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RESEARCH HIGHLIGHT

The Other Face of the Nucleus Accumbens: Aversion

Ying Han[1,2] · **Lin Lu**[1,2,3]

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The nucleus accumbens (NAc) is thought to integrate information that is conveyed by (1) dopaminergic inputs from the midbrain and (2) glutamatergic inputs from limbic and cortical regions, including the amygdala, prefrontal cortex (PFC), hippocampus, and thalamus [1], and signal to the basal ganglia motor system to guide appropriate behaviors. Addictive drug use is proposed to hijack this system, enhancing the brain's reactivity to drug cues and triggering drug-seeking and relapse after prolonged withdrawal [2, 3]. Both positive reinforcement (rewarding effects of drugs) and negative reinforcement (aversive emotional state associated with withdrawal) have been considered to play critical roles in the etiology and maintenance of drug addiction, and NAc neurons are capable of processing both reward and aversion [4, 5]. Optogenetic activation of inputs from the PFC, ventral hippocampus (vHipp), and basolateral amygdala (BLA) to the NAc drives positive reinforcement and facilitates reward-seeking behavior [6, 7], but a recent paper in *Nature* [8] has identified another face of the NAc. The pathway from the paraventricular nucleus of the thalamus (PVT) to the NAc is key to the aversive emotional state of drug withdrawal.

✉ Lin Lu
linlu@bjmu.edu.cn

[1] Institute of Mental Health, National Clinical Research Center for Mental Disorders, Key Laboratory of Mental Health, and Peking University Sixth Hospital, Peking University, Beijing 100191, China

[2] National Institute on Drug Dependence and Beijing Key Laboratory of Drug Dependence, Peking University, Beijing 100191, China

[3] Peking-Tsinghua Center for Life Sciences and PKU-IDG/McGovern Institute for Brain Research, Peking University, Beijing 100871, China

Glutamatergic synaptic transmission within the NAc has been recognized as a primary target for addictive drugs to produce adaptive synaptic changes and modulate behavioral output. Cocaine selectively increases the presynaptic release probability of excitatory synapses within the PFC-NAc pathway but not the BLA-NAc pathway, and amygdala fibers have a relatively low probability of transmitter release [7, 9]. Chronic non-contingent or contingent cocaine exposure and withdrawal evoke input- and cell type-specific plasticity in the NAc, which may underlie behavioral adaptations in addiction, such as craving and relapse [7, 10]. Optogenetic-mediated, pathway-specific stimulation reveals that the activation of inputs from the PFC, vHipp, and BLA to the NAc is rewarding and can reinforce instrumental behavior [6, 7]. However, still unknown is the specific NAc circuitry that underlies negative emotional and motivational states after withdrawal.

Using retrograde neuronal tracing, Zhu *et al.* [8] showed that the NAc is densely innervated by the PVT, in addition to its well-characterized inputs from the PFC, vHipp, and BLA. Brief light stimulation of fibers that project from the PVT to the NAc evoked robust α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR)-mediated excitatory postsynaptic currents in medium spiny neurons (MSNs), indicating that the PVT is a source of glutamatergic afferents to the NAc. Behaviorally, optogenetically activating the PVT-NAc pathway evokes avoidance of a light-paired chamber in the real-time place preference assay, which depends on glutamatergic but not dopaminergic transmission in the NAc. Thus, in contrast to other inputs to the NAc, the PVT input mediates aversion rather than reward. This suggests the possibility that this pathway is a specific neuronal circuit involved in the negative emotional state associated with drug withdrawal.

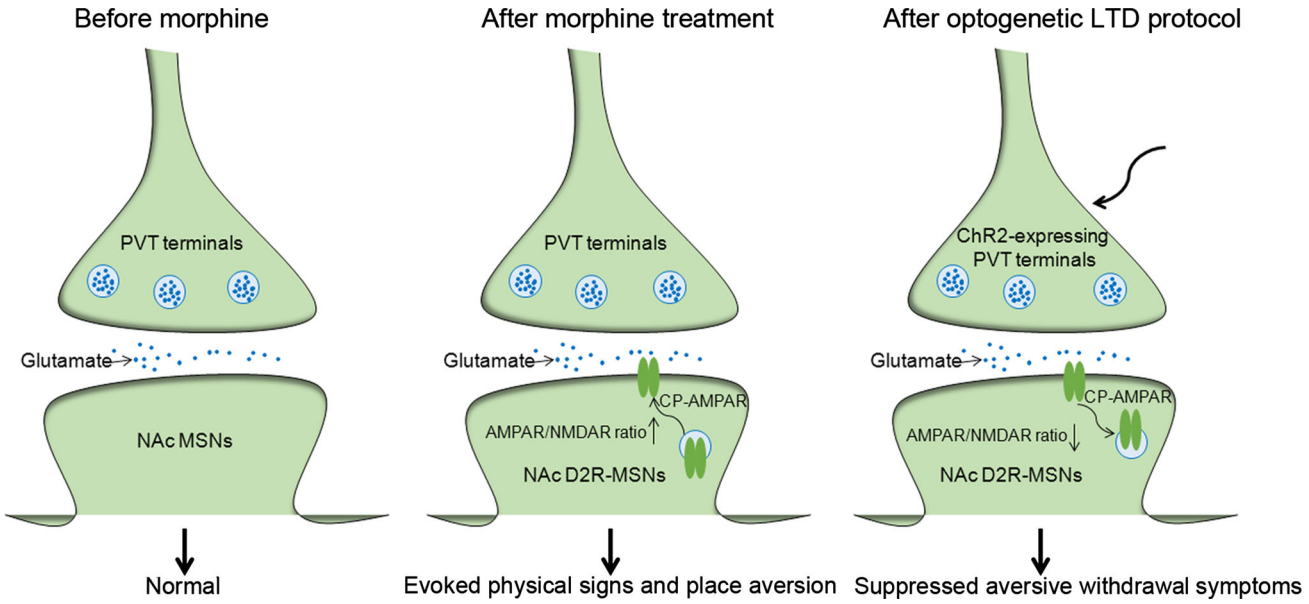

Fig. 1 Synaptic changes in the paraventricular nucleus of the thalamus-to-nucleus accumbens pathway after opiate withdrawal. *Left* glutamatergic fibers that originate in the paraventricular nucleus of the thalamus (PVT) innervate medium spiny neurons (MSNs) in the nucleus accumbens (NAc) and control motivated behaviors. *Middle* chronic morphine treatment selectively strengthens PVT → D_2 receptor (D2R)-MSN synapses *via* the insertion of GluA2-lacking Ca^{2+}-permeable AMPARs (CP-AMPARs), triggering strong physical signs and robust aversive memory. *Right* depotentiation of the PVT input onto D2R-MSNs by optogenetic induction of long-term depression (LTD) restores normal transmission at these synapses and suppresses aversive withdrawal symptoms.

Zhu *et al.* [8] used optogenetic and chemogenetic approaches to selectively silence the PVT-NAc pathway and test the effects of this manipulation on opiate withdrawal-induced somatic signs and place aversion. Robust Fos expression in PVT neurons that project to the NAc was precipitated by naloxone and induced by spontaneous withdrawal. Optogenetic inhibition of PVT axons expressing archaerhodopsin-3 in the NAc during naloxone-precipitated withdrawal suppressed physical signs and avoidance of the withdrawal chamber in morphine-dependent mice but not in drug-naive mice. Using inhibitory designer receptors exclusively activated by designer drugs, silencing the PVT-NAc pathway by intra-NAc injection of clozapine-*N*-oxide before four conditioned place aversion (CPA) training sessions prevented the formation of aversive memory.

However, foot-shock and LiCl injection also increased Fos expression in PVT neurons that project to the NAc. Silencing this pathway during conditioning reduced the expression of foot-shock- and LiCl-induced CPA, indicating that the PVT-NAc pathway also mediates aversion induced by these stimuli. Together, it is speculated that the PVT-to-NAc circuit plays important roles in the modulation and encoding of general aversion such as stress and fear conditioning.

MSNs can be classified into two groups based on the dopamine receptors that they express (D_1 or D_2 [D1R or D2R]). These subtypes have different projection targets (direct or indirect to the midbrain) and exert complementary and sometimes opposing actions on behaviors that are controlled by the corticostriatal system [11–13]. Previous studies have reported an increase in synaptic strength in D1R-MSNs but not D2R-MSNs after cocaine withdrawal, most likely through a postsynaptic mechanism [10, 14]. Zhu *et al.* [8] showed that chronic morphine treatment increased the AMPAR/N-methyl-D-aspartate receptor ratio and the insertion of GluA2-lacking Ca^{2+}-permeable AMPARs at PVT → D2R-MSN synapses but not PVT → D1R-MSN synapses. Moreover, they used an established *in vivo* long-term depression (LTD) protocol to reduce synaptic transmission at PVT → D2R-MSN synapses (i.e., light pulses at 1 Hz for 15 min). This optogenetic protocol restored normal transmission at PVT → D2R-MSN synapses, without influencing synaptic strength at PVT → D1R-MSN synapses, and ultimately reduced the expression of opiate withdrawal symptoms and CPA of the withdrawal chamber.

Previous studies have shown that orexin/hypocretin transmission in the PVT primarily originating from the lateral hypothalamus plays an important role in drug-seeking behavior [15, 16]. Besides the NAc, the PVT also specifically projects to the ventral tegmental area, PFC, and hippocampus, which are widely implicated in reward-related behaviors [16]. Further exploration of the specific neuronal subpopulations and circuits in the PVT mediating reward-seeking and aversive symptoms seems warranted.

The study by Zhu *et al.* [8] is a landmark in our understanding of the neuronal circuitry that underlies opiate withdrawal and highlights the role of plasticity at PVT → D2R-MSN synapses in the negative emotional and motivational states associated with opiate withdrawal (Fig. 1). Their results suggest that some of the neuronal adaptations associated with opiate dependence may be reversible. Optogenetic protocols that target specific synapses and use specific stimulation parameters to cause potentiation or de-potentiation may inspire novel treatments for opiate addiction. In humans, novel deep brain stimulation or transcranial magnetic stimulation protocols may restore normal synaptic transmission, thus relieving withdrawal symptoms [17].

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