Developmental Disruption of Gamma-Aminobutyric Acid Function in the Medial Prefrontal Cortex by Noncontingent Cocaine Exposure During Early Adolescence

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Background: Drug experimentation during adolescence is associated with increased risk of drug addiction relative to any other age group. To further understand the neurobiology underlying such liability, we investigate how early adolescent cocaine experience impacts medial prefrontal cortex (mPFC) network function in adulthood.

Methods: A noncontingent administration paradigm was used to assess the impact of early adolescent cocaine treatment (rats; postnatal days [PD] 35–40) on the overall inhibitory regulation of mPFC activity in adulthood (PD 65–75) by means of histochemical and in vivo electrophysiological measures combined with pharmacologic manipulations.

Results: Cocaine exposure during early adolescence yields a distinctive hypermetabolic prefrontal cortex state that was not observed in adult-treated rats (PD 75–80). Local field potential recordings revealed that early adolescent cocaine exposure is associated with an attenuation of mPFC gamma-aminobutyric acid (GABA)ergic inhibition evoked by ventral hippocampal stimulation at beta and gamma frequencies that endures throughout adulthood. Such cocaine-induced mPFC disinhibition was not observed in adult-exposed animals. Furthermore, the normal developmental upregulation of parvalbumin immunoreactivity observed in the mPFC from PD 35 to PD 65 is lacking following early adolescent cocaine treatment.

Conclusions: Our data indicate that repeated cocaine exposure during early adolescence can elicit a state of mPFC disinhibition resulting from a functional impairment of the local prefrontal GABAergic network that endures through adulthood. A lack of acquisition of prefrontal GABAergic function during adolescence could trigger long-term deficits in the mPFC that may increase the susceptibility for the onset of substance abuse and related psychiatric disorders.

Key Words: Adolescence, cocaine, electrophysiology, GABA, parvalbumin, prefrontal cortex

Adolescence is a vulnerable period not only for the onset of major psychiatric disorders, such as schizophrenia and depression, but also for drug use and abuse (1–3). For instance, drug experimentation during this developmental stage is associated with increased risk of drug addiction relative to any other age group (2,4,5). Although the neurobiology underlying such vulnerability is not well understood, it has been proposed that drug exposure during adolescence may elicit maladaptive modifications within the mesocorticolimbic-prefrontal cortex (PFC) loop (1–3,6), which is known to mediate a variety of addiction-related behaviors, including enhanced drug-cue associations and drug seeking (7–10). Importantly, the PFC continues to undergo major structural and functional changes throughout the adolescent transition to adulthood (11–15). Repeated drug exposure during this critical period could therefore interfere with key neurodevelopmental processes required for normal prefrontal maturation, a disruption that could endure through adulthood and trigger long-lasting impairments in the PFC.

At the cellular level, the maturation of PFC activity during adolescence is dependent on the remodeling of local inhibitory circuits by the influence of glutamatergic inputs from the ventral hippocampus and the recruitment of dopamine facilitatory action on gamma-aminobutyric acid (GABA)ergic interneurons (16,17). Among the different subsets of GABAergic interneurons in the PFC, the parvalbumin (PV)-positive/fast-spiking cells play an important role in determining the timing and spatial selectivity of pyramidal cell firing (18). Thus, the acquisition of an increased prefrontal GABAergic function during the normal adolescent period (19,20) is thought to be associated with the maturation of cognitive abilities such as working memory, decision making, and impulse control (21,22). Consequently, a developmental impairment of GABAergic transmission in the PFC is expected to trigger prefrontal disinhibition and deficits in PFC-dependent functions as revealed by studies from animal models (17,23–25). Here, we sought to determine whether a disinhibited PFC would emerge following repeated noncontingent cocaine exposure during adolescence and if such a disruption results from a developmental alteration of the local GABAergic network. The noncontingent administration paradigm was chosen to determine the pharmacological action of cocaine. We assessed the impact of early adolescent cocaine treatment on the overall inhibitory regulation of medial PFC (mPFC) activity in adulthood by means of histochemical measures and in vivo electrophysiological local field potential recordings combined with pharmacological manipulations. Specifically, changes in medial prefrontal processing of frequency-dependent facilitation and depression of local field potential responses exerted by ventral hippocampal

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stimulation were compared across age and treatment groups. As shown recently (26), this approach is suitable for assessing changes in mPFC network responses resulting from a developmental disruption of local GABAergic transmission.

Methods and Materials

All experiments were carried out according to the US Public Health Service Guide for Care and Use of Laboratory Animals and were approved by the Rosalind Franklin University Institutional Animal Care and Use Committee. All chemicals were obtained from Sigma-Aldrich (St. Louis, Missouri) except for Indiplon, which was obtained from Tocris Bioscience (Ellisville, Missouri). Different age groups of male Sprague-Dawley rats (Harlan, Indianapolis, Indiana) were used. They were group housed (2 to 3 rats per cage) under conditions of constant temperature (21°C to 23°C) and humidity in a 12:12 hour light/dark cycle with food and water available ad libitum. All animals were allowed to acclimate for at least 5 days before receiving any experimental manipulation.

Experimental Groups

Early adolescent (postnatal day [PD] 35) rats were randomly assigned to receive daily single noncontingent (home cage) injections of cocaine (20 mg/kg in saline, intraperitoneal) or saline for 5 consecutive days. All histochemical and electrophysiological measures were conducted within PD 65 to PD 75. To determine if the effects of cocaine are age dependent, prefrontal changes in adult (PD 75)-treated rats following an equivalent duration of exposure and washout period (25–35 days, PD 105–115) were compared with those from the early adolescent-treated group. To control for the age of testing, electrophysiological recordings from another cohort of early adolescent-treated rats were conducted within the PD 105 to PD 115 range.

Cytochrome Oxidase Histochemistry and Densitometry

Brain metabolic activity was determined by means of cytochrome oxidase staining using a previously reported protocol (Supplement 1) (27,28). A single value per structure per animal was obtained by averaging measurements from at least three sections per rostrocaudal level.

Medial PFC Local Field Potentials Evoked by Ventral Hippocampal Stimulation In Vivo

All recordings were conducted following a previously reported protocol (Supplement 1) (26). Briefly, ventral hippocampal train stimulations at 10, 20, and 40 Hz were used to assess whether the altered mPFC network response could result from a developmental disruption of local GABAergic transmission (26). Furthermore, changes in prefrontal local field potential responses following ventral hippocampal high-frequency stimulation (50 pulses at 100 Hz/15 sec × 4) were examined to determine whether a history of early adolescent cocaine exposure is sufficient to alter plasticity within the hippocampal-mPFC pathway. It is well known that changes in synaptic plasticity within the ventral hippocampal-prefrontal pathway can be assessed in vivo by means of local field potentials (29).

Local Prefrontal Microinfusions of Picrotoxin and Indiplon

The experimental procedure for local microinfusions of picrotoxin (gamma-aminobutyric acid-type A [GABA-A] receptor antagonist) and Indiplon (GABA-A receptor positive allosteric modulator) was conducted using a 28-gauge cannula (Plastics One Inc., Roanoke, Virginia) secured to the mPFC recording electrode, as previously described (28). The cannula was filled with artificial cerebrospinal fluid-containing vehicle, picrotoxin (50 μmol/L/.1% dimethyl sulfoxide) or Indiplon (5 μmol/L/.02% dimethyl sulfoxide). All microinfusions (1 μL) were performed at .1 μL per minute and changes in mPFC local field potential responses were assessed within the 35-minute postinjection period.

Immunohistochemical Analyses of Parvalbumin Immunofluorescence

See Supplement 1 for details. Briefly, coronal sections of 50 μm thick containing the mPFC were mounted on Superfrost

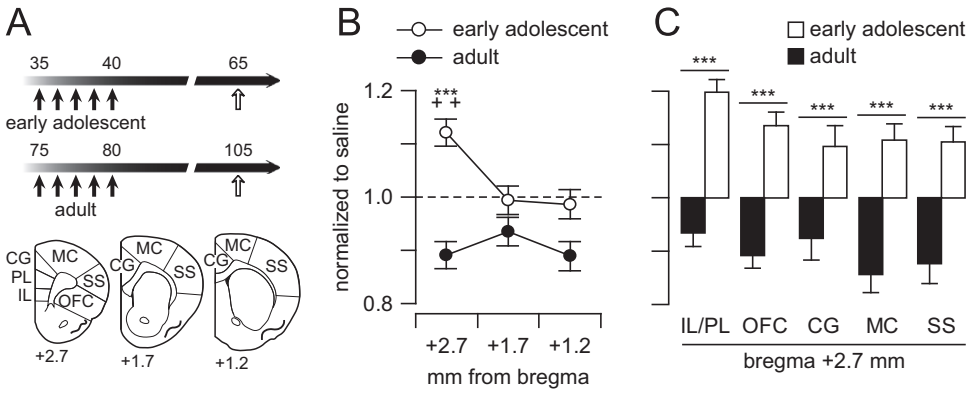

Figure 1. Cocaine exposure induces age- and region-specific metabolic changes in the frontal cortex. **(A)** Diagram illustrating the experimental design. Five noncontingent injections of saline or cocaine were performed in early adolescent (postnatal day [PD] 35–40) and adult (PD 75–80) rats. Metabolic changes in the frontal cortex (three rostrocaudal levels: +2.7, +1.7, +1.2 mm from bregma) were assessed by means of cytochrome oxidase I (CO-I) histochemistry on PD 65 in the adolescent-treated group and PD 105 in the adult-treated group. **(B)** Regional analyses revealed that cocaine exposure during early adolescence elicited a distinct metabolic activity elevation in the rostral frontal cortex (i.e., bregma +2.7), whereas an overall downregulation of CO-I staining was observed in adult-treated animals (n = 10–12 per group; main age effect $F_{1,66} = 26.29$, $p < .00001$; age × region interaction $F_{2,66} = 4.32$, $p = .017$; $^{***}p < .0005$ vs. adult, $^{++}p < .005$ vs. bregma +1.7 and +1.2, least significant difference post hoc test after significant two-way analysis of variance). **(C)** Cytochrome oxidase I staining across different areas in the prefrontal cortex (PFC) (i.e., rostral frontal cortex, bregma +2.7). Two-way analysis of variance revealed that metabolic activity in all PFC areas becomes elevated when cocaine exposure occurs during early adolescence. In contrast, an opposite pattern of CO-I staining in all PFC areas was observed in the adult-treated group (main age effect $F_{1,110} = 137.2$, $p < .00001$; $^{***}p < .0005$ vs. adult, least significant difference post hoc). CG, cingulate cortex; IL, infralimbic; MC, motor cortex; OFC, orbitofrontal cortex; PL, prelimbic; SS, somatosensory cortex.