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The Role of Dopamine and GABA in the Frontal Cortex of Mice in Modulating a Motor-Stimulant Effect of Amphetamine and Cocaine

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KARLER, R., L. D. CALDER, D. K. THAI AND J. B. BEDINGFIELD. *The role of dopamine and GABA in the frontal cortex of mice in modulating a motor-stimulant effect of amphetamine and cocaine.* PHARMACOL BIOCHEM BEHAV **60**(1) 237–244, 1998.—The results of previous studies have indicated that the activation of dopaminergic and GABAergic systems in the prefrontal cortex can decrease dopaminergic and glutamatergic activity in the striatum, ostensibly by the inhibition of corticofugal glutamatergic pathways. The present studies were designed to investigate the cortical influence of dopamine and GABA agonists and antagonists on the motor response to systemically administered amphetamine and cocaine in the mouse. The results show that both dopamine and THIP, the $GABA_A$ agonist, injected intracortically (IC) depress amphetamine- or cocaine-induced stereotypy. That these responses are functionally significant is illustrated by the IC effects of sulpiride and bicuculline; they enhance the motor activity of the stimulants, suggesting that both dopaminergic and GABAergic systems in the cortex are activated by systemically administered amphetamine or cocaine. Additional experiments demonstrated that bicuculline IC can antagonize the depressant effect of dopamine IC; therefore, the dopaminergic inhibition in the cortex appears to be mediated by the activation of a cortical GABA system. These results show that systemically administered amphetamine or cocaine causes dopaminergic effects not only in the striatum but also in the cortex, and that the dopaminergic effect in the cortex may activate a cortical GABAergic system, which in turn, may account for the noted cortical inhibition of the dopaminergic motor-stimulatory action in the striatum. © 1998 Elsevier Science Inc.

Amphetamine Cocaine Mouse Motor effects Dopamine GABA Cortex

CONSIDERABLE evidence supports the hypothesis that the frontal cortex modulates the release of neurotransmitters in subcortical structures such as the striatum, presumably affecting the function of these structures; for example, stimulation of the prefrontal cortex, either electrically (20,37,50) or pharmacologically (28,40), has been shown to increase the amount of dopamine and excitatory amino acids detected in the striatum by dialysis or voltammetry. Cortical control over subcortical structures has also been demonstrated by injecting tetrodotoxin into the prefrontal cortex, which decreased the amount of dopamine recovered in the striatum by dialysis (28). That the observed cortical influence on neurotransmitters in the striatum may be functionally significant is suggested by an enhanced motor response to psychostimulants following cortical lesions (6,9,17,22,48).

The cortical influence is thought to be mediated by glutamatergic efferents because lesions of these efferents have been reported to decrease the motor-stimulant effects of the psychomotor stimulants (10). The prevailing view is that control of the cortical excitatory efferents may involve several transmitters, including dopamine, GABA, glutamate, serotonin, and norepinephrine. A role for dopamine in cortical inhibitory control is suggested by reports that intracortical (IC) injections of dopaminergic agonists decrease the amount of

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dopamine measured by in vivo dialysis and voltammetry in the striatum (23,28,31,34). Additionally, electrophysiological studies support this conclusion, because electrical stimulation of the VTA inhibits cortical neurons that are activated by the antidromic stimulation of neurons in the striatum or thalamus (18,51,52); the direct application of dopamine in the cortex also inhibits the antidromic excitation (45).

The cortical inhibitory control of the striatum also appears to involve GABAergic activity, because bicuculline injected into the cortex has been reported to increase the amount of dopamine (28) and excitatory amino acids (40) recovered by dialysis in the striatum; while THIP, the GABA agonist, injected IC blocked amphetamine-induced stereotypy (24). A dopaminergic–GABAergic–glutamatergic interaction in the cortex is explicable neuroanatomically, for there are data that demonstrate that dopaminergic afferents from the midbrain synapse on cortical glutamatergic (21,44,46) and on GABAergic neurons (12,46), potentially enabling dopamine to affect both the excitatory and inhibitory systems. Furthermore, there is also evidence that cortical GABAergic neurons synapse on and modulate glutamatergic neurons in the cortex (12,41,42), which raises the possibility that the cortical dopaminergic inhibition of the neurotransmitters recovered in the striatum is, in part, mediated by a dopaminergic–GABAergic interaction.

That the cortex, by whatever mechanism, can control the release of both striatal dopamine and excitatory amino acids is important because both of these types of transmitters in the striatum are involved in mediating the motor-stimulant effects of cocaine and amphetamine (8,25,26,30,43). What is not known in how the GABAergic inhibitory systems actually function is the cortex vis-à-vis the characteristic dopaminergic behavioral effects of amphetamine and cocaine. The present work extends the previous neurochemical and lesion studies to a description of the influence of the cortical dopaminergic and GABA systems on the motor activity of amphetamine and cocaine. In these studies the role of both dopamine and GABA in the frontal cortex of mice was investigated pharmacologically by the IC administration of dopamine and GABA agonists and antagonists, and the subsequent assessment of their effects on stimulant-induced stereotypy.

METHOD

Experimental Animals and Drugs

Male CF-1 mice, weighing 25–30 g, were housed in groups of 15, fed ad lib, and maintained on a 12 L: 12 D cycle that corresponded with the day/night cycle. D-Amphetamine sulfate and cocaine HCl were obtained from the National Institute on Drug Abuse (Rockville, MD); the D_2 dopamine receptor antagonist sulpiride, the $GABA_A$ receptor antagonist (−)-bicuculline methiodide and dopamine HCl from Sigma Chemical Company (St. Louis, MO); and the $GABA_A$ receptor agonist gaboxadol (THIP) HCl, the D_1 dopamine receptor agonist (±)-SKF 38393, N-allyl-HCl, and the D_2 dopamine receptor agonist (±)-2-(N-phenylethyl-N-propyl)amino-5-hydroxytetraline (PPHT) HCl from Research Biochemicals Int. (Natick, MA). All drug solutions were prepared using sterile isotonic saline immediately prior to administration. Drug dosages for systemic administration were calculated as mg/kg of body weight and were administered intraperitoneally (IP) in a volume of 0.1 ml/20 g body weight. IC injections were bilateral; doses were expressed in μg/side. Drug weights of the salts were not corrected for the weight of the free form.

Experimental Procedures

The experiments were designed to measure inhibitory or excitatory effects of drugs that were administered IC on the motor response induced by the IP administration of the psychomotor stimulants. The studies to determine inhibitory effects were designed as follows: psychomotor-stimulant doses were selected that induced stereotypy in about 80–90% of the animals. The high response facilitated the identification of antagonistic effects following the IC administration of drugs, yet avoided supramaximal doses that might complicate drug effects. For amphetamine, the dose required to produce 80–90% stereotypy was 12 mg/kg; the comparable cocaine dose was 80 mg/kg. Studies to assess an excitatory influence on stereotypy induced by the IC administration of drugs were conducted in animals given a dose of amphetamine or cocaine that yielded 0–20% stereotypy in the controls; the relatively low response enabled the detection of an enhanced effect. In these experiments, the dose of amphetamine ranged from 5–7 mg/kg; for cocaine, it was 60 mg/kg. All of the studies were conducted between 1000 and 1500 h in naive animals given single treatment.

Motor responses were measured in terms of stereotypy, which was described previously (4,5). In the CF-1 mouse, in contrast to the rat, stereotypy manifests itself in very limited behaviors: At relatively low doses of amphetamine (6–10 mg/kg) the mice exhibit some intermittent head and paw movements similar to grooming behavior, but these are constantly interrupted by locomotor activity. Because the repetitive motor responses are similar to normal grooming behaviors, the interrater reliability for the use of these behaviors as a measure of stereotypy is very poor. In contrast, higher doses (12–20 mg/kg) produce a readily identifiable end point, as evidenced by a high interrater reliability; the response constitutes a stationary animal exhibiting exaggerated repetitive head and forelimb movements. This end point appears to be the maximum stereotypic effect attainable by systemic drug administration of nonlethal doses of amphetamine (10–20 mg/kg) and was used, therefore, as a quantal end point to measure stereotypy. The validity of the behavioral end point as a quantitative measure of stimulant activity in mice was established by obtaining dose–response curves, which demonstrate that the effect, like most effects, is proportional to the dose [see, e.g., (25,27)].

Stereotypy was assessed by an observer blind to the specific treatment during a 5-min period 30 min after stimulant administration (approximate peak-effect time). The duration of action of a motor-stimulant dose of amphetamine in the mouse is about 2 h; for cocaine, about 1 h. The 5-min observation period was found to be adequate to determine the number of animals exhibiting stereotypy, because, unless the animals are disturbed, they tend to remain "locked" in stereotypy, which facilitates the measurement.

For the IC drug studies, cannulae were bilaterally implanted in the cortex of pentobarbital-anesthetized mice by standard stereotactic techniques, as described previously (25). The coordinates for the cortical placement of cannulae were: anterior to bregma, 1.0 mm; lateral, 2.0 mm; ventral, 0.5 mm [corresponding to Fig. 22 in Franklin and Paxinos (16)]; the tip of the cannulae rested on the surface of the dura. At the time of the experiments, the injectors were inserted 1.0 mm below the tip of the cannulae into the frontal cortex. Placements were verified by histological examination. Experiments were conducted about 1 week after surgery. In selected experiments tissue damage by the IC injections was assessed visually following cresyl violet staining; and functional damage, by the

administration of standard stereotypic doses of amphetamine. None of the tested cannulated animals displayed an abnormal quantitative or qualitative response to amphetamine-induced stereotypy.

For the IC drug administration, the injectors were connected by polyethylene tubing (PE-20) to two Hamilton 1-μl syringes. Drugs were infused simultaneously into each hemisphere in a volume of 0.15 μl over a period of 30 s; 60 s later the injectors were removed and the obturators replaced. All IC injections were made 5 min prior to the systemic administration of amphetamine and cocaine.

RESULTS

The rationale for the placement of the cannulae in the cortex was determined in a previous study in which three placements in the cortex were initially investigated functionally in terms of the influence of IC drug effects on stimulant-induced stereotypy (24). One placement was 2 mm anterior to bregma, another, 1 mm anterior to bregma, and the third placement was 1 mm posterior to bregma; all the placements were 2 mm lateral and 0.5 mm ventral. Most of the reported cortical dopamine studies have focused on the prefrontal cortex of the rat, but the mouse does not have an anatomically defined prefrontal cortex (16). In our studies, the most anterior placement was found to be impractical and the other placement anterior to bregma yielded dopaminergic, GABAergic, and glutamatergic effects on stimulant-induced stereotypy. The injector placement is illustrated in Fig. 1, and is in the primary motor area of the frontal cortex; the posterior to bregma placement studied earlier is in the sensory cortex, which was generally inactive in the pharmacological studies and was used originally as a control for the responses obtained from the motor cortex. All of the IC studies in the present article were at the injection sites shown in Fig. 1.

The data shown in Table 1 represent the results of a study designed to test the proposition that dopamine agonists administered IC can inhibit the motor effects of amphetamine and cocaine in mice. As the data indicate, either amphetamine or dopamine injected IC blocks stereotypy induced by the systemic administration of amphetamine or cocaine. This inhibitory property is shared by the D_2 agonist PPHT, but not by the D_1 agonist SKF 38393, at least in the dosage range tested; doses of SKF 38393 greater than 1 μg/side were not investigated because of the drug's limited water solubility. With respect to the inhibitory dose of PPHT, in addition to the indicated dose of 0.2 μg/side, we also tested 0.02 μg/side, which was ineffective.

TABLE 1

INFLUENCE OF DOPAMINE AGONISTS ADMINISTERED IC ON AMPHETAMINE- AND COCAINE-INDUCED STEREOTYPY

Pretreatment (IC)	Treatment (IP)	% Stereotypy
Control, amphetamine	Saline	0*
Control, saline	Amphetamine	88
Control, saline	Cocaine	88
Amphetamine	Amphetamine	25*
Dopamine	Amphetamine	25*
Dopamine	Cocaine	13†
SKF 38393	Amphetamine	75
PPHT	Amphetamine	13*

Each treatment group consisted of eight animals prepared for IC injections. All IC drug effects were measured against the effect of 12 mg/kg amphetamine or 80 mg/kg cocaine injected IP. The IC dose of amphetamine was 5 μg/side; dopamine, 5μg/side; SKF 38393, 1.0 μg/side; and PPHT, 0.2 μg/side. The IC injections were given 5 min prior to IP drug administration; 30 min later, the stereotypic response to amphetamine or cocaine was noted.

*Significantly different from the amphetamine-treated saline control, as determined by a χ^2-test ($p < 0.05$).

†Significantly different from the cocaine-treated saline control, as determined by a χ^2-test ($p < 0.05$).

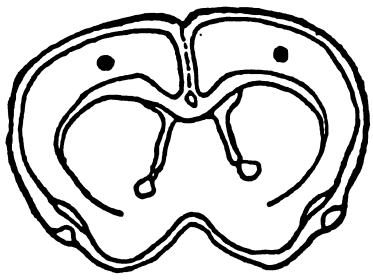

FIG. 1. Cortical injection sites for the administration of drugs. The designations (●) shown in the brain section represent the approximate location of the injection sites determined histologically in a group of 10 mice. Coordinates for the placement are given in the Method section. Histological representation is adapted from Franklin and Paxinos (16).

The data illustrated in Fig. 2A and B represent a more extensive assessment of the dopaminergic inhibition of amphetamine- and cocaine-induced stereotypy. Figure 2A shows the dose–response curves for the influence of variable IC doses of dopamine or amphetamine on stereotypy evoked by a fixed dose of amphetamine; Fig. 2B shows similar dose–response data for the dopamine inhibition of stereotypy induced by a fixed dose of cocaine. The data in Fig. 2 demonstrate that either amphetamine or dopamine IC can depress the motor effect of amphetamine and cocaine administered systemically.

The above study demonstrated that pharmacologically IC dopamine and amphetamine can inhibit the motor-stimulant response to IP amphetamine and cocaine; but the question remained: does the dopamine that is released in the cortex by systemically administered stimulants serve functionally to inhibit the motor response? To test for the functional significance, the dopamine antagonist sulpiride and the GABA antagonist bicuculline were injected IC and their effect on the response to both high and low doses of amphetamine was determined; the results are shown in Table 2. The high-dose results demonstrate that neither antagonist inhibits the amphetamine response, but the low-dose study showed that both antagonists enhanced the effect of amphetamine. The dose–response curves for the bicuculline and sulpiride enhancement of amphetamine-induced stereotypy are shown in Fig. 3. In these experiments all animals were treated with a fixed dose of amphetamine (5 mg/kg, IP), a dose that by itself does not evoke stereotypy in CF-1 mice. Prior to the amphetamine treatment, the animals were given varying IC doses of either bicuculline or sulpiride, as indicated in Fig. 3. These data define the dosage ranges of sulpiride and bicuculline that enhance the motor activity of amphetamine.

Figure 4 represents dose–response curves resulting from the administration of a fixed IC dose of sulpiride (2 μg/side) IC and the influence of this dose on the motor response to varying doses of amphetamine compared with the response to

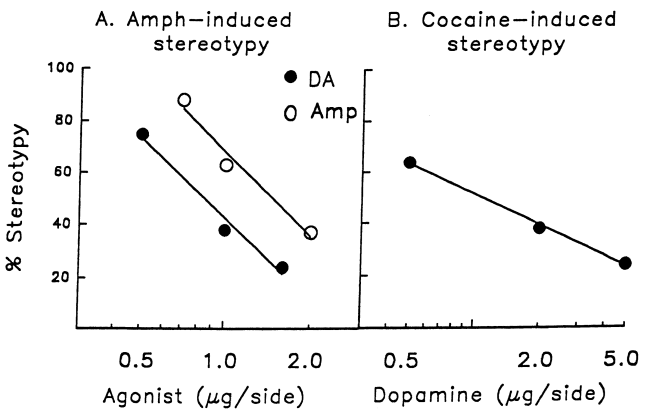

FIG. 2. Dose–response curves for the antagonism of amphetamine- or cocaine-induced stereotypy by IC administered amphetamine and dopamine. (A) IC dopamine and amphetamine antagonism of amphetamine-induced stereotypy. Each group represents eight animals. All animals were pretreated IC with an agonist 5 min prior to the IP administration of amphetamine (12 mg/kg); stereotypy was observed 30 min later. One hundred percent of the saline IC controls displayed stereotypy. The ED_{50} and 95% confidence limits for the IC amphetamine antagonism of amphetamine-induced stereotypy is 1.5 (1.4–1.7) μg/side; for IC dopamine, 0.9 (0.8–1.0) μg/side; values calculated by the method of Litchfield and Wilcoxon (33). The two slopes are significantly different from 0, as determined by a χ^2-test ($p < 0.05$). (B) IC dopamine antagonism of cocaine-induced stereotypy. Design identical to A, but stereotypy induced by IP administration of cocaine (80 mg/kg). Eighty-eight percent of the saline IC controls displayed stereotypy. The ED_{50} and 95% confidence limits, calculated by the method of Litchfield and Wilcoxon (33) for the dopamine antagonism of cocaine-induced stereotypy is 1.0 (1.05–0.95) μg/side.

TABLE 2

INFLUENCE OF IC ADMINISTERED SULPIRIDE AND BICUCULLINE ON HIGH- AND LOW-DOSE AMPHETAMINE-INDUCED STEREOTYPY

Pretreatment (IC)	Amphetamine Treatment (IP)	% Stereotypy
Control	12 mg/kg	75
Sulpiride		
0.01 μg/side	12 mg/kg	88
1.0 μg/side	12 mg/kg	88
Bicuculline		
0.05 μg/side	12 mg/kg	88
Control	7 mg/kg	0
Sulpiride		
2 μg/side	Saline	0
Sulpiride		
2 μg/side	7 mg/kg	63*
Bicuculline		
0.005 μg/side	Saline	0
Bicuculline		
0.005 μg/side	7 mg/kg	75*

Each treatment group consisted of eight animals. The antagonists were administered IC 5 min prior to amphetamine, 12 mg/kg (high dose) or 7 mg/kg (low dose). Controls represent saline IC. Stereotypy was noted 30 min after amphetamine.

*Significantly different from control, as determined by a χ^2-test ($p < 0.05$).

a saline IC control. The data shown in Figs. 3 and 4 illustrate the excitatory influence of sulpiride and bicuculline IC on the stereotypic activity of amphetamine.

The study of the IC effects of sulpiride and bicuculline were extended to cocaine, and these data are given in Table 3. As in the case of amphetamine, neither sulpiride nor bicuculline affected the high dose response to cocaine, but both enhanced the effect of a low dose of cocaine.

Because both dopamine and GABA systems in the cortex appear to be capable of influencing the motor activity of the psychostimulants, experiments were designed to determine if the inhibitory effect of dopamine IC is mediated in the cortex by the inhibitory transmitter GABA; these results are shown in Table 4. The data indicate that both dopamine and THIP IC decrease the activity of amphetamine. Because bicuculline blocks the effect of dopamine and sulpiride does not block the effect of THIP, the results suggest that the inhibitory activity of dopamine is mediated through GABA. A similar conclusion obtains for the dopaminergic inhibition of cocaine-induced stereotypy.

DISCUSSION

There have been many studies, including electrophysiological, neuroanatomical, and lesion studies, which were designed to assess the role of the cortex in controlling striatal function. Except for the lesion studies, however, very few have employed a behavioral end point as a measure of the functional interaction. The studies described above are distinguished from most previous studies because they involved a pharmacological approach to the identification of cortical–striatal interactions, as well as the use of a behavioral end point. Furthermore, these studies include not only the role of the dopamine system in the cortex, but also that of the GABA system, which has seldom been investigated in terms of the

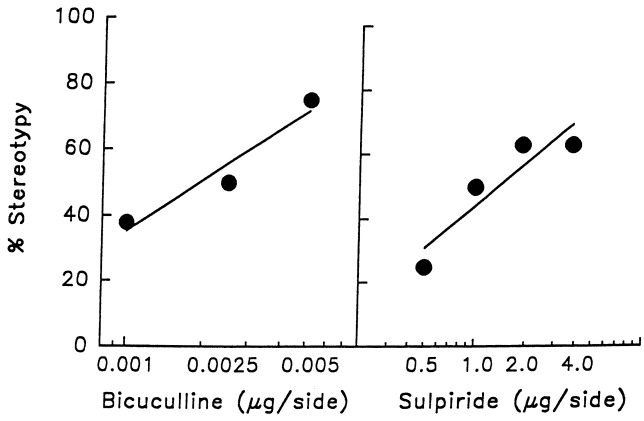

FIG. 3. The dose–response curve for the enhancement of amphetamine-induced stereotypy by sulpiride or bicuculline administered IC. Five groups of eight mice each were pretreated bilaterally with the indicated sulpiride doses 5 min prior to amphetamine (5 mg/kg, IP). Amphetamine treatment in the IC saline control with amphetamine (5 mg/kg, IP) yielded 0% stereotypy. The ED_{50} and 95% confidence limits for the effects were 0.0022 (0.0011–0.0033) bicuculline μg/side; comparable values for the sulpiride effects were 1.25 (1.06–1.46) μg/side. Values calculated by the method of Litchfield and Wilcoxon (33).

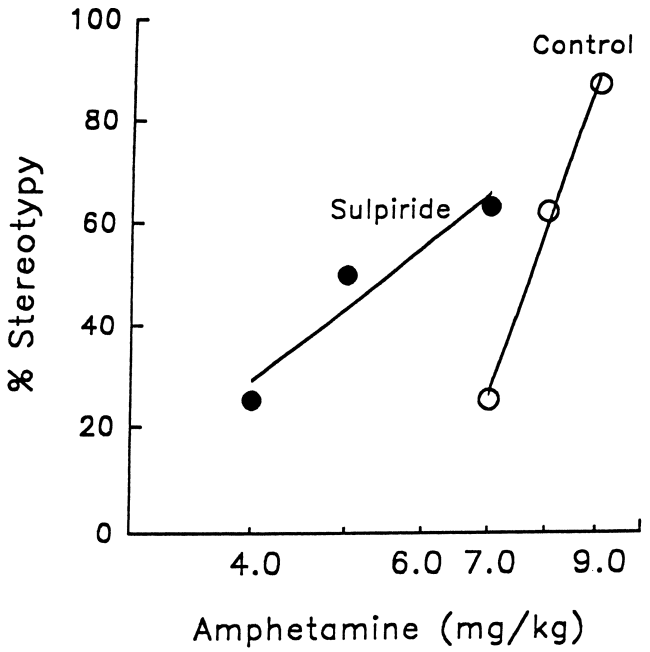

FIG. 4. Influence of a fixed dose of IC sulpiride on the amphetamine dose–response curves for stereotypy. Six groups of eight mice each were pretreated IC with either vehicle (○) or sulpiride, 2 μg/side (●) 5 min prior to the IP administration of amphetamine. The ED_{50} and 95% confidence limits for vehicle pretreated are 7.6 (6.9–8.4) mg/kg amphetamine; for sulpiride pretreated, 5.6 (4.6–6.9) mg/kg. The ED_{50} values for sulpiride pretreated are significantly different from their controls, as determined by a relative potency test ($p < 0.05$) (33).

cortical–striatal interaction. In these experiments amphetamine and cocaine were administered systemically and were used as tools to activate dopaminergic systems in the brain; and the behavioral effects were measured in terms of stereotypy, which represents the result of dopaminergic activation of the striatum. The cortical influence on stimulant-induced striatal activity was assessed by the IC administration of relatively selective agonists and antagonists of both dopaminergic and GABAergic systems.

TABLE 3

INFLUENCE OF IC ADMINISTERED SULPIRIDE AND BICUCULLINE ON COCAINE-INDUCED STEREOTYPY

Pretreatment (IC)	High-Dose Cocaine Response (% Stereotypy)	Low-Dose Cocaine Response (% Stereotypy)
Control	88	13
Sulpiride 2 μg/side	75	88*
Bicuculline 0.005 μg/side	88	75*

The conditions were the same as those described for Table 2, except that cocaine IP was used to induce stereotypy. The high dose of cocaine was 80 mg/kg; the low dose, 60 mg/kg.

*Significantly different from control, as determined by a χ^2-test ($p < 0.05$).

TABLE 4

GABAERGIC ROLE IN THE CORTICAL DOPAMINERGIC INHIBITION OF STIMULANT-INDUCED STEREOTYPY

Pretreatment (IC)	Treatment (IP)	% Stereotypy
Saline control	Amphetamine	100
Dopamine control	Amphetamine	25*
THIP control	Amphetamine	0*
Bicuculline + dopamine	Amphetamine	75**
Sulpiride + THIP	Amphetamine	0*
Saline control	Cocaine	88
Dopamine control	Cocaine	13*
Bicuculline + dopamine	Cocaine	75†

Each treatment group consisted of eight animals prepared for IC injections. Pretreatment included dopamine, 2 μg/side; THIP, 1 μg/side; bicuculline, 0.005 μg/side; and sulpiride, 2 μg/side. All drug pretreatments were administered 5 min prior to the IP treatment with either amphetamine, 12 mg/kg, or cocaine, 80 mg/kg. Stereotypy was noted 30 min after stimulant administration.

*Significantly different from saline control, as determined by a χ^2-test ($p < 0.05$).

**Significantly different from dopamine control, as determined by a χ^2-test ($p < 0.05$).

†Significantly different from dopamine controls, as determined by a χ^2-test ($p < 0.05$).

The data presented show that dopamine agonists injected into the frontal cortex can block the stereotypy induced by systemically administered amphetamine and cocaine. These results, therefore, are consistent with previous observations that the agonists administered IC decrease dopamine activity in the striatum (23,28,31,34). One view of the inhibitory effect of dopamine in the cortex is that dopamine inhibits the corticostriatal glutamatergic pathway, and the resulting decrease in the release of excitatory transmitter in the striatum, in turn, results in a decrease in the release of striatal dopamine [(13), review]. That a glutamatergic–dopaminergic interaction in the striatum is possible is corroborated by the neuroanatomical observations that both dopaminergic and glutamatergic neurons synapse in close proximity to each other on GABA dendrites (39,47). This hypothesis, therefore, assumes that the released glutamate acts as a neurohumoral agent to cause the release of striatal dopamine. Whether this actually occurs is not known, but it is known that stimulation of the cortical glutamatergic efferents results in an increase in both glutamate and dopamine detected by dialysis in the striatum (20,38,40, 49,50), which suggests that glutamate may affect the release of dopamine in the striatum.

There is, however, another view to explain the cortical effects of dopamine; that is, that cortical dopamine inhibits the cortical glutamatergic efferents to the dopaminergic cell bodies in the midbrain that project to the striatum (28,29). According to this postulate, the cortical inhibition of striatal activity is the result of a decrease in excitatory input to the dopaminergic projection neurons. Such a pathway could account for the reported decrease in the dopamine recovered in the striatum, as well as the decrease in stereotypy described above. This hypothesis is consistent with the results of previous studies in which stereotypy was shown to require not only the activation of the dopamine system but also the activation of the glutamate system, as demonstrated by both the systemic and by the intrastriatal administration of drugs (25,26).

The role of the glutamate system in the striatum is of particular interest with regard to the nature of the dopaminergic–glutamatergic interaction because the observations indicate that not only are both dopamine and glutamate agonists in the striatum necessary for stereotypy, but dopamine-induced stereotypy is the result of the dopaminergic activation of the glutamate system, and not vice versa [see also (19,36)]. These data, therefore, favor the point of view that the dopaminergic inhibitory effect in the cortex is mediated by the inhibition of the cortical excitatory input to the dopaminergic cell bodies in the midbrain, which decreases the release of dopamine in the striatum, which in turn, decreases the release of glutamate in the striatum. This hypothesis, therefore, can explain not only the dopaminergic cortical depression of recovered striatal dopamine (28), but also the previously described dopaminergic–glutamatergic relationship in the striatum to stereotypy (25,26).

Because dopamine agonists administered IC blocked stimulant-induced stereotypy and because the antagonism appeared to be D_2-receptor mediated, a study of the effect of IC-administered sulpiride on stimulant-induced stereotypy was undertaken, and the results showed that sulpiride administered IC can enhance the stimulant-induced stereotypy, which was reported previously with the use of flupenthixol (15). These data are also consistent with those of earlier studies demonstrating that lesioning the prefrontal cortex enhances the motor activity of the stimulants (6,9,17,22,48). The effects suggest that when the stimulants are administered systemically, they cause a degree of cortical inhibition of the motor activity of these drugs by virtue of their dopaminergic activity in the cortex. Although dopamine agonists injected into the cortex can block the stimulant-induced stereotypy, it is obvious that this effect does not dominate the dopaminergic motor-stimulatory effect in the striatum; rather, it appears to modulate the effect, as shown by the enhancement of the motor response to the stimulants by IC sulpiride.

The role of the GABAergic system in the frontal cortex was also investigated because it has been reported that bicuculline administered IC increased the amounts of dopamine and excitatory amino acids recovered by dialysis in the striatum (40), and that, like dopamine, the $GABA_A$ agonist THIP, administered IC, blocked amphetamine-induced stereotypy (24). These data implicate a cortical GABAergic system in the control of stimulant-induced motor activity. The present data demonstrate that bicuculline, like sulpiride, when injected into the cortex enhances the stereotypic activity of amphetamine and cocaine. In addition, THIP injected into the cortex resembled dopamine because it inhibited the motor effect of the stimulants. These results indicate that, like a dopaminergic system, a GABAergic system in the cortex exerts a modulatory role in the motor response to stimulant drugs.

Because of the similarities in the functional roles of the dopaminergic and the GABAergic systems in the frontal cortex, the relationship between the two systems was investigated vis-à-vis the motor activity of the stimulant drugs. The results of these studies indicate that bicuculline injected into the cortex can block the cortical dopaminergic inhibition of stimulant-induced stereotypy; but sulpiride injected into the cortex does not block the THIP-induced inhibition of stimulant-induced stereotypy. These results suggest that the inhibitory effect of dopamine injected into cortex is mediated by GABA; therefore, the cortical inhibition of striatal dopaminergic activity appears to be the result of the stimulant-induced release of cortical dopamine, which releases cortical GABA, which inhibits the glutamatergic efferents that modulate the motor activity originating from a dopaminergic stimulus in the striatum. This conclusion was also proposed as a result of recent electrophysiological studies, which suggested that the cortical dopamine inhibition of the corticofugal output is mediated by GABA [(12,41,42); see also (3)]. Underpinning this scenario of stimulant-induced events in the frontal cortex, there is evidence that dopaminergic terminals synapse on GABA neurons, which then synapse on cortical glutamatergic neurons; therefore, a dopaminergic–GABAergic interaction in the frontal cortex may constitute the neurochemical basis for the dopaminergic inhibition of stereotypy (12,21,44,46).

The work described above represents a study of the influence of relatively selective dopaminergic and GABAergic drugs administered IC on the motor response to the psychomotor stimulants. The results suggest that both dopamine and GABA systems in the cortex serve to modulate the motor-stimulatory effect of the stimulants, presumably by inhibiting corticofugal pathways. These conclusions, which were derived from a pharmacological characterization of the motor response to amphetamine and cocaine, are consistent with those previously proposed on the basis of electrophysiological (12,41,42) and neuroanatomical (12,21,44,46) studies. Inhibition by the psychomotor stimulants of the corticofugal pathways, however, may not be limited to their action on dopamine and GABA systems because other neuroeffectors that can be released by these drugs may also be involved. There is, for example, electrophysiological data to indicate that serotonin in the cortex also exerts inhibitory effects (1,2,11). Of special interest is the recent observation that antagonism of inhibitory 5-HT_{1A} receptors on pyramidal neurons in the frontal cortex enhanced NMDA-induced striatal glutamate and aspartate release (14). These data support a role for both glutamate and serotonin in control of corticofugal pathways. Additionally, norepinephrine may also be involved because noradrenergic fibers arising from the locus coeruleus are distributed to all layers and regions of the neocortex (32); and there is considerable evidence to indicate that this monamine exerts inhibitory activity in the cortex (7,35). Whether these inhibitory systems directly interact with the dopamine–GABA systems described above or whether they act on independent pathways to inhibit the corticofugal neurons remains to be determined.

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