effects. Furthermore, recent researches also find that $\text{Ca}_v1.2$ and $\text{Ca}_v1.3$ play an important role in the acquisition and expression of cocaine-induced behavioral sensitization through different molecular mechanisms in specific brain regions. For instance, $\text{Ca}_v1.3$ in the ventral tegmental area (VTA) affects the development of cocaine sensitization by activating extracellular regulated protein kinases 2 (ERK2); While in the expression of cocaine sensitization, on the one hand, $\text{Ca}_v1.2$ opening in the nucleus accumbens (NAc) regulated by dopamine 1 (D1) receptor, activates its downstream Ca^{2+} /calmodulin-dependent protein kinase II (CaMK II) and ERK2, leading to the phosphorylation at GluA1^{Ser831} of α -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor (AMPA) and the membrane insertion of AMPA receptor GluA1 subunit. This process needs the activation of $\text{Ca}_v1.3$ in the VTA. On the other hand, activation of $\text{Ca}_v1.3$ in the dorsal striatum (DS), which is regulated by D2 receptor, suppresses its downstream activation, including CREB, DARPP-32, Akt and GSK-3 β , leading to the reduction of phosphorylation at GluA1^{Ser845} and the expression level of membrane GluA1. Besides, LTCCs are also involved in the acquisition, expression and reinstatement of addiction memory. Recent studies indicate that LTCCs play different roles in different phases of addiction memory. For example, LTCCs in the VTA are involved in the acquisition of morphine conditioned place preference (CPP) by activating *N*-methyl-D-aspartate receptor (NMDAR); Whereas LTCCs in the NAc regulate development and expression of morphine CPP via interacting with the RyR2 which can induce the calcium release from the ER. Moreover, it has been demonstrated that the scaffold protein A-kinase anchor proteins79/150 (AKAP79/150) can anchor LTCCs to synaptic membranes, which might be a potential mechanism underlying the reinstatement of addiction memory induced by drugs. Therefore, in this review, we will focus on summarizing the role and the potential cellular and molecular mechanisms of LTCCs in drug addiction, with the expectation of expanding the perspectives onto further exploration of the neurobiological mechanisms of addiction memory.

LTCCs, addiction memory, synaptic plasticity, $\text{Ca}_v1.2$, $\text{Ca}_v1.3$

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