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AMPA receptor trafficking in the dorsal striatum is critical for behavioral sensitization to cocaine in juvenile mice

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ABSTRACT

Advances in understanding the neurobiology of addiction indicate that not only dopaminergic neurotransmissions but also glutamatergic neurotransmissions within the mesolimbic system play important roles. While the role for the nucleus accumbens (NAc) shell and core in addiction has been extensively studied, the function of the dorsal striatum is not clear. Here, we demonstrate that repeated cocaine injections cause increases in surface-expressed AMPA receptors in the dorsal striatum. The increased AMPAR expression is more robust in juvenile mice than in young adult mice. Furthermore, expression of the G1CT peptide, which prevents the delivery of AMPARs to the surface, attenuates the locomotor sensitization in juvenile mice. Our results strongly suggest that glutamatergic synaptic plasticity in the dorsal striatum may have an important role in behavioral sensitization to cocaine and that there may be different age-dependent control mechanisms.

Drugs of abuse have different acute effects but exhibit common effects on the brain's reward circuits. The mesolimbic dopaminergic system has been the focus of addiction research because some addictive drugs directly alter dopaminergic neurotransmission. However, recent research indicates that the alterations in glutamatergic synaptic transmission in the reward circuits also play a critical role in drug addiction. For example, repeated cocaine administration *in vivo* induces a change in excitatory synapses to the rat ventral tegmental area (VTA) dopaminergic neurons such that subsequent induction of long-term potentiation (LTP) is facilitated [1]. The cocaine-induced plastic changes in the VTA may be mediated by several different mechanisms. Orexin-A, released from hypothalamic neurons, has been shown to transiently enhance *N*-methyl-D-aspartate receptors (NMDARs)-mediated excitatory postsynaptic currents (EPSCs), and then subsequently, to lead to a delayed potentiation of α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (AMPARs)-mediated EPSCs in the VTA [2]. Furthermore, an orexin receptor 1 (OXR1) antagonist prevented cocaine-induced locomotor sensitization and acquisition of conditioned place preference when injected into the VTA [3].

Inhibitory inputs to the VTA also play a critical role in the plastic changes induced by cocaine. Repeated injections of cocaine cause a decrease in A type γ-aminobutyric acid (GABA) receptor-mediated miniature inhibitory postsynaptic currents (mIPSCs) in the VTA, which may contribute to facilitation of LTP induction [1]. Drug-induced changes in glutamatergic synaptic transmissions in the NAc have also been reported. Repeated injections of cocaine followed by 10–14 days of withdrawal and a subsequent challenge injection caused a decrease in the AMPAR to NMDAR ratio in the shell of the NAc, while a single administration of cocaine did not change this ratio [4]. The surface expression of AMPARs increases during the withdrawal period after repeated injections of cocaine [5], which results in the increase in the AMPAR/NMDAR ratio [6]. However, surface expression of AMPARs quickly decreased in a LTD-like fashion after a subsequent challenging injection of cocaine. Inhibiting clathrin-mediated endocytosis using an AMPAR-derived peptide in the NAc of amphetamine-sensitized rats, and thus, inhibiting LTD, prevented the increase in locomotor activity, which was used as a measure of behavioral sensitization [7].

While it is widely accepted that the dopaminergic inputs to the NAc shell subserve the primary reinforcing effects of drugs such as cocaine, the role of the dorsal striatum in addiction has not been extensively studied. However, Everitt and colleagues recently hypothesized that the striatum as a whole plays a role in drug abuse and addiction [8]. While initial acquisition of drug-seeking behavior is dependent on the integrity of the NAc shell, as well as the NAc core [9] and basolateral amygdala [10], habitual drug-seeking after prolonged drug abuse appears to engage the control of the dorsal striatum [11]. Since the dorsolateral striatum is known to be critical for stimulus–response habit learning, these results support the idea that the switch from voluntary drug use to habitual compulsive drug-seeking behavior may be mediated by

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a transition at the neural level from the NAc to the dorsal striatum [8].

However, whether plastic changes at glutamatergic synapses, which are commonly associated with drug addiction, also occur in the dorsal striatum is unknown. Here, we show that repeated injections of cocaine to mice cause an upregulation of surface-expressed AMPARs in the dorsal striatum. In order to assess the functional significance of this increase in surface AMPAR expression, we expressed a peptide, G1CT, which prevents the delivery of AMPARs to the surface using the HSV-mediated gene transfer system. HSV–G1CT expression in the dorsal striatum substantially suppressed locomotor sensitization induced by repeated cocaine injections.

Materials and methods

Animals. Juvenile (3–4 weeks old, 9–15 g) and young adult (8–9 weeks old, 23–26 g) male C57BL/6 mice were used in this study. All mice were housed under a 12 h light/12 h dark cycle with the light period beginning at 7 AM.

Slice preparation and surface receptor biotinylation. Surface AMPAR measurements in brain slices using biotinylation was performed as described previously [12]. Briefly, acute coronal slices (300 μm) including the dorsal striatum were prepared by vibratome sectioning in ice-cold high sucrose dissection buffer (in mM, 87 NaCl, 2.5 KCl, 1.25 NaH_2PO_4, 25 $NaHCO_3$, 1 $CaCl_2$, 3 $MgCl_2$, 10 dextrose, and 212 sucrose) continuously superfused with carbogen (5% CO_2 and 95% O_2). After a 1-h recovery in artificial cerebrospinal fluid (ACSF, in mM, 124 NaCl, 5 KCl, 1.23 NaH_2PO_4, 26 $NaHCO_3$, 10 dextrose, 1 $MgCl_2$, and 2 $CaCl_2$), the slices were transferred to ice-cold sulfo-NHS-LC-biotin (Pierce) in PBS (1 mg/ml) and incubated for 20 min, followed by washes with ice-cold TBS (5 min, 3×). Microdissected dorsal striata were homogenized in RIPA buffer (150 mM NaCl, 10 mM NaH_2PO_4, 2 mM EDTA, 50 mM NaF, 10 mM Na-pyrophosphate, 10 mM Na-iodoacetamide, 1 mM Na-orthovanadate, 1% Triton X-100, 0.5% SDS, and 0.5% deoxycholate) supplemented with phenylmethanesulfonyl fluoride (100 nM, Sigma). Biotinylated surface proteins were purified by avidin–agarose (NeutrAvidin Agarose, Thermo Scientific) binding and subsequent pull down. The surface fraction was subjected to quantitative immunoblotting for AMPARs using anti-GluR1 (AB 1504, Millipore) and anti-GluR2 (MAB 397, Millipore).

Viral construct/delivery. HSV–G1CT was constructed as described previously [13]. For intra-dorsostriatal viral injections, animals were prepared for electrode implantation as described earlier. After small holes were bilaterally made in the skull overlaying the striatum (stereotaxic coordinates; +1.0 mm anterior/posterior, ±1.0 mm medial/lateral from the bregma), a glass micropipette filled with either HSV–GFP or HSV–G1CT and attached to an injection system (Nanoliter 2000, WPI) was inserted to a depth of 3.0 mm. The total volume of 920 nl virus was gradually injected (18.4 nl injection every 20 s, 50×).

Locomotive behavioral tests. Mice were injected with saline to measure the locomotive baseline at 48 h post-virus injection. Four age-matched mice formed one experimental set: a mouse injected with HSV–GFP then treated with cocaine (GFP-Coc), a mouse injected with HSV–GFP then treated with saline (GFP-Sal), a mouse injected with HSV–G1CT then treated with cocaine (G1CT-Coc), and a mouse injected with HSV–G1CT then treated with saline (G1CT-Sal). Cocaine (15 mg/kg, Sigma, C-5776) was injected intraperitoneally into the mice, five consecutive times at 12 h intervals. Every cocaine/saline injection was preceded by habituation for 10 min in an activity chamber (Med Associates). Cocaine/saline was then administered and the mice were returned to the activity chamber to measure locomotor activity for 30 min. Locomotive measures, such as total distance traveled and number of jumps, were analyzed using the Activity Monitor software (Version 5, Med Associates). Significant differences were determined by analysis of variance (ANOVA).

Results

Repeated cocaine injections increase surface-expressed GluR1 in the dorsal striatum of juvenile mice

Recent studies have indicated that AMPAR transmission is altered in the NAc during behavioral sensitization to cocaine, with corresponding changes in AMPAR expression on the cell surface. Surface-expressed AMPARs in the NAc did not increase immediately after repeated injections [14], but increased during the withdrawal period. AMPARs were internalized after a post-withdrawal challenge of cocaine injection [5]. In order to examine whether AMPAR expression in the dorsal striatum also changes in response to repeated cocaine exposures, we measured the level of AMPARs on the cell surface in the dorsal striatum of mice injected with cocaine (15 mg/ml every 24 h) for 5 days. We used two different age groups, juveniles and young adults, to test whether there is any age-dependent change in the response to cocaine. Surface receptors were labeled with membrane-impermeable biotin in acute coronal brain slices prepared 24 h after the last cocaine injection. The dorsal and ventral striata were microdissected and biotinylated surface receptors from each area were purified. The ratio of surface to total AMPAR protein was determined by quantitative immunoblotting.

Surprisingly, surface-expressed AMPARs significantly increased in the dorsal striatum of cocaine-injected juvenile mice (P26–28 when sacrificed), when compared to saline-injected age-matched controls (Fig. 1A and B). However, surface AMPARs in the NAc shell area did not change significantly in response to repeated cocaine injections over 5 days. We repeated the same experiments with young adult mice (P66–68 when sacrificed). Unlike juvenile mice, increases in surface AMPARs caused by repeated cocaine injections were highly variable and did not reach statistical significance (Fig. 1C and D). These results raise the possibility that there is an age-dependent regulation of cocaine-mediated synaptic modifications in the dorsal striatum. Adolescents (12–14 years of age) are reported to have a fourfold higher risk of becoming addicts when exposed to addictive drugs than young adults (21–25 years of age) [15]. Furthermore, a recent study indicated that adolescent rats require longer extinction sessions than adult rats to lose cocaine place-preferences [16]. Our results provide a possible mechanism to explain this age-dependent susceptibility to addiction.

HSV–G1CT expression in the dorsal striatum prevents the increase in surface AMPARs by repeated cocaine injections

The regulation of AMPAR trafficking in and out of the plasma membrane of neurons is not completely understood. However, studies carried out in the hippocampus and the cortex led to the hypothesis that AMPAR trafficking is an important mechanism underlying synaptic plasticity and is regulated by subunit specific rules [17]. In the hippocampus and the cortex, most AMPARs are expressed on the synaptic surface as heteromeric receptor complexes. There are four subunits (GluR1/2/3/4) that can participate in forming a heteromeric AMPAR complex but the major forms found in the hippocampus and cortex are composed of the GluR1/GluR2 or GluR2/GluR3 subunits. The major form of AMPARs that are inserted into the synaptic membrane during plasticity seems to be the GluR1/GluR2 heteromer and the interaction of the GluR1 subunit with PDZ domain proteins plays a critical role

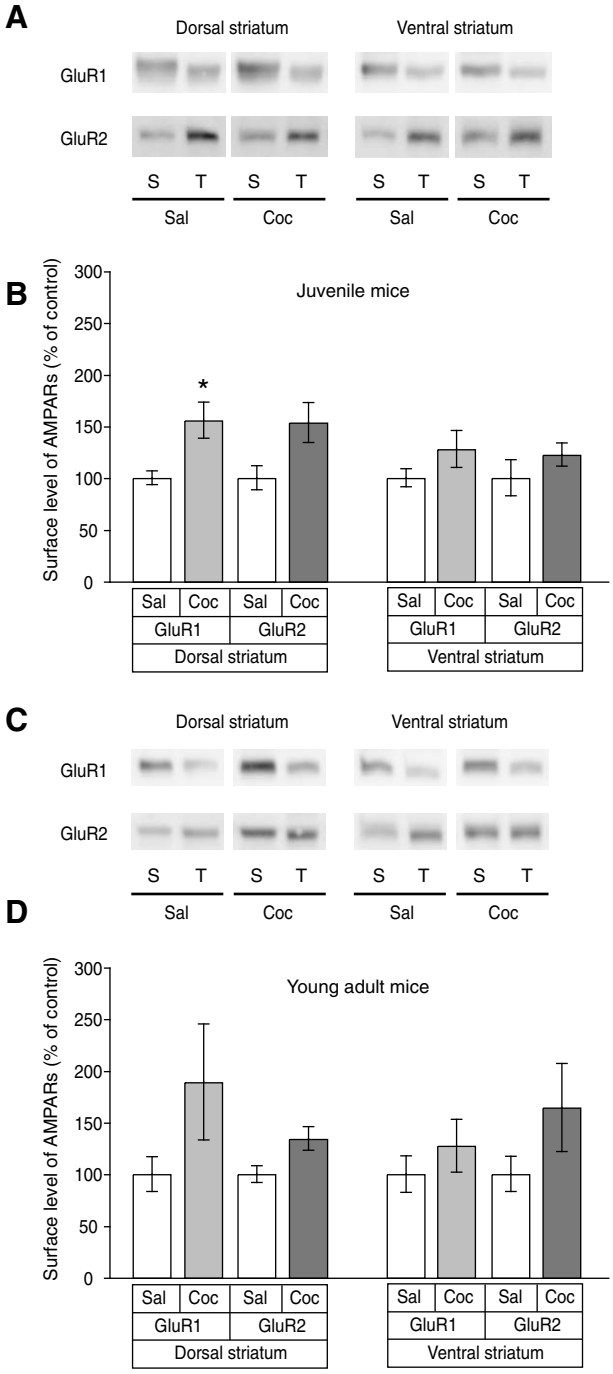

Fig. 1. Changes in surface expression of AMPA receptors in the dorsal striatum of juvenile mice by repeated cocaine treatments. (A) Immunoblots show that the expression of surface AMPA receptors is increased in the dorsal striatum of juvenile mice by 5-day cocaine administrations. Changes in surface expression of AMPARs were not observed in the ventral striatum, or the NAc. (B) Quantified results of (A) are summarized in graphs. The expression of GluR1 in the dorsal striatum increased ($n = 7$; saline (Sal), 100 ± 6.6%; cocaine (Coc), 155.85 ± 17.47%, $p < 0.032$), but that increases in GluR2 failed to reach statistical significance (Sal, 100 ± 11.6%; Coc, 153.56 ± 19.43%, $n = 8$, $p > 0.12$). AMPARs in the NAc did not show meaningful increases by cocaine treatments (Sal vs. Coc, GluR1, 100 ± 8.8% vs. 128 ± 17.8%, $p > 0.32$; GluR2, 100 ± 17.4% vs. 123 ± 11.4%, $n = 8$, $p > 0.5$). (C) Immunoblots showing the expression of surface AMPA receptors in the striatum of young adult mice treated with cocaine for 5 days. (D) Quantified results of (C) are summarized in graphs. Changes in the level of surface GluR1 in the dorsal striatum were highly variable (Sal vs. Coc, 100 ± 16.8% vs. 189 ± 56.25%, $n = 6$, $p > 0.09$). Changes in GluR2 also failed to reach a significant level (Sal vs. Coc, 100 ± 8.2% vs. 134.4 ± 11.3%, $n = 6$, $p > 0.06$). Surface AMPARs in the NAc did not increase in response to cocaine treatments (Sal vs. Coc, GluR1, 100 ± 17.6% vs. 127 ± 25.7%, $n = 6$, $p > 0.62$; GluR2, 100 ± 17% vs. 164 ± 42.7%, $n = 5$, $p > 0.14$).

in this type of trafficking [18]. Therefore, preventing the interaction between GluR1 and the intracellular proteins is an effective way to block AMPAR trafficking to plasma membrane and, thus, LTP. Expressing only the intracellular carboxy-tail of GluR1 (G1CT) in the cortex has successfully blocked naturally occurring LTP-like visual response potentiation in mice [13].

We examined whether G1CT could function as a dominant negative for AMPAR surface expression in the dorsal striatum as well. In order to express G1CT in large amounts, so that G1CT prevents endogenous GluR1 from interacting with intracellular binding partners for proper trafficking, we made use of the Herpes simplex virus (HSV) based gene delivery system. A viral vector that expresses G1CT (HSV–G1CT) was bilaterally injected into the dorsal striata of juvenile mice (Fig. 2A). After recovery, mice were subjected to repeated injections of cocaine. In this experiment, we altered our injection intervals to 12 h from the conventional 24 h interval to ensure that HSV-mediated expression is robust and strong during cocaine exposures. When we compared the locomotor sensitization results of this new paradigm to that of the conventional 5-day paradigm, we found no significant differences (data not shown). The HSV–G1CT completely blocked the cocaine-induced increase in surface-expressed AMPARs in the dorsal striatum, while HSV–GFP did not affect the increase (Fig. 2B). These data suggest that repeated exposure to cocaine mobilizes AMPARs to the cell surface in the dorsal striatum in an LTP-like fashion in which GluR1 plays a critical role.

HSV–G1CT expression in the dorsal striatum significantly suppresses locomotor sensitization to cocaine

Drugs of abuse such as cocaine and amphetamine induce behavioral sensitization of motor activity when administered repeatedly. Behavioral sensitization is a long-lasting, enhanced motor-stimulant response. Based on the long-lasting and context-dependent nature, the mechanism of behavioral sensitization

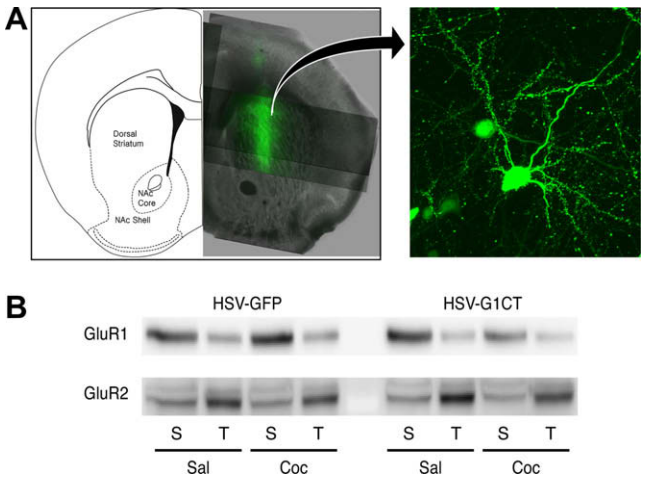

Fig. 2. HSV–G1CT expression prevents the cocaine-mediated increase in surface AMPA receptors in the dorsal striatum. (A) The expression of HSV–G1CT is limited to the dorsal striatum. The left panel shows overlayed GFP expression and DIC image of the dorsal striatum injected with HSV–G1CT. The dorsostriatal expression of GFP signal was verified for every mouse used in the behavioral experiments. Higher magnification images (40×) reveal that HSV–G1CT is primarily expressed in medium-spiny neurons. (B) At the conclusion of behavioral tests, a subset of the animals was used for the biochemical assays quantifying surface AMPAR levels. Increases in surface AMPARs in the dorsal striatum of mice infected with HSV–GFP and treated with cocaine are evident. However, the increase in expression of surface AMPARs in the dorsal striatum of mice injected with HSV–G1CT and treated with cocaine was completely blocked. The surface AMPARs in the dorsal striatum may be even decreased by HSV–G1CT and cocaine treatments. Experiments were repeated three times with similar results.

has been thought to underlie drug craving and relapse to drug abuse. Although much effort has been made to elucidate the neural mechanisms of sensitization, many studies have focused on dopaminergic inputs to the ventral striatum. However, the role for the dorsal striatum, particularly the function of glutamatergic neurotransmission in the dorsal striatum, in behavioral sensitization is unknown. Therefore, we assessed the functional role of AMPAR trafficking in the dorsal striatum in the context of behavioral sensitization to cocaine. The dorsal striata in both hemispheres of age-matched juvenile mice were injected with either HSV–GFP or HSV–G1CT. Cocaine injection and measuring locomotive behavior was begun 48 h post-infection and continued for three consecutive days. The behavioral sensitization in mice injected with HSV–GFP was comparable to that of uninjected juvenile mice. However, locomotive behavior was substantially suppressed in mice injected with HSV–G1CT. The locomotor responses of mice injected with HSV–G1CT were significantly reduced compared to those of mice injected with HSV–GFP (Fig. 3). Our results indicate that cocaine-induced AMPAR mobilization to the surface of neurons in the dorsal striatum plays an important role in the establishment of behavioral sensitization to cocaine.

Discussion

Synaptic plasticity has been suggested to be the cellular mechanism by which information processing and storage is mediated in the brain. While some memories are labile and short-lived, other memories last a lifetime. Drugs of abuse are thought to cause long-term modifications to behavior by inducing long-lasting alterations in the relevant neural circuits. Therefore, learning and memory may share mechanisms, such as synaptic plasticity, with addictive behavior. Studies, indeed, have shown that synaptic plasticity in the mesolimbic system and/or interconnected input structures such as the prefrontal cortex and hippocampus is observed when animals are sensitized to addictive drugs [19–21]. Within a given area involved in addiction, such as the NAc, the balance between LTP and LTD at different inputs have been proposed to control the patterns of behavioral outputs, and drugs of abuse can disrupt this balance [21]. However, the role of the dorsal striatum in addiction is less clear than the role of the NAc. In drug self-administration experiments, the early phase drug-taking behavior seems to depend on control of the instrumental response-outcome contingencies in which neuronal integration at the NAc plays a critical role. However, the late-phase drug-seeking behavior that occurs after protracted self-administration may be mediated by the stimulus–response instrumental process, which confers an automatic or habitual property to the behavior. This transition is hypothesized to be accompanied by the progressive engagement of the dorsal striatum [22].

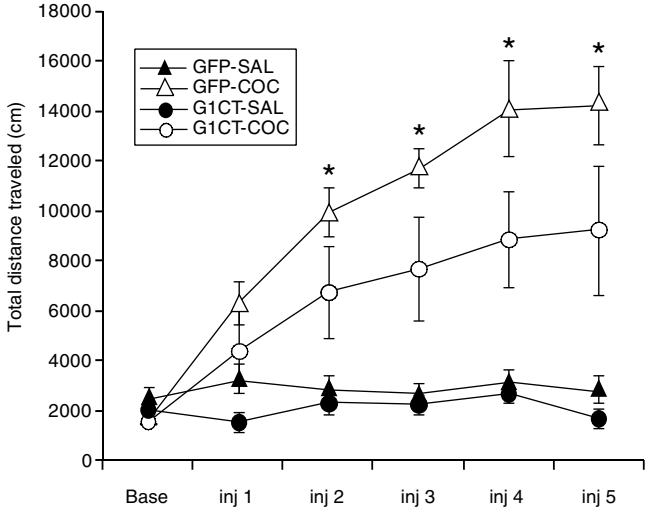

Fig. 3. The locomotor sensitization to cocaine is attenuated in juvenile mice infected with HSV–G1CT. Locomotive responses to cocaine injections were measured (traveled distance, TD; $n = 5$ from base to the third injection (inj 3); $n = 4$ for inj 4 and inj 5). The TD of both HSV–GICT and HSV–GFP injected groups that were cocaine treated (G1CT-coc and GFP-coc) increased gradually. However, the overall sensitizations of G1CT-coc mice was greatly attenuated. A one-way ANOVA (Student–Newman–Keuls method) revealed that the locomotor behavior of the two groups was significantly different in after each injection from the second injection onward (inj 2, $p > 0.05$; inj 3, $p > 0.023$; inj 4, $p > 0.018$; inj 5, $p > 0.01$).

Here, we have shown that repeated injections of cocaine into juvenile mice significantly increase the surface-expressed AMPARs in the dorsal striatum. Interestingly, juvenile mice were more sensitive to cocaine injections than young adult mice, in terms of the AMPAR mobilization, although locomotor sensitization did not differ between two age groups. Adolescence is a transitional period when postnatal neuronal development is complete and neural transformations take place. Studies show that adolescents are more vulnerable to addiction in response to drug exposure than young adults [15], although the mechanisms that underlie this age-dependent difference in vulnerability are not known. It is tempting to view this phenomenon as an extension of the well-characterized age-dependent synaptic modifications seen in sensory systems. A critical period when experience-dependent synaptic modifications are actively occurring is present in various sensory systems. Our result suggests that these age-dependent synaptic modifications may provide a time window of vulnerability to addiction.

We demonstrated that blocking AMPAR trafficking in the dorsal striatum suppresses locomotive sensitization to cocaine. Our results suggest that changes in glutamatergic synapses in the dorsal striatum may underlie addiction. This result is striking, considering that the dorsal striatum was previously suggested to be involved in the late-phase habit formation in the drug self-administration paradigm. Control of habit formation by the dorsal striatum may possibly be initiated earlier in juveniles, thus facilitating habitual learning in response to drugs of abuse in adolescents. Although whether the same changes in AMPAR trafficking can be induced by the self-administration paradigm remains to be determined, our results suggest that the dorsal striatum may be involved in addiction control by modifying glutamatergic synaptic transmissions.

Acknowledgments

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