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The Role of the Striatum in the Mouse in Behavioral Sensitization to Amphetamine

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BEDINGFIELD, J. B., L. D. CALDER, D. K. THAI AND R. KARLER. *The role of the striatum in the mouse in behavioral sensitization to amphetamine.* PHARMACOL BIOCHEM BEHAV **56**(2) 305–310, 1997.—Previous results of pharmacological studies of the mechanisms of amphetamine- and cocaine-induced stereotypy in the mouse suggest the involvement of dopaminergic, glutamatergic and GABAergic systems in the striatum. The present experiments were designed to evaluate pharmacologically the role of these neuroeffector systems in behavioral sensitization. Whether administered systemically or in the striatum, pretreatment with the neurotransmitter antagonists, sulpiride, bicuculline and CPP, blocked both the induction and the expression of behavioral sensitization. Efforts to induce sensitization or evoke expression with intrastriatal microinjections of amphetamine, NMDLA or THIP were not successful. The data indicate that these three neuroeffector systems interact at the level of the striatum to mediate the induction and expression of behavioral sensitization to amphetamine. The results are discussed in light of our previous reports and lead to the conclusion that two groups of drugs that affect sensitization can be defined: (1) antagonists of the dopaminergic, GABAergic and glutamatergic systems which block the acute effects of amphetamine as well as the induction and expression of sensitization and (2) another group of drugs which antagonize only sensitization-associated phenomena. The mouse data suggest that both the induction and the expression of sensitization involve not only multiple loci but also novel neuroeffector systems.

Amphetamine Striatum Mouse Behavioral sensitization Stereotypy Dopamine Glutamate GABA

THE motor effects of amphetamine and cocaine are mediated by their indirect dopaminergic activity; in the case of stereotypy, the dopaminergic activity takes place specifically in the striatum (4). We recently reported that in mice at least three neurotransmitter systems, dopamine, glutamate and GABA, participate in the acute stereotypy response to amphetamine and cocaine (13,14); these results were obtained following the systemic administration of relatively selective antagonists of the three systems. Additionally, when the antagonists are administered intrastriatally they also block the effect of systemically administered amphetamine and cocaine, which suggests that all three systems within the striatum are necessary for the psychostimulants to manifest stereotypy. Consistent with this conclusion are the observations that the corresponding agonists of the three systems all induce stereotypy when locally administered in the striatum. That these three neurotransmitter systems interact within the striatum is consonant with neuroanatomical evidence; for example, both dopaminergic and glutamatergic afferents are known to terminate on striatal GABAergic neurons, the principal efferents from the striatum (20,23). In the present work we have extended the functional studies to determine what role the three neurotransmitter systems play in behavioral sensitization in the mouse. Because behavioral sensitization can be separated pharmacologically into two phases, induction and expression (16), the role of the three transmitter systems was also investigated in both phases of sensitization. As described earlier for the acute studies, the effects of the neurotransmitter antagonists on sensitization were first determined after systemic administration; these results then served as a basis for the identification of the striatum as a locus of their systemic effects on sensitization.

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-h light/dark cycle which corresponded with the day/night cycle. *d*-Amphetamine sulfate was obtained from the National Institute on Drug Abuse (Rockville, MD); sulpiride, (+)-bicuculline and (−)-

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bicuculline methiodide from Sigma Chemical Company (St. Louis, MO); (±)-3-(2-carboxypiperazin-4-yl)-propyl-L-phosphonic acid (CPP) and THIP HCl from Research Biochemicals Int. (Natick, MA); and *N*-methyl-DL-aspartic acid (NMDLA) from Chem. Biochem. Research (Salt Lake City, UT). All drugs were prepared using sterile isotonic saline immediately prior to administration. Drug dosages for systemic administration were calculated as mg of drug/kg of body weight; drug weights of the salts were not corrected for the weight of the free form. Systemically administered drugs were injected IP, except bicuculline, which was given SC. The volume of systemic injections was 0.1 ml/20 g of body weight. Due to its greater solubility, bicuculline methiodide was used for intracranial microinjections. Drugs administered directly into the striatum were expressed in μg/0.15 μl/bilateral injection.

Experimental Procedures

Sensitization was studied in terms of stereotypy, which was evaluated by a blinded observer. 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, for the response constitutes a stationary animal exhibiting repetitive head and fore-limb movements similar to grooming behavior. This end point appears to be the maximum stereotypic effect attainable by systemic drug administration in either control or sensitized animals and was used, therefore, as a quantal end point to measure stereotypy. This end point corresponds to a score of 8 on the graded scale of 9 described earlier for the motor responses of the Sprague-Dawley rat to increasing doses of amphetamine (6).

Animals were sensitized to stereotypy with a single, high dose of amphetamine (12 mg/kg) which acutely produced stereotypy in about 80% of the animals (1). Following sensitization, about 80% of the animals displayed stereotypy when challenged with a relatively low dose of amphetamine (6 mg/kg). Studies of the induction and expression of sensitization were generally conducted 24–48 h after sensitization, and the stereotypic response was measured 30 min after the challenge dose of amphetamine (approximate peak-effect time). All systemic studies employed 15 mice/group. Treatments and testing were in a test cage (as compared to a home cage) with three animals per cage (25 cm × 15 × cm × 13 cm), which eliminated the amphetamine lethality associated with aggregation (3).

For the intracranial drug studies, cannulae were bilaterally implanted in the striata of pentobarbital-anesthetized mice (10/group) by standard stereotactic techniques, as described previously (13). The coordinates for the placement of cannulae were: anterior to bregma, 1.0 mm; lateral, 2.0 mm; vertical, 3.5 mm. Mice were housed individually and all experimental procedures were conducted in their home cages. The injectors were connected by polyethylene tubing (PE-20) to two Hamilton 1 μl syringes. Drugs were bilaterally infused simultaneously in a volume of 0.15 μl/injection site over a period of 30 s. Antagonist and vehicle control were injected 2 min prior to systemic amphetamine. Experiments were performed about 7 days after surgery; placements were verified by histological examination.

TABLE 1

INFLUENCE OF SYSTEMICALLY ADMINISTERED NEUROTRANSMITTER ANTAGONISTS ON AMPHETAMINE-INDUCED SENSITIZATION

	% Stereotypy	
Pretreatment	Acute Response	Sensitization Test
Saline + saline	0	0
Saline + amphetamine	93*	87*
Sulpiride + amphetamine	27	7
CPP (low) + amphetamine	80*	13
CPP (high) + amphetamine	13	27
Bicuculline +amphetamine	20	20

Six groups of mice were pretreated with: either saline, sulpiride 75 mg/kg, CPP (low) 8 mg/kg, CPP (high) 20 mg/kg, or bicuculline 0.5 mg/kg. Except for the bicuculline group, the pretreatment was 30 min prior to receiving 12 mg/kg amphetamine; for bicuculline the pretreatment time was 15 min. All groups were tested for sensitization by a 6 mg/kg amphetamine challenge 24 h after pretreatment.

*Values significantly different from saline + saline control, as determined by a χ^2-test ($p < 0.01$).

RESULTS

The data shown in Table 1 were obtained from experiments designed to test the hypothesis that behavioral sensitization to amphetamine involves not only dopaminergic but also glutamatergic and GABAergic pathways. In these experiments all drugs were administered systemically and the acute response noted. As can be seen, the dopaminergic D_2 receptor antagonist sulpiride, the glutamatergic (NMDA) antagonist CPP, and the $GABA_A$ antagonist bicuculline all blocked the acute response to amphetamine. Only the relatively low dose of CPP (8 mg/kg) failed to block acutely induced amphetamine stereotypy. The high- and low-dose CPP data are generally consistent with those published previously (13,14). The sensitization test represents the results of a relatively low-dose amphetamine challenge (6 mg/kg) 24 h after the pretreatment in order to determine if the acute test induced sensitization. That sensitization occurred is shown in the saline + amphetamine pretreatment group in which 87% of the group in the sensitization test displayed stereotypy compared to 0% in the saline + saline control group. All of the antagonists used in the acute test blocked induction of sensitization. It appears that not only is the dopaminergic system required but also glutamatergic and GABA pathways are necessary for the induction of sensitization, as well as for the acute response to amphetamine.

The data shown in Table 2 were obtained from experiments specifically designed to test the possibility that the blockade of induction by the various antagonists shown in Table 1 resulted from a 24-h residual effect of the prior exposure to the antagonists. As can be seen, however, there was no apparent residual effect on a subsequent amphetamine test. It is also important to note that at no time during these experiments did the administered doses of the antagonists by themselves cause any behavioral effects; therefore, the observed blockades of the acute amphetamine response cannot be attributed to a masking effect. The dose of bicuculline, for example, caused no convulsions or preconvulsive motor activity, such as running; the threshold dose for such activity is about 0.75 mg/kg. These data argue that the antagonist-induced inhibition of sensitization shown in Table 1 represents a true blockade of

TABLE 2

24 H DRUG CONTROLS FOR THE DATA SHOWN IN TABLE 1

	% Stereotypy	
Pretreatment	Acute Response	Amphetamine Test
Saline + saline	0	80
Sulpiride + saline	0	87
CPP (low) + saline	0	80
CPP (high) + saline	0	80
Bicuculline + saline	0	80

Five groups of 15 mice each were pretreated with the antagonists or saline 30 min prior to saline. Antagonist doses were the same as those used in Table 1. All groups were challenged with amphetamine (12 mg/kg) IP 24 h following pretreatment. Drug-treated groups were compared to the saline control by a χ^2-test ($p > 0.05$).

sensitization rather than an effect of a drug-induced behavioral interaction.

To test if the locus of the blockade of the induction of sensitization shown in Table 1 is in the striatum, we obtained the results listed in Table 3 by administering the antagonists directly into the striatum instead of systemically. As reported previously (13,14), all three antagonists administered intrastriatally blocked the acute response to amphetamine given systemically; in addition, the same table shows that all three blocked the induction of sensitization, as indicated by the sensitization-test data. These results imply that a locus of action for the systemic effects of the antagonists is in the striatum.

The CPP data were obtained with the use of two doses, the high dose blocked the acute response to amphetamine while the low dose did not; both doses, however, blocked induction. These results are comparable to the high- and low-dose effects of systemic CPP shown in Table 1; however, the dose differential is enormous when CPP is administered intrastriatally. The CPP dose required to block induction alone was about two orders of magnitude less than that required to block the acute response. The validity of the dose differential was confirmed by other comparable studies which indicated that the minimum dose that consistently blocked the acute amphetamine response was 0.2 μg/injection site, and the minimum dose that consistently blocked induction of sensitization was 0.003 μg/injection site; to illustrate, a dose of 0.1 μg/injection did not consistently block the acute response and 0.001 μg/injection did not consistently block induction. All doses tested (0.0001–1 μg) indicated that any dose that blocked the acute response also blocked induction. A dose differential for the blockade of induction appeared to be unique for CPP because no such differential was observed for sulpiride and bicuculline; that is, for the last two drugs, the dose necessary to block induction also blocked the acute response. The significance of the observed dose differential for CPP is unclear; however, a possible explanation is that it reflects the existence of two distinct NMDA pathways: one involved in sensitization, the other in the acute effects.

The data in Table 4 result from a study designed to determine if the antagonism of sensitization by the neurotransmitter antagonists shown in Table 3 is the result of neural damage arising from the local application of the drugs. To test for this possibility we pretreated mice with the antagonists or vehicle and their acute response to an ED50 test dose of amphetamine

TABLE 3

INFLUENCE OF INTRASTRIATALLY ADMINISTERED NEUROTRANSMITTER ANTAGONISTS ON AMPHETAMINE-INDUCED SENSITIZATION

	% Stereotypy	
Pretreatment	Acute Response	Sensitization Test
Saline + saline	0	0
Saline + amphetamine	80*	80*
Sulpiride + amphetamine	0	0
CPP (low) + amphetamine	70*	10
CPP (high) + amphetamine	0	0
Bicuculline + amphetamine	0	20

Six groups of mice were pretreated in the striatum with an antagonist or saline 2 min prior to 12 mg/kg amphetamine IP. Antagonist doses in μg/side: sulpiride 0.01, CPP (low) 0.003, CPP (high) 0.2, bicuculline methiodide 0.01. All groups were tested for sensitization by a 6 mg/kg amphetamine challenge 24 h following pretreatment.

* Values significantly different from saline + saline control, as determined by a χ^2-test ($p < 0.03$).

evaluated 24 h later. The intrastriatal doses and volumes were identical to those used in Table 3 and were themselves behaviorally inactive. The data presented in Table 4 indicate that intrastriatal injection of antagonists did not alter the animals ability to respond subsequently to an ED50 dose of amphetamine; none of the drug pretreatments significantly affected the control response to amphetamine.

The data shown in Tables 5 and 6 represent the results of experiments that were designed to determine the effect of the three antagonists on the expression of sensitization. As shown in Table 5, the systemically administered antagonists all blocked the expression of sensitization. Similarly, in Table 6 all the antagonists administered intrastriatally also blocked the expression of sensitization.

The above results indicate that antagonists of D_2, NMDA and $GABA_A$ receptors all block the expression of sensitization evoked by systemically administered amphetamine. The data in Table 7 result from our attempts to evoke an enhanced

TABLE 4

FUNCTIONAL RESPONSIVITY TO AMPHETAMINE-INDUCED STEREOTYPY 24 H AFTER I.C. ADMINISTRATION OF DA, GLUTAMATE AND GABA ANTAGONISTS

	Amphetamine Challenge
Pretreatment	% Sterotypy
Saline	50
Sulpiride (0.01 μg)	60
CPP (0.2 μg)	60
CPP (0.003 μg)	50
Bicuculline (0.01 μg)	60

Five groups of 10 mice were pretreated with the antagonists or saline i.c. 2 min prior to saline IP administration. All groups were challenged with amphetamine (10 mg/kg) i.p. 24 h following pretreatment. Each drug-treated group was compared to the saline control by a χ^2-test ($p > 0.05$).

TABLE 5

INFLUENCE OF SYSTEMICALLY ADMINISTERED NEUROTRANSMITTER ANTAGONISTS ON THE EXPRESSION OF SENSITIZATION

Condition	Treatment	% Stereotypy
Control	Saline + amphetamine	20
Sensitized	Saline + amphetamine	93*
Sensitized	Sulpiride + amphetamine	20
Sensitized	CPP + amphetamine	33
Sensitized	Bicuculline + amphetamine	40

Four groups were sensitized with amphetamine (12 mg/kg) IP; a control group received saline only. 24 h later, mice were pretreated with antagonists 30 min prior to the test for sensitization by 7 mg/kg amphetamine IP. Antagonist doses were: sulpiride 75 mg/kg, CPP 20 mg/kg, bicuculline 0.5 mg/kg.

*Values significantly different from non-sensitized saline-amphetamine control, as determined by a χ^2-test ($p < 0.01$).

TABLE 7

FAILURE OF INTRASTRIATAL DOPAMINERGIC, GLUTAMATERGIC AND GABAERGIC AGONISTS TO EVOKE A SENSITIZED RESPONSE IN AMPHETAMINE-SENSITIZED MICE

Pretreatment	Treatment (i.c.)	% Stereotypy
Control	Amphetamine (7 μg)	20
Sensitized	Amphetamine (7 μg)	20
Control	NMDLA (0.5 μg)	20
Sensitized	NMDLA (0.5 μg)	30
Control	THIP (2 μg)	30
Sensitized	THIP (2 μg)	20

Three groups were pretreated IP with 12 mg/kg amphetamine (sensitized) and three received saline (control). 24 h following pretreatment, groups were challenged intrastriatally with agonist and observed for stereotypy. Each response from a sensitized group was compared statistically to its corresponding control by a χ^2-test ($p > 0.05$).

response in sensitized animals by the intrastriatal administration of the corresponding agonists of the three neurotransmitter systems involved. To insure that the groups designated as sensitized were in fact sensitized, two additional pretreatment groups (control and sensitized) were given amphetamine (8 mg/kg) intraperitoneally; no animals in the control group displayed stereotypy, whereas 90% of the animals in the sensitized group exhibited stereotypy. Relatively low doses of agonists were used in order to detect an enhanced response in sensitized animals. As indicated in Table 7, none of the agonists, amphetamine, NMDLA or THIP, applied locally to the striatum evoked a response significantly different from their respective controls, which suggests either that the expression of sensitization does not originate in the striatum, or that, if it originates in the striatum, factors other than the local effects of the agonists are involved.

DISCUSSION

The systemic drug data presented suggest that behavioral sensitization to stereotypy in the mouse requires functional dopaminergic, glutamatergic and GABAergic systems. These three neurotransmitter systems, which were previously shown to be essential for the acute response to amphetamine and cocaine (13,14), are also necessary for both the induction (Table 1) and the expression (Table 5) of amphetamine-induced sensitization. The results of the systemic drug studies, therefore, indicate that the three systems appear to be basic components of the mechanism of amphetamine-induced stereotypy in both sensitized and non-sensitized animals.

TABLE 6

INFLUENCE OF INTRASTRIATALLY ADMINISTERED NEUROTRANSMITTER ANTAGONISTS ON THE EXPRESSION OF SENSITIZATION

Condition	Pretreatment	Sensitization Test
Control	Saline	0
Sensitized	Saline	80*
Sensitized	Sulpiride (0.01 μg)	0
Sensitized	CPP (0.2 μg)	0
Sensitized	Bicuculline (0.01 μg)	0

Four groups were sensitized with amphetamine (12 mg/kg) IP, another group (control) received saline only. 24 h following sensitization mice were pretreated intrastriatally with the drug doses indicated as μg/side and challenged 30 min later with amphetamine (7 mg/kg, IP).

*Significantly different from control, as determined by a χ^2-test ($p < 0.01$).

The locus of the interaction for the three neurotransmitters was originally postulated to be in the striatum because there exists an abundance of neuroanatomical, neurochemical and electrophysiological evidence of interrelationships among these three systems within that structure (2,19,20,22,23,28). On this basis we determined earlier that the three transmitters in the striatum of naive animals are essential components in the reaction sequence initiated by the acute administration of indirect dopamine agonists, amphetamine and cocaine (14). The data described above similarly indicate that all three transmitter systems in the striatum are also essential for both the induction (Table 3) and expression (Table 6) of sensitization to amphetamine.

The results of the drug studies conducted to date in our laboratory implicate the existence of two distinct groups of drug antagonists that affect amphetamine-induced sensitization to stereotypy in the mouse: One group, described above, consists of antagonists of dopamine (D_2), glutamate (NMDA) and GABA ($GABA_A$); these drugs characteristically block the acute response to amphetamine, as well as both the induction and the expression of sensitization. In contrast, the other group of drugs is ineffective against the acute response; nevertheless, they block both induction and expression of sensitization; therefore, their activity appears to be relative only to sensitization. This group of drugs includes the calcium-channel blockers (18), protein-synthesis inhibitors (17), non-NMDA glutamate-receptor antagonists (15), and nicotinic-cholinergic antagonists (12). A summary of the results of these studies with representative drugs is given in Table 8. The comparative pharmacological data shown in Table 8 indicate that the sensitized response, although behaviorally indistinguishable from the response in naive animals, involves the participation of novel components in its mechanism of action. How these novel effectors function or which brain structures are involved remains to be determined.

The ability of the antagonists administered intrastriatally to block the induction of sensitization may also bear on the locus of the phenomenon. Others have shown that amphetamine applied locally in the rat striatum does not result in sensitization (5,7,11); we have obtained similar negative results

TABLE 8

SUMMARY OF QUALITATIVE EFFECTS OF VARIOUS DRUGS ADMINISTERED SYSTEMICALLY ON THE NON-SENSITIZED AND SENSITIZED RESPONSES TO AMPHETAMINE

Drugs	Non-sensitized	Sensitized	
		Induction	Expression
D_2 antagonist: sulpiride (13,14)	+	+	+
NMDA antagonist: CPP (13,14)	+	+	+
$GABA_A$ antagonist: bicuculline (14)	+	+	+
Calmodulin inhibitor: calmidazolium (unpublished data)	+	+	+
Nicotine antagonist: mecamylamine (12)	−	+	+
Calcium channel blocker: diltiazem (18)	−	+	+
Protein synthesis inhibitor: anisomycin (17)	−	+	+
Non-NMDA glutamine antagonist: DNQX (13,15)	−	+	+

All drugs administered intraperitoneally. + = blockade; − = no effect.

following the local application of amphetamine in the mouse striatum (unpublished data). Sensitization, however, can be produced by injecting amphetamine in the area of the dopamine cell bodies in the ventral tegmental area and the substantia nigra (8,10,11,25). Consistent with the assumption that sensitization occurs at the cell-body region are the results from in vivo dialysis studies which indicate that amphetamine administered systemically releases dopamine in the cell-body region and that the local administration of dopamine (24) or glutamate (9) antagonists in this area block the development of sensitization. The locus of the induction of sensitization, however, is complicated by the observations described above that sensitization induced systemically can also be blocked by the local administration of antagonists in the striatum. In these experiments, there is no antagonist physically present in the dopamine cell-body region; nevertheless, sensitization fails to develop. Similarly, others have reported that lesioning the fimbria fornix, a hippocampo-accumbal glutamatergic projection (27) or antagonizing NMDA receptors in the amygdala (9) can also block induction of sensitization. These data suggest that, although induction of sensitization may originate from an effect on dopamine cell bodies, the phenomenon involves multiple loci and may be visualized as the activation of a circuit encompassing many brain structures.

The complexity of sensitization is further compounded by the data shown in Table 7 in which none of the drugs, whether they be dopaminergic, glutamatergic or GABAergic, that were previously shown to evoke stereotypy when applied intrastriatally could produce a sensitized response in the striatum in previously sensitized animals. In contrast, others have shown that amphetamine applied to the nucleus accumbens of sensitized rats will evoke a sensitized locomotor response (21). Whether these differences between the rat and mouse data are species related or methodological remain to be determined; nevertheless, the mouse data suggest that to evoke a sensitized response requires functions in addition to those activated by the direct stimulation of the basic neuroeffectors for stereotypy in the striatum.

The present communication, as well as data previously reported (26), reveal an emerging complexity of the brain mechanisms that constitute sensitization. The stereotypic response in sensitized and non-sensitized animals appears to involve at least three basic neurotransmitter systems in the striatum, the dopaminergic, glutamatergic and GABAergic systems; however, sensitization, both its induction and its expression, is associated with the introduction of novel systems which do not normally function in the non-sensitized response to amphetamine. Furthermore, the data indicate that sensitization may not occur in a specific brain locus; rather, it appears to require a circuit involving multiple brain loci. These intricacies are further complicated by the observation that persistence of the sensitized response to direct dopaminergic agonists is greatly diminished compared to that of mice induced by the indirect agonists (1). This observation implies that the characteristic persistence of sensitization, like induction and expression, also involves a specific mechanism. At present, the prevailing theory of psychostimulant sensitization is that induction occurs by an action of released dopamine in the area of the dopamine cell bodies and that expression results from the enhanced release of dopamine in the accumbens and striatum (10). How the complex characteristics of sensitization described above relate to this theory of sensitization remains to be determined.

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