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Group II metabotropic glutamate receptors in the striatum of non-human primates: dysregulation following chronic cocaine self-administration

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Abstract

A growing body of evidence has demonstrated a role for group II metabotropic glutamate receptors (mGluRs) in the reinforcing effects of cocaine. These receptors are important given their location in limbic-related areas, and their ability to control the release of glutamate and other neurotransmitters. They are also potential targets for novel pharmacotherapies for cocaine addiction. The present study investigated the impact of chronic cocaine self-administration (9.0 mg/kg/session for 100 sessions, 900 mg/kg total intake) on the densities of group II mGluRs, as assessed with *in vitro* receptor autoradiography, in the striatum of adult male rhesus monkeys. Binding of [^{3}H]LY341495 to group II mGluRs in control animals was heterogeneous, with a medial to lateral gradient in binding density. Significant elevations in the density of group II mGluRs following chronic cocaine self-administration were measured in the dorsal, central and ventral portions of the caudate nucleus ($P<0.05$), compared to controls. No differences in receptor density were observed between the groups in either the putamen or nucleus accumbens. These data demonstrate that group II mGluRs in the dorsal striatum are more sensitive to the effects of chronic cocaine exposure than those in the ventral striatum. Cocaine-induced dysregulation of the glutamate system, and its consequent impact on plasticity and synaptic remodeling, will likely be an important consideration in the development of novel pharmacotherapies for cocaine addiction.

Keywords

cocaine self-administration; non-human primate; striatum; group II metabotropic glutamate receptors

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Introduction

Cocaine abuse remains a significant problem worldwide with close to 40 million Americans age 12 and older reported to have tried cocaine or crack at least once, according to the National Survey on Drug Use and Health [1]. Of these individuals, nearly 4 million are considered regular users. Despite significant efforts effective treatment strategies for cocaine addiction have remained elusive. Thus, the identification of new therapeutic targets is of great importance. While research investigating the neurochemical effects of cocaine has traditionally focused on monoamine systems, recent studies have shown that there are also significant adaptations in glutamate systems [2], particularly following chronic cocaine exposure [3].

Group II metabotropic glutamate receptors (mGluRs), comprised of mGluR2 and mGluR3, are inhibitory G_i/G_o-coupled G-protein receptors that are located both pre- and post-synaptically [4, 5]. When located pre-synaptically they function as autoreceptors, reducing glutamatergic transmission via negative feedback [6, 7]. Acting as heteroceptors, they can also influence the release of other neurotransmitters [8–10]. Group II mGluRs are heterogeneously distributed throughout the brain, and are particularly dense in areas such as the hippocampus, thalamus, striatum, amygdala and cortex [5, 11–14]. Given their location in limbic-related regions and their ability to modulate neurotransmission, it is not surprising that these receptors have been implicated in a variety of psychiatric disorders, such as schizophrenia and depression [15–17].

Recent data suggests that group II mGluRs are also involved in the reinforcing effects of cocaine [18–20]. For example, selective agonists of group II mGluRs, such as LY379268, block cocaine- and cue-induced reinstatement of cocaine-seeking in rats [21] when administered either systemically or directly into the nucleus accumbens [22]. In a similar fashion, LY379268 reduces cocaine self-administration and attenuates both cue- and cocaine-induced reinstatement of cocaine-seeking in non-human primates [23]. Few studies to date, however, have assessed how chronic cocaine exposure affects the regulation of group II mGluRs, an important consideration given the current interest in these receptors as targets for cocaine medications [24]. Thus, the present study investigated the impact of chronic cocaine self-administration on the densities of group II mGluRs, as assessed by *in vitro* receptor autoradiography, in the striatum of non-human primates. The cocaine self-administration paradigm involved 100 sessions of high-dose (0.3 mg/kg/injection) cocaine injections that resulted in a cumulative intake of 900 mg/kg; this regimen and total cocaine intake has been shown to significantly impact monoamine neurotransmission [25–28]. A non-human primate model was chosen because of the close homology of non-human primates to humans both in terms of striatal neuroanatomy and the glutamate system.

Materials and Methods

Subjects

Ten experimentally-naïve adult male rhesus monkeys (*Macaca mulatta*) weighing between 8.1–12.0 kg (mean ± SD; 10.1 ± 0.4 kg) at the start of the study served as subjects. All monkeys were individually housed with water available *ad libitum* in the home cage. Monkeys were weighed weekly and fed enough food daily (Lab Diet Monkey Chow and fruit supplementation) to maintain body weights at approximately 95% of free-feeding weights. Experimental procedures were approved by the Wake Forest University Institutional Animal Care and Use Committee.

Self-administration

Details of surgical and self-administration procedures for this group of monkeys have been previously described [28, 29]. Briefly, monkeys were initially trained in operant chambers to respond on one of two levers under a fixed-interval (FI) 3-min schedule for 1g banana-flavored pellets. Daily training sessions terminated after 30 reinforcers were obtained and a minimum of 20 sessions with stable performance (± 20% of the mean for 3 consecutive sessions) satisfied training requirements. Upon achieving response stability, the feeder was unplugged and the effects of extinction on responding were examined for 5 consecutive sessions. Following extinction, food-maintained responding was reinstated for all monkeys. These extinction rates were used later to determine whether cocaine acted as a reinforcer in each monkey. Indwelling intravenous catheters were implanted into the femoral vein and subcutaneous ports were positioned in the lower back in all monkeys. After surgery, food-reinforced responding was re-established after which monkeys were divided into two groups. Control monkeys (n = 6) continued responding under the food-reinforced FI 3-min schedule for the duration of the study. Experimental monkeys (n = 4) began self-administration of cocaine (FI 3-min; 0.3 mg/kg per injection) for a period of 100 sessions. Daily sessions ended after 30 reinforcers were obtained. Animals obtained all of the reinforcers available each session. Detailed analyses of the behavioral data have been reported previously [28].

Tissue Processing

Monkeys utilized in this study were also used for 2-deoxy-d-[^{14}C] glucose (2-DG) analysis. This technique enables us to visualize how patterns of functional brain activity shift as a consequence of chronic cocaine self-administration. The 2DG data from these animals has been reported previously [29–32]. The 2-DG experiment was initiated within 2 min of the final reinforcer on the last self-administration session (either food or cocaine reinforcement) and involved timed sampling of arterial blood for ~ 45 min. Immediately after the 2-DG procedure, animals were euthanized with sodium pentobarbital (100 mg/kg, i.v.). Brains were immediately removed, blocked, frozen in isopentane (−35 ºC to −50 ºC) and then stored at −80 ºC. Coronal sections (20 μm) were cut on a cryostat, thaw-mounted onto electrostatically charged slides, desiccated and stored at −80 ºC until autoradiography processing.

[^{3}H]LY341495 Autoradiography

Autoradiography procedures for labeling group II mGluRs with the selective antagonist [^{3}H]LY341495 were adapted for use in nonhuman primate tissue from those of Wright et al. [33]. Tissue sections were pre-incubated at room temperature in buffer (10 mM potassium phosphate buffer with 100 mM potassium bromide, pH 7.6) for 30 min. Pre-incubation removed any endogenous ligand, residual cocaine, and 2-DG. Sections were then incubated for 2 hours in buffer containing 4 nM [^{3}H]LY341495 (40 Ci/mmol; Perkin-Elmer Life Sciences, Boston, MA) in the presence (non-specific binding) or absence (total binding) of 1 mM glutamate. Sections were rinsed 2 times (30 sec each) in ice-cold buffer, with a final 10 sec rinse in ice-cold water. Sections were immediately dried under a stream of cold air, dessicated overnight and apposed, along with calibrated [^{3}H] autoradiographic standards (Amersham, Piscataway, NJ), to Kodak Biomax MR film (Perkin Elmer, Waltham, MA) for 9 weeks.

Densitometry and Data Analysis

Binding of [^{3}H]LY341495 to group II mGluRs in the striatum was measured via densitometric quantification of autoradiograms. The level of striatum chosen for analysis was that at which the nucleus accumbens could most clearly be differentiated into core and

shell divisions (Bregma 0.45 to – 0.45 mm; [34]). The striatum was then further divided into dorsal, central and ventral caudate nucleus and dorsal, central and ventral putamen, according to the atlas of Paxinos and colleagues (Panel A, Figure 1; [34]). Analyses of autoradiograms were conducted by quantitative densitometry with a computerized image processing system (MCID, InterFocus Imaging Ltd., Linton, United Kingdom). Tissue / mg wet weight tissue) were determined from optical densities using a calibration curve obtained by densitometric analysis of [^{3}H] standards on each autoradiogram. Specific binding was determined by subtracting non-specific binding values from the total binding values, measured in adjacent sections. Statistical analysis was performed for each brain structure by means of a two-way independent Student's t-test.

Results

[^{3}H]LY341495 binding in control animals

Binding of [^{3}H]LY341495 to group II mGluRs was seen throughout the striatum of non-human primates (Table 1). Specific binding of [^{3}H]LY341495 accounted for greater than 85% of total binding (see Figure 1 supplementary data). In agreement with previous reports, group II mGluRs were observed throughout the caudate, putamen and nucleus accumbens [14, 35–38]. The topography of group II mGluR binding sites in non-drug exposed control animals was heterogeneous with a gradual medial to lateral gradient (highest to lowest) in binding density. Higher densities of binding were observed in the medial aspects of the central and ventral caudate, while more moderate levels of binding were observed in the medial aspects of the putamen. The lowest levels of binding were measured in the lateral portions of the caudate nucleus, putamen and nucleus accumbens core and shell (Panel A Figure 2).

Effect of chronic cocaine self-administration on [^{3}H]LY341495 binding sites

In those animals that chronically self-administered cocaine, densities of [^{3}H]LY341495 binding sites were significantly higher in all portions of the caudate nucleus (dorsal, +19 %, central, +13 % and ventral, +14 %; Table 1, Panel B Figure 2), compared to control animals. In contrast, there were no differences between control and cocaine-exposed animals in [^{3}H]LY341495 binding sites in either the putamen or the nucleus accumbens core or shell (Table 1).

Discussion

The present study demonstrates that there are significant adaptations in the striatal glutamatergic system in response to chronic cocaine self-administration, though these appear to be restricted to the more dorsal territories of the striatum. We chose to focus on the striatum in this study based on three facts: 1) the striatum plays an essential role in the reinforcing effects of cocaine [39, 40], 2) group II mGluRs attenuate the reinforcing effects of cocaine [18–20] and 3) group II mGluRs are localized in the striatum [14, 35]. The finding of significantly higher densities of group II mGluRs in the caudate nucleus as a result of chronic cocaine self-administration indicates the presence of considerable plasticity within the dorsal striatum. In contrast, no differences in receptor density were observed between the groups in either the putamen or nucleus accumbens. These data suggest, therefore, that elements of the glutamate system within the dorsal striatum may be more sensitive, compared with the ventral striatum, to the effects of chronic cocaine exposure in the non-human primate.

The localization of [^{3}H]LY341495 binding sites within the non-human primate striatum agrees with previous autoradiographic and immunohistochemical labeling studies [14, 35,

37]. A novel finding of the present study was the identification of a medial-lateral gradient (high to low) in the binding density of group II mGluRs. The highest levels were found in the medial caudate nucleus and lowest in the lateral portions of the caudate, putamen and nucleus accumbens core and shell. Given the topographical organization of glutamatergic projections to different regions of the striatum [41–43], the differential distribution of group II mGluRs within the medial and lateral portions of the striatum may have functional implications for how glutamate regulates the striatum.

Group II mGluRs in the striatum are thought to be localized primarily pre-synaptically [5, 11], where they can modulate the release of neurotransmitters [44–46]. As exposure to cocaine increases, there is hypothesized to be a gradual and escalating involvement of the glutamatergic system [2, 47]. Indeed, previous data in rodents have shown that acute administration of cocaine does not induce the release of glutamate [3, 48], whereas following chronic self-administration, levels of extracellular glutamate are progressively increased with each dose of cocaine [3]. One mechanism explaining our results, then, may be a compensatory increase in the levels of group II mGluRs autoreceptors in response to these sustained elevations in extracellular glutamate concentration. One of the predicted consequences of these up-regulated group II mGluR autoreceptors may be lower basal levels of glutamate, which have been reported to occur in cocaine-exposed rodents [3, 49, 50] and humans [51]. In agreement with our data, Weiss and colleagues reported functional increases in group II mGluRs in a number of brain areas such as the prefrontal cortex, central nucleus of the amygdala, and hippocampus following escalation of cocaine self-administration in rats [52]. Thus, future studies will be aimed at investigating how group II mGluRs are dysregulated in response to cocaine self-administration in these and other brain areas.

One of the interesting outcomes from the present study was the lack of effects in the ventral striatum (incorporating both ventral putamen and nucleus accumbens). A recent investigation in rodents also failed to observe any impact on the function of group II mGluRs in the nucleus accumbens following chronic cocaine self-administration [52]. Although the initial effects of cocaine have been shown to be primarily located in limbic-related areas, such as the ventral striatum [31], with longer exposure the effects of cocaine expand to incorporate more dorsal regions [53, 54]. Given the extended duration of cocaine self-administration in the present study, therefore, it is possible that group II mGluRs may have been transiently affected in the ventral striatum earlier in the course of exposure. Thus, the compartmentalization of effects and relative sensitivity of the glutamate system in the dorsal striatum following chronic exposure to cocaine self-administration is in accordance with these studies.

In contrast to the data reported here, data from rodent studies have reported decreased function, or lower levels, of group II mGluRs following repeated cocaine exposure [55, 56]. There are, however, important differences between these studies. First, there are considerable species differences in the glutamate system [57–59], as well as in the response of the brain to cocaine [60, 61]. Second, the monkeys in our study self-administered cocaine, while the rodents in the other studies received cocaine non-contingently. There is evidence of behavioral and neurochemical differences in the effects of cocaine delivered contingently versus non-contingently [62–65]. Third, the total intake of cocaine received by the animals between the studies was very different (180–200 mg/kg in the rodent studies, 900 mg/kg in the present study) and fourth, these previous studies involved a period of abstinence (up to 3 weeks) before measuring either the density or functionality of group II mGluRs. As it relates to the latter point, future studies are needed to investigate the role of cocaine abstinence following chronic cocaine self-administration to determine how malleable group II mGluR

densities are in response to long-term cocaine exposure and abstinence in non-human primate brains.

Conclusions

Thus, our data suggests that group II mGluRs are altered as a direct consequence of chronic cocaine exposure, potentially leading to impaired regulation of glutamate transmission. As reviewed recently by Kalivas and O'Brien [47], the transition to addiction likely involves a shift in the pattern of neural circuits that control cocaine-related behavior. Correspondingly, there may also be a change to a more dominant role for glutamate versus dopamine in mediating the effects of chronic cocaine. Since there is a critical role for glutamate in the control of plasticity and synaptic remodeling, it is essential to understand how this system is impacted by long-term cocaine exposure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- Group II metabotropic glutamate (mGluRs) are involved in the effects of cocaine
- We studied the density of group II mGluRs following chronic cocaine in monkeys
- We found higher levels of binding in the dorsal striatum, not the ventral striatum
- Therefore the dorsal striatum may be more sensitive to the effects of cocaine
- Treatments for cocaine that target these receptors may be efficacious

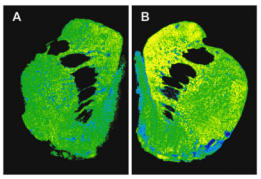

Figure 2.
Pseudocolor-enhanced autoradiogram of [^{3}H]LY341495 binding in the striatum of a control (Panel A) and cocaine self-administering (Panel B) monkey.

Table 1

Effect of chronic cocaine self-administration on the distribution of [^{3}H]LY341495 binding to group II mGluRs in non-human primate striatum.

Brain Region	Food Controls (N=6)	Chronic cocaine self-administration (N=4)
Dorsal caudate (1)	440 ± 19.8	524 ± 29.8*
Central caudate (2)	534 ± 16.8	606 ± 24.4*
Ventral caudate (3)	508 ± 16.2	581 ± 22.7*
Dorsal putamen (4)	406 ± 14.8	470 ± 39.4
Central putamen (5)	423 ± 16.5	481 ± 30.7
Ventral putamen (6)	457 ± 18.9	522 ± 29.2
Nucleus accumbens core (7)	387 ± 13.5	388 ± 39.2
Nucleus accumbens shell (8)	402 ± 14.7	422 ± 16.2

Mean ± S.E.M. data are presented as specific binding in fmols/mg of wet weight tissue.

Numbers in parentheses next to brain regions indicate their location in Figure 1, supplementary data.

*P<0.05 compared to food controls, two-way unpaired Student's t-test.