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研究论文

伏隔核壳部巴氯芬灌注阻断吗啡成瘾小鼠条件位置性偏爱记忆再巩固

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摘 要：γ-氨基丁酸B型受体($GABA_B$受体)是治疗药物成瘾的潜在靶点，伏隔核壳部(nucleus accumbens shell, AcbSh)是成瘾环路的关键节点，但AcbSh $GABA_B$受体与记忆再巩固的关系尚不清楚。本文旨在探讨AcbSh微量灌注$GABA_B$受体激动剂巴氯芬(baclofen, BLF)对吗啡奖赏记忆再巩固及复吸行为的影响。建立吗啡条件位置性偏爱(conditioned place preference, CPP)小鼠模型，采用吗啡奖赏记忆提取激活实验，对比观察环境线索激活吗啡奖赏记忆后，双侧AcbSh灌注BLF对吗啡CPP、吗啡激发CPP重建以及自主活动量的影响。结果表明，吗啡奖赏记忆激活后，AcbSh单次注入0.06 nmol/0.2 μL/侧或0.12 nmol/0.2 μL/侧BLF显著抑制吗啡CPP，且吗啡激发不能重建CPP，而0.01 nmol/0.2 μL/侧BLF灌注不能抑制吗啡CPP。激活后注入生理盐水及未激活组BLF灌注均未抑制CPP。无论是否激活吗啡奖赏记忆，BLF注入AcbSh都不影响小鼠自主活动。以上结果提示，AcbSh $GABA_B$受体参与了吗啡CPP的记忆再巩固。记忆激活后激动AcbSh $GABA_B$受体可通过阻断吗啡CPP的记忆再巩固，消除奖赏记忆，抑制复吸行为。

关键词：吗啡成瘾；记忆再巩固；条件位置性偏爱；伏隔核壳部；巴氯芬
中图分类号：Q42；R338

Intra-nucleus accumbens shell injection of baclofen blocks the reconsolidation of conditioned place preference in morphine-addicted mice

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Abstract: Preclinical studies suggest that the $GABA_B$ receptor is a potential target for treatment of substance use disorders. Baclofen (BLF), a prototypical $GABA_B$ receptor agonist, is the only specific $GABA_B$ receptor agonist available for application in clinical addiction treatment. The nucleus accumbens shell (AcbSh) is a key node in the circuit that controls reward-directed behavior. However, the relationship between $GABA_B$ receptors in the AcbSh and memory reconsolidation was unclear. The aim of this study was to investigate the effect of intra-AcbSh injection of BLF on the reconsolidation of morphine reward memory. Male C57BL/6J mice were used to establish morphine conditioned place preference (CPP) model and carry out morphine reward memory retrieval and activation experiment. The effects of intra-AcbSh injection of BLF on morphine-induced CPP, reinstatement of CPP and locomotor activity were observed after environmental cues activating morphine reward memory. The results showed that intra-AcbSh injection of BLF (0.06 nmol/0.2 μL/side or 0.12 nmol/0.2 μL/side), rather than vehicle or BLF (0.01 nmol/0.2 μL/side), following morphine reward memory retrieval abolished morphine-induced CPP by disrupting its reconsolidation in mice. Moreover, this effect persisted for more than 14

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days, which was not reversed by a morphine priming injection. Furthermore, intra-AcbSh injection of BLF without morphine reward memory retrieval had no effect on morphine-associated reward memory. Interestingly, administration of BLF into the AcbSh had no effect on the locomotor activity of mice during testing phase. Based on these results, we concluded that intra-AcbSh injection of BLF following morphine reward memory could erase morphine-induced CPP by disrupting its reconsolidation. Activating $GABA_B$ receptor in AcbSh during drug memory reconsolidation may be a potential approach to prevent drug relapse.

Key words: morphine addiction; memory reconsolidation; conditioned place preference; nucleus accumbens shell; baclofen

药物成瘾是一种慢性、复发性脑病[1]。成瘾药物与环境线索反复匹配所形成的长期病理性记忆是复吸的主要原因，消除此病理性记忆成为预防复吸的关键[2]。记忆再巩固是指已经巩固的记忆再暴露于环境线索后被重新唤起，进入不稳定状态，经过再次巩固重返稳定状态的过程[3]。再巩固为记忆修饰提供了一个重要窗口，也为消除成瘾记忆，预防复吸提供了可能[4, 5]。伏隔核由核与壳部 (nucleus accumbens shell, AcbSh) 构成，是奖赏环路的核心环节[6]，研究显示，AcbSh 对奖赏记忆形成有重要作用[7]。γ- 氨基丁酸 B 型受体 ($GABA_B$ 受体) 是治疗药物成瘾的潜在靶点[8]，巴氯芬 (baclofen, BLF) 被认为是目前唯一可用于临床治疗成瘾的 $GABA_B$ 受体激动剂[9]，但 AcbSh $GABA_B$ 受体在记忆再巩固中的作用尚不清楚。目前，阻断记忆再巩固后的条件位置性偏爱 (conditioned place preference, CPP) 重建范式是评估消除成瘾记忆及预防复吸行为的主要行为学实验[10, 11]。本研究建立吗啡 CPP 小鼠模型，采用行为药理学方法观察双侧 AcbSh 灌注 $GABA_B$ 受体激动剂 BLF 对吗啡奖赏记忆再巩固及复吸行为的影响，为进一步理解药物成瘾的神经生物学机制，以及药物依赖的防治，特别是复吸行为提供新的思路。

1 材料与方法

1.1 实验动物及分组 SPF 级雄性 C57BL/6J 小鼠，6~8 周龄，体重 20~24 g，由宁夏医科大学实验动物中心提供。自由摄食饮水，饲养温度 20~25 °C，湿度 30%~40%，光线昼夜循环 12 h/12 h。实验获得宁夏医科大学伦理委员会批准。实验前 1 周对小鼠进行抚摸，使其逐渐熟悉并适应实验人员的操作。

1.2 CPP 实验仪器 小鼠 CPP 实验使用 Smart 3.0 小动物行为分析系统 (深圳瑞沃德生命科技有限公司)，实验箱外形尺寸：55 cm × 14 cm × 25 cm，两个侧箱为规格相同的黑白箱，中间为灰色过渡箱。系统自动记录黑 / 白箱停留时间及百分比、总运动距离、运动轨迹追踪图像等资料。

1.3 吗啡 CPP 获得阶段[12] 适应环境期：允许小鼠箱间自由穿梭，每天 1 次，每次 30 min，共 2 天。预测试期 (D0, Pre-C)：箱内自由活动 15 min，确定小鼠自然偏爱倾向。将自然非偏爱侧作为伴药箱，另一侧为非伴药箱，剔除无明显偏爱小鼠。条件化期 (D1~8, conditioning)：封闭三箱间通道，分别于第 2、6 天上午，第 4、8 天下午腹腔注射吗啡 (10 mg/kg)，置于伴药箱 45 min；第 1、5 天下午，第 3、7 天上午腹腔注射生理盐水 (1 mL/kg)，置于非伴药箱 45 min。测试期 (D9，Post-C) 开放三箱间通道，检测 15 min 内在各箱停留时间，计算小鼠对伴药箱的偏爱系数。CPP 评分为小鼠在 CPP 测试时吗啡伴药箱内的停留时间。

1.4 吗啡 CPP 测评阶段 第 10 天 (D10)，动物随机分为 6 组：(1) 激活 +0.01BLF 组 (n = 10)、(2) 激活 +0.06BLF 组 (n = 12)、(3) 激活 +0.12BLF 组 (n = 11)、(4) 激活 + 生理盐水组 (n = 13)、(5) 未激活 +0.06BLF 组 (n = 12)、(6) 未激活 + 生理盐水组 (n = 12)。激活处理：将小鼠放入吗啡伴药箱，停留 15 min，唤起吗啡奖赏记忆。根据预实验及文献，双侧 AcbSh 微量灌注 BLF 剂量如下，0.01 nmol/0.2 μL/ 侧[13]，0.06 nmol/0.2 μL/ 侧[13–15]，0.12 nmol/0.2 μL/ 侧[14]，激活 + 生理盐水组注入 0.2 μL 生理盐水。非激活处理：饲养笼取出小鼠，BLF 注入 0.06 nmol/0.2 μL/ 侧或生理盐水，随后将小鼠放回饲养笼。复测 CPP (D11/D24)：吗啡奖赏记忆激活后第 1 天 (PT-D1) 和第 14 天 (PT-D14)，复测 CPP。小剂量吗啡 CPP 点燃 (D25, Priming)：吗啡奖赏记忆唤起后第 15 天，小剂量吗啡 (5 mg/kg) 点燃[16]，15 min 后检测 CPP。

1.5 药物微量灌注模型建立

1.5.1 核团置管手术 小鼠麻醉后固定于脑立体定位仪上，牙科钻颅骨钻孔，根据小鼠脑图谱将长 4 mm 的双管不锈钢引导套管 (外径 0.48 mm，内径 0.34 mm，双管间距：1.5 mm，深圳瑞沃德生命科

技有限公司) 植入双侧 AcbSh 上 1 mm 处 (AP: 1.9 mm, ML: ±0.75 mm, DV: −3.5 mm)，引导套管使用牙科水泥固定在颅骨上，并插入不锈钢帽 (外径 0.30 mm) 进行封闭。青霉素预防感染，术后恢复 1 周开始吗啡 CPP 实验等操作。

1.5.2 药物及微量注射 药物及微量注射：盐酸吗啡注射液 (沈阳第一制药有限公司)，浓度 10 mg/mL，每只动物腹腔注射 10 mg/kg。BLF (美国 Sigma 公司) 溶于生理盐水，配制不同浓度的 BLF 溶液 (0.01 nmol/0.2 μL，0.06 nmol/0.2 μL 及 0.12 nmol/0.2 μL)。微量注射泵 (WPI, nanoliter-2010) 连接 PE 硅胶软管及注射内管 (外径 0.30 mm，内径 0.14 mm)，每侧注药 0.2 μL，速度 382 nL/min，30 s 完成注射。注药后留置内芯 30 s，以保证充分扩散 [18]。拔出针芯，插入导管帽，封闭注药套管。

1.5.3 靶点验证 5% 水合氯醛腹腔麻醉，4% 多聚甲醛心脏灌注，断头取脑。全脑冠状冰冻切片，厚度 25 μm。Nissl 染色，中性树胶封片，与脑图谱比对，显微镜下观察注药套管末端位置。

1.6 统计学方法 应用 SPSS 23.0 及 GraphPad Prism 8 软件进行统计学处理，数据以 mean ± SD 表示。以各组吗啡条件匹配为组间因素，测试点 (Pre-C 及 Post-C) 为组内因素，采用两因素重复测量方差分析 (two-way repeated measures analysis of variance, two-way rmANOVA) 验证药物灌注前是否建成 CPP 及在 BLF 灌注前 CPP 评分有无显著性差异；以 AcbSh 内灌注不同剂量 BLF 为组间因素，测试点 (Post-C, PT-D1, PT-D14, Priming) 为组内因素，采用 two-way rmANOVA 对药物灌注后各组 CPP 评分及自主活动量进行统计分析。单因素方差分析 (one-way ANOVA) 每一个测试点的 CPP 评分差异，并继之以 Newman-Keuls 事后检验。$P < 0.05$ 时认为统计学差异具有显著性。

2 结果

2.1 Nissl染色验证注药套管末端位置

实验共用小鼠 95 只，因注药靶点不准确剔除 25 只，共 70 只小鼠的数据进入统计分析。如图 1 显示，置管末端位置处于 AcbSh 内，靶点位置正确，模型建立可靠。

2.2 吗啡奖赏记忆激活后，BLF AcbSh内灌注阻断奖赏记忆再巩固

如图 2*B* 所示，在 AcbSh 灌注 BLF 前，two-way rmANOVA 显示 4 组动物均建成 CPP [$F(1, 42) = 843.75$, $P < 0.001$]，且在 BLF 灌注前 4 组 CPP 评分无显著性差异 [$F(3, 42) = 0.34$, $P = 0.8$]。在 AcbSh 内灌注 BLF 后，激活 +0.01BLF 组与激活 +NS 组 CPP 评分无显著性差异 [$F(1, 21) = 0.02$, $P = 0.9$]。在 AcbSh 内灌注 BLF 后，与激活 +NS 组相比，激活 +0.06BLF 组和激活 +0.12BLF 组 CPP 评分显著降低 [$F(1, 23) = 25.73$, $P < 0.001$; $F(1, 22) = 24.87$, $P < 0.001$]，提示奖赏记忆激活后 AcbSh 内灌注 0.06 nmol/0.2 μL/ 侧、0.12 nmol/0.2 μL/ 侧 BLF 通过阻断记忆再巩固，消除吗啡奖赏记忆至少 14 天。One-way ANOVA 显示，在 PT-D1、PT-D14 及 Priming，激活 +0.06BLF 组及激活 +0.12BLF 组 CPP 评分较激活 +NS 组显著降低 ($P < 0.001$)；且吗啡激发后，激活 +0.06BLF 组及激活 +0.12BLF 组小鼠未能重建 CPP [$F(1, 23) = 0.46$, $P = 0.51$; $F(1, 21) = 0.36$, $P = 0.55$]，提示激活后 AcbSh 内灌注 0.06 nmol/0.2 μL/ 侧、0.12 nmol/0.2 μL/ 侧 BLF 可抑制复吸行为。如图 2*C* 所示，two-way rmANOVA 显示 4 组动物自主活动量无显著性差异 [$F(3, 42) = 0.19$, $P = 0.9$]，提示吗啡奖赏记忆激活后 BLF 灌注对小鼠自主活动无影响。

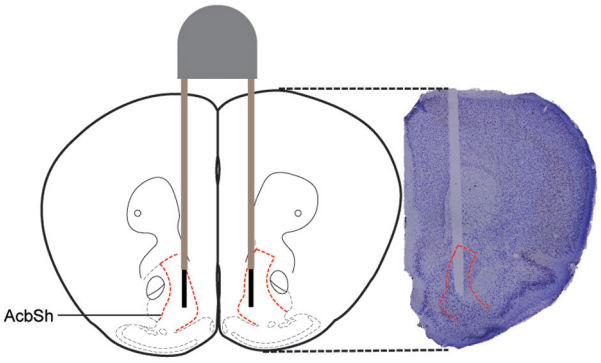

图 1. 双侧伏隔核壳部置入注药管示意图及Nissl染色靶点定位图

Fig. 1. The schematic representation of the cannula and the photomicrographs of representative needle tip in the nucleus accumbens shell (AcbSh) stained with cresyl violet. Scale bar, 1 mm.

2.3 吗啡奖赏记忆未激活时，BLF AcbSh内灌注对奖赏记忆再巩固无影响

如图 3*B* 所示，在 AcbSh 内灌注 BLF 前，two-way rmANOVA 显示未激活 +BLF 组和未激活 +NS 组均建成 CPP [$F(1, 22) = 306.8$, $P < 0.001$]，并且 BLF 灌注前两组 CPP 评分无显著性差异 [$F(1, 22) =$

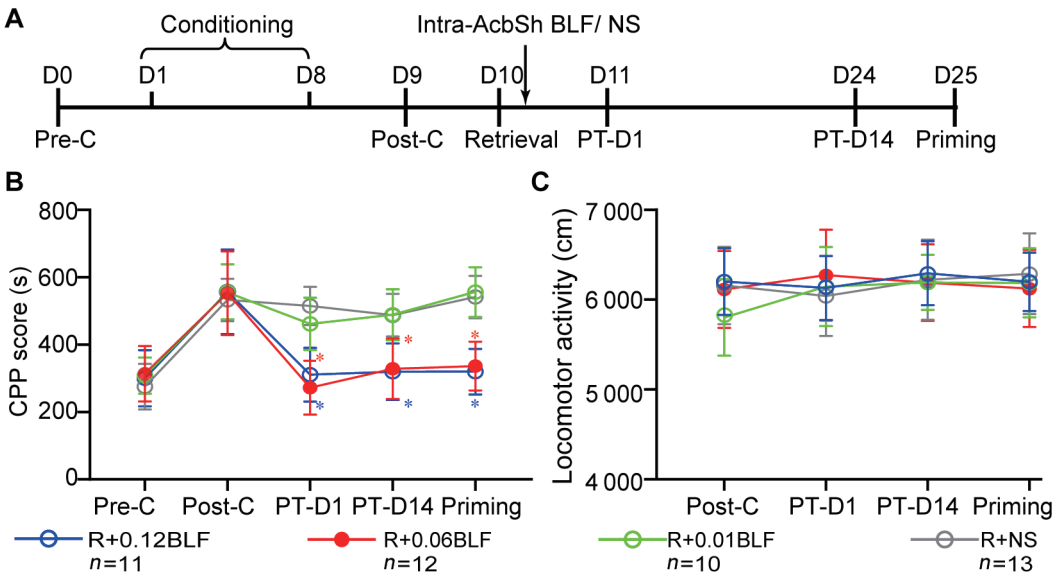

图 2. 激活吗啡奖赏记忆后AcbSh巴氯芬灌注对奖赏记忆再巩固的影响

Fig. 2. The effect of intra-AcbSh injection of BLF following memory retrieval on the reconsolidation of morphine reward memory. *A*: Timeline of experimental procedure. *B*: Intra-AcbSh BLF (0.06 nmol/0.2 μL/side, 0.12 nmol/0.2 μL/side) following memory retrieval blocked the reconsolidation of morphine reward memory [$F(1, 23) = 25.73$, $P < 0.001$; $F(1, 22) = 24.87$, $P < 0.001$; two-way rmANOVA]. *C*: Intra-AcbSh NS or BLF following memory retrieval had no effect on the locomotor activity of mice [$F(3, 42) = 0.19$, $P = 0.9$; two-way rmANOVA]. R+0.01BLF = Intra-AcbSh BLF (0.01 nmol/0.2 μL/side) following the memory retrieval; R+0.06BLF = Intra-AcbSh BLF (0.06 nmol/0.2 μL/side) following the memory retrieval; R+0.12BLF = Intra-AcbSh BLF (0.12 nmol/0.2 μL/side) following the memory retrieval; R+NS = Intra-AcbSh 0.9% sterile saline 0.2 μL/side following the memory retrieval; PT-D1= 1 day post drug treatment; PT-D14 = 14 days post drug treatment; Priming = the morphine priming (5 mg/kg, i.p.) reinstatement test. $^{*}P < 0.001$ *vs* R+NS group at the same time point.

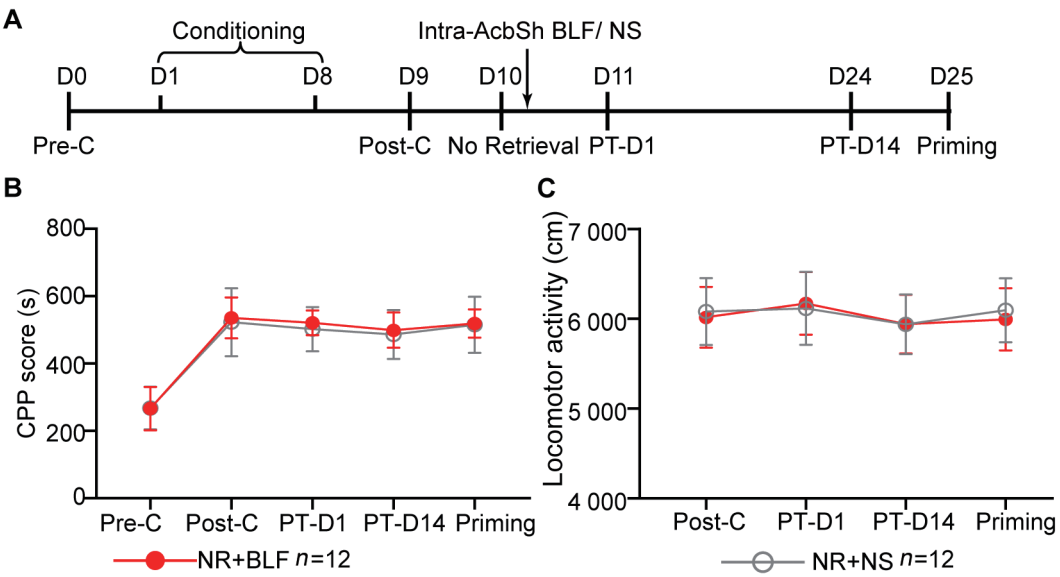

图 3. 未激活吗啡奖赏记忆时AcbSh巴氯芬灌注对奖赏记忆再巩固的影响

Fig. 3. The effect of intra-AcbSh injection of BLF without memory retrieval on the reconsolidation of morphine reward memory. *A*: Timeline of experimental procedure. *B*: Intra-AcbSh BLF or NS without memory retrieval had no effect on the reconsolidation of morphine reward memory [$F(1, 22) = 0.24$, $P = 0.63$; two-way rmANOVA]. *C*: Intra-AcbSh NS or BLF without memory retrieval had no effect on the locomotor activity of mice [$F(1, 22) = 0.03$, $P = 0.86$; two-way rmANOVA]. NR+BLF = Intra-AcbSh BLF (0.06 nmol/0.2 μL/side) without memory retrieval; NR+NS = Intra-AcbSh 0.9% sterile saline without memory retrieval.

0.04, P = 0.84]。在 AcbSh 内灌注 BLF 后，未激活 + NS 组和未激活 +BLF 组 CPP 评分无显著性差异 [F(1, 22) = 0.24, P = 0.63]，提示未激活奖赏记忆时，在 AcbSh 内灌注 BLF 不影响奖赏记忆再巩固。如图 3*C* 所示，two-way rmANOVA 显示两组动物自主活动量无显著性差异 [F(1, 22) = 0.03, P = 0.86]，提示吗啡奖赏记忆未激活时，BLF 灌注对小鼠自主活动无影响。

3 讨论

复吸是药物成瘾的主要特征，CPP 作为研究精神依赖药物相关的环境线索的常用模型，为研究复吸提供了良好工具 [16, 18]。记忆再巩固在环境线索诱导的复吸中起到关键作用 [19]。GABA 是脑内奖赏环路的主要抑制性神经递质 [20]，其突触效应由两大主要受体介导：离子型 $GABA_A$ 受体以及代谢型 $GABA_B$ 受体，$GABA_A$ 受体主要分布于突触后，$GABA_B$ 受体在突触前和突触后均有分布，二者在伏隔核中均有表达 [21, 22]。有研究表明，AcbSh 中的 $GABA_A$ 受体抑制性控制多巴胺介导的行为，而 AcbSh 中的 $GABA_B$ 受体对乙酰胆碱介导的行为施加抑制性控制 [23]。研究表明 AcbSh $GABA_A$ 受体和 $GABA_B$ 受体与酒精成瘾密切相关，并且在 AcbSh 内灌注 $GABA_A$ 受体和 $GABA_B$ 拮抗剂均可减少酒精消耗 [24]。$GABA_B$ 受体成为治疗成瘾、抑制复吸的特异性靶点之一 [25]。本研究结果显示，在吗啡奖赏记忆激活后 AcbSh 单次微量注入 $GABA_B$ 受体激动剂 BLF (0.06 nmol/0.2 μL/ 侧 或 0.12 nmol/0.2 μL/ 侧) 可以有效阻断吗啡奖赏记忆再巩固，长期抑制吗啡诱导的 CPP，且小剂量吗啡点燃后，亦未能重建吗啡 CPP，提示奖赏记忆激活后激动 AcbSh $GABA_B$ 受体能有效防止吗啡的复吸行为。

本研究结果显示，在缺乏记忆激活的状态下，BLF 注入 AcbSh 不能阻断吗啡奖赏记忆再巩固，究其原因可能是记忆再巩固假说的一个重要前提，记忆再巩固的阻断取决于记忆的重新激活 [26]。符合上述前提情况下，激活吗啡奖赏记忆后，此时该记忆处于不稳定阶段，激活 AcbSh 内 $GABA_B$ 受体可阻断吗啡奖赏记忆再巩固，进而消除吗啡 CPP，小剂量吗啡点燃亦未能使 CPP 重建。反之，在缺乏记忆激活的状态下，巩固的成瘾记忆未能进入记忆不稳定阶段的再巩固，此时激活 AcbSh 内 $GABA_B$ 受体没有消除成瘾记忆作用。

吗啡奖赏记忆激活后，AcbSh 内灌注 BLF 通过阻断奖赏记忆再巩固过程，进而长期消除吗啡 CPP 的分子生物学机制目前尚未完全明确。有研究显示其机制可能与 Arc 的表达调节有关。*Arc* 是一种特殊的即早基因，不但能在神经活性刺激下迅速表达，且其蛋白产物会迅速移动、积聚于被激活的神经元突触，作用于神经元骨架，影响突触可塑性 [27]。同时 Arc 是多种记忆再巩固的重要分子生物学基础，包括恐惧记忆、空间记忆、物体识别记忆及成瘾奖赏记忆 [28–30]。成瘾记忆提取激活后，特异性提高了 Arc 蛋白表达，其对维持成瘾记忆再巩固发挥重要作用 [28]。有研究显示，$GABA_B$ 受体激动剂可降低 Arc 蛋白表达 [31]；因此我们推测，吗啡奖赏记忆激活时，AcbSh 内灌注 BLF 后，激动 AcbSh $GABA_B$ 受体可能通过抑制 Arc 表达增加，阻断记忆再巩固，消除吗啡奖赏记忆，抑制吗啡 CPP 重建。

本研究证实，激活奖赏记忆后，AcbSh 内单次微量注入 BLF 不影响小鼠的自主活动，提示单次核团内给予 BLF 没有出现常见的镇静、肌肉松弛等副作用，这也排除了 AcbSh 内注入 BLF 对吗啡奖赏记忆的消除作用是其影响小鼠运动能力所导致的可能性。

综上，本研究显示，AcbSh $GABA_B$ 受体在吗啡奖赏记忆再巩固中发挥着重要的作用。记忆激活后，双侧 AcbSh 内灌注 $GABA_B$ 受体激动剂 BLF 可阻断记忆再巩固，长期消除吗啡奖赏记忆，抑制吗啡复吸行为。

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