Pharmacology Biochemistry and Behavior, Vol. 44, pp. 843–850, 1993
Printed in the U.S.A.

0091-3057/93 $6.00 + .00

Fetal Behavior and the Dopamine System: Activity Effects of D_1 and D_2 Receptor Manipulations

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Received 28 May 1992

MOODY, C. A., S. R. ROBINSON, L. P. SPEAR AND W. P. SMOTHERMAN. *Fetal behavior and the dopamine system: Activity effects of D_1 and D_2 receptor manipulations.* PHARMACOL BIOCHEM BEHAV **44**(4) 843–850, 1993.—Binding studies have indicated that D_1 and D_2 dopamine receptor subtypes are present in rats before birth, but it is not known whether these receptors are functional during the prenatal period. In the present study, day-21 rat fetuses were prepared for direct observation after pharmacological manipulation of D_1 and/or D_2 receptors. The D_1 agonist SK&F38393 induced a marked increase in fetal activity (i.e., forelimb, rearlimb, and head movements) while the D_2 agonist quinpirole produced a slight suppression in activity. Coadministration of both agonists resulted in low levels of fetal activity, suggesting an interaction between D_1 and D_2 receptors. Administration of the D_2 antagonist sulpiride resulted in little change in fetal behavior but was effective in blocking the behavioral activation induced by the D_1 agonist. The D_1 antagonist SCH23390, administered alone or in combination with the D_2 antagonist, produced a modest increase in fetal activity that included mouthing and facial wiping behavior. These data provide evidence that the dopamine system is functional and capable of mediating behavioral effects in the near-term rat fetus. Further, manipulation of dopamine receptors results in a different pattern of behavioral effects than has been reported in older animals. The observation that fetal behavior is influenced by these pharmacological challenges suggests that drugs of abuse known to affect the dopamine system, such as cocaine, may cause profound changes in fetal behavior in utero that could consequently lead to alterations in behavioral and CNS development.

Dopamine | D_1 receptor | D_2 receptor | Rat fetus | Prenatal behavior | SK&F38393 | SCH23390 | Quinpirole | Sulpiride

BIOCHEMICAL and ligand binding studies have demonstrated the existence of at least two dopamine (DA) receptor subtypes, termed D_1 and D_2 (4,9,16). Selective agonist stimulation at either receptor has been shown to elicit behavioral responding in developing animals, although the behavioral responses elicited are not always adult-typical in nature (24). Administration of both the D_1 agonist SK&F38393 as well as the D_2 agonist quinpirole induces forward locomotion, probing (pushing of the snout against a solid surface or object), headlifting, and mouthing in 3-day-old rat pups (24). At 10 days of age, a moderate dose of SK&F38393 elicits a sniffing response (24), whereas a higher dose of this compound induces adult-typical grooming behavior (21). In contrast, quinpirole administration in infant rat pups decreases grooming (21,24). By 21 days of age, a moderate dose of either the D_1 agonist SK&F38393 or D_2 agonist quinpirole are both able to elicit the adult-typical behavioral response of grooming (D_1 specific) and vertical movements (D_2 specific) (24). Specific D_1 and D_2 receptor antagonists also exert behavioral effects in developing animals. The D_1 antagonist SCH23390 and the D_2 antagonist spiroperidol have been shown induce catalepsy during the second and third weeks of life (3,8). These experimental results demonstrate that both D_1 and D_2 receptors are capable of engaging behavior in the developing rat during the early postnatal period.

In addition to the ability of these receptors to function independently, D_1 and D_2 receptors appear to be positively coupled in developing and adult animals (5,21,24,25,37,38), although some instances of inhibitory coupling have also been reported (6,21,24,25,27). Coadministration of selective D_1 and D_2 agonists elicits synergistic increases in vertical movements, roll/curling (at P3), and forward locomotion (at P10), as well as stereotypic licking behavior at 21 days of age and adulthood (2,5,20,24,38). In some instances, stimulation of D_1 receptors by endogenous or exogenous agonists is necessary for (or "enables") the expression of D_2-specific behavioral effects (1,

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19,21,25,37,38), whereas the converse does not appear to be true, with D_1 receptor-mediated responses being either unaffected or enhanced by D_2 receptor blockade (10,21,22). However, in developing rats depletion of endogenous dopamine reduces responding to both D_1 and D_2 agonists administered separately, suggesting a reciprocal codependence of these receptor subtypes early in life (25).

Ligand binding studies have revealed that D_1 and D_2 receptors are present early in development (11,28). D_1 and D_2 receptor gene expression can be detected as early as gestational days 17 and 14, respectively (12,13). The finding that DA receptors are coupled to guanine nucleotides early in development (28) suggests that they are functional during the prenatal period. However, the specific role that D_1 and D_2 receptor subtypes play in the regulation of fetal behavior has yet to be determined. The present set of experiments was conducted to examine the functionality of the dopamine system in mediating fetal motor behavior. This is of particular importance given that prenatal exposure to various drugs of abuse (i.e., cocaine), which directly influence dopaminergic functioning, may alter the natural course of endogenous dopamine system development. These experiments manipulated activity at D_1 and D_2 receptors with selective agonist and antagonist drugs, administered either separately or in combination, to examine behavioral responses of fetal rats on day 21 of gestation (E21).

GENERAL METHOD

SUBJECTS

Fetal rats used as subjects in this study were produced in timed matings of Sprague-Dawley rats (Charles River Laboratories, Wilmington, MA). Adult females were housed in groups of three in breeding cages (36 × 47 × 20 cm) and maintained at constant room temperature (22°C) under a 12 L : 12 D cycle (lights on at 0700 h). Food and water were available ad lib. Vaginal smears were collected daily during a 4-day breeding period to date conception (presence of sperm = day 0). Rats were maintained in accordance with guidelines for animal care established by the National Institutes of Health (PHS publication 86-23) and the International Society for Developmental Psychobiology. Animal subjects were humanely sacrificed at the conclusion of experimental testing.

Prenatal preparation

Subject fetuses were prepared for behavioral observation on day 21 of gestation (term = 21.5 days). Pregnant rats were briefly anesthetized with ether before receiving a 100-μl injection of 100% ethanol into the spinal cord between vertebrae L1-L2. This procedure results in an irreversible chemical transection of the spinal cord at the low thoracic level that eliminates sensation in the pregnant rat's abdomen and lower extremities (34). Upon confirmation that the spinal preparation was complete, the pregnant rat was placed in a Plexiglas holding apparatus and immersed in a buffered isotonic saline bath maintained at 37.5°C. To observe fetal subjects, both horns of the uterus were externalized through a low midline incision and individual fetal subjects were delivered from the uterus and amniotic sac into the bath. Throughout these procedures, care was taken to preserve the subject's attachment via the umbilical cord to the placenta and uterus. Fetal condition was monitored throughout the observation session to ensure that the subject remained fully oxygenated. A 20-min period elapsed before the onset of observation to provide time for the pregnant rat and subject fetuses to accommodate to the bath environment.

Administration of agonist and antagonist drugs

Dopamine D_1 and D_2 receptor agonists, antagonists, agonist-antagonist mixtures, or vehicle controls were administered to individual fetal subjects. Drugs were administered via an IP injection of 50 μl of the drug or vehicle solution into the mid-abdominal cavity of the fetal subject with a 30-ga hypodermic needle. During the injection, the fetus remained submerged within the saline bath. Drug solutions were prepared daily from frozen aliquots. In experimental protocols calling for administration of two drugs (e.g., agonist and antagonist), solutions containing a mixture of the two drugs at the desired dosages were prepared and delivered in a single 50-μl IP injection. In all experiments, the observer was blind to the drugs administered to fetal subjects.

Two dopamine agonist drugs were employed. SK&F38393 (SKF; Research Biochemicals Inc., Natick, MA) is a D_1 receptor agonist that was administered at a dosage of 1.0 mg/kg. Quinpirole (Eli Lilly, Indianapolis, IN) is a D_2 receptor agonist that was administered at a dosage of 1.0 (Experiment 1) or 5.0 (Experiment 2) mg/kg. The two dopamine antagonist drugs used in this study included the D_1 antagonist SCH23390 (SCH; Research Biochemicals) administered in a dosage of 5.0 mg/kg and the D_2 antagonist sulpiride (Sigma Chemical Co., St. Louis, MO) administered in a dosage of 5.0 mg/kg. Dosages for dopamine agonists were selected on the basis of dose-response studies conducted with 3-day-old rat pups (24); dosages for dopamine antagonists were within the range demonstrated to exert behavioral effects in developing and adult rats (15,21).

Behavioral Observations

Immediately after drug administration, the behavior of each subject fetus was observed in an 8-min observation session. All instances of fetal activity, including individual movements of the forelimbs, rearlimbs, head, and mouth, were noted and entered into a microcomputer serving as a real-time event recorder, preserving information about the frequency and timing of fetal behavioral events. In addition to these general categories of fetal behavior, each occurrence of facial wiping behavior by the subject fetus was recorded. An instance of facial wiping was defined as the placement of one or both forelimbs in contact with the side of the face and movement of the limb(s) in a rostral direction (31,32). Each movement was treated as a discrete event, permitting the sum of independent events in the five movement categories to provide a measure of overall fetal activity (30).

Data Analysis

Behavioral records, comprising frequency counts of overall activity and the specific categories of forelimb, rearlimb, head, mouth, and facial wiping behavior, were divided into eight 1-min intervals and compared in a series of five (treatments) × eight (time intervals) repeated-measures analyses of variance (ANOVAs). In both experiments, the treatment factor included drugs administered to manipulate the dopamine system and the vehicle injection control. Where a significant main effect of drug treatment or interaction effect was evident, separate planned comparisons involving two-factor

ANOVAs were conducted to assess whether the behavior induced by each drug treatment differed from the behavior of saline-injected controls. Facial wiping behavior was rare in all but a few treatment groups and was subjected to log (× +1) transformation prior to analysis.

EXPERIMENT 1: FETAL BEHAVIORAL RESPONSES TO D_1 OR D_2 RECEPTOR AGONISTS AND ANTAGONISTS

Although DA receptors have been detected in the perinatal nervous system early in development (11,28), little information is available on the functional status of these receptors with respect to their ability to engage motor behavior in the fetus. The objective of Experiment 1 was to examine the effects of selective DA receptor agonist and antagonist drugs on fetal motor behavior.

METHOD

A total of 86 fetal subjects was tested in Experiment 1. A maximum of two fetuses in each pregnancy were assigned to each of the five treatment groups: isotonic saline (SAL, n = 10), SK&F (1.0 mg/kg; n = 20), quinpirole (1.0 mg/kg; n = 20), SCH (5.0 mg/kg; n = 18), or sulpiride (5.0 mg/kg; n = 18). Immediately following IP injection of the drug or saline vehicle, fetuses were observed for 8 min and their behavior continuously recorded.

RESULTS AND DISCUSSION

The two-factor ANOVAs comparing various measures of fetal behavior all indicated significant interactions of drug treatment with time after injection, $F(28, 567) = 11.1$, $p < 0.001$ (overall activity), $F = 5.2$, $p < 0.001$ (forelimb), $F = 7.2$, $p < 0.001$ (rearlimb), $F = 9.0$, $p < 0.001$ (head), $F = 5.4$, $p < 0.001$ (mouth), and $F = 5.1$, $p < 0.001$ (facial wiping) (Figs. 1 and 2). Subjects in the saline control group did not exhibit a change in activity over the 8-min observation session. The results of the planned comparison of each drug treatment with the saline control group are presented in Table 1. The D_1 agonist (SK&F) promoted a pronounced increase in overall fetal activity that was evident during the last 4–5 min of the observation session. This fourfold increase in activity involved forelimb, rearlimb and head movements. The D_1 antagonist (SCH) also increased fetal activity, although the specific behaviors induced by the D_1 antagonist differed from those seen following administration of the D_1 agonist. Specifically, the doubling in overall fetal activity induced by the D_1 antagonist was predominantly a result of increases in mouthing and facial wiping behavior. The frequency of mouthing and wiping activity appeared to peak about min 5–6 of the session and diminished thereafter. The D_2 agonist (quinpirole) resulted in a significant decrease in overall fetal activity relative to saline controls. Among individual behavioral categories, decreased activity was significant for the forelimb and rearlimb measures, which constitute the most common categories of movement in control fetuses. The D_2 antagonist (sulpiride) did not produce any significant changes in fetal behavior.

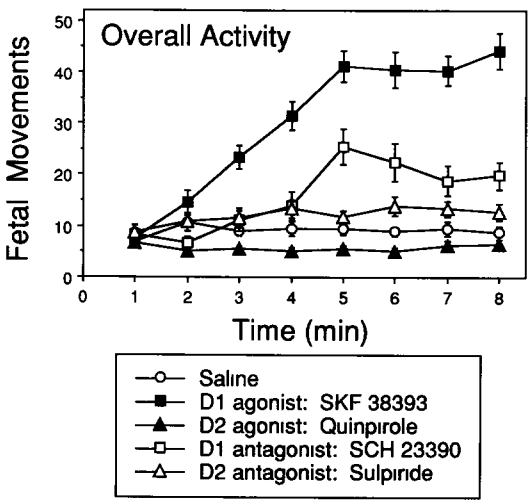

FIG. 1. Overall activity expressed by E21 fetuses in Experiment 1. Points represent mean number of movements per min; vertical lines depict SEM.

The results of Experiment 1 suggest that D_1 receptor activation produces marked changes in fetal behavior. This conclusion is consistent with previous reports that D_1 agonist administration results in increased activity in 3-day-old rat pups (24). In contrast to the increase in activity that has been observed in neonatal to adult rats following D_2 receptor stimulation, fetal rats exhibit a suppression in limb movements following administration of the D_2 agonist quinpirole. The fetal response to the D_1 and D_2 antagonists also differed from that seen postnatally. Blockade of either the D_1 or D_2 receptor with selective antagonists did not produce the typical inactivity described in infant to adult rats (3,8,18). Administration of SCH resulted in substantial increases in mouthing movements, a response different from the induction of catalepsy observed later in life, whereas sulpiride had little or no observable effect on fetal behavior.

EXPERIMENT 2: INTERACTION EFFECTS OF D_1 AND D_2 RECEPTORS

The findings of Experiment 1 demonstrated that the dopamine system is functional in the near-term rat fetus. In addition, the results raised a series of questions regarding the effects of D_1 and D_2 receptor manipulation: a) Are fetal D_1 and D_2 receptors coupled in a fashion similar to that reported in older, postnatal subjects (24)? More specifically, will combined administration of both agonists result in a synergistic behavioral response? b) Are the effects induced by SK&F due solely to D_1 receptor stimulation or does D_2 receptor activity, stimulated by endogenous DA, also play a role? c) Is the suppression in activity induced by the D_2 agonist quinpirole due to stimulation of D_2 autoreceptors? d) Are the increases in mouthing and wiping movements promoted by the D_1 antagonist SCH due to an increase in endogenous DA activity at the D_2 receptor in the absence of interference from D_1 receptor activation? In Experiment 2, these questions were addressed, respectively, by treating subjects with a combination of D_1 and D_2 agonists (SK&F + quinpirole), a combination of D_1 agonist and D_2 antagonist (SK&F + sulpiride), a higher dosage of the D_2 agonist (5.0 mg/kg quinpirole) to eliminate potential autoreceptor effects, and a combination of D_1 and D_2 antagonists (SCH + sulpiride).

METHOD

A total of 89 fetal subjects was tested in Experiment 2. A maximum of two fetuses per dam were assigned to one of five treatment groups: isotonic saline (SAL, n = 9), SK&F +

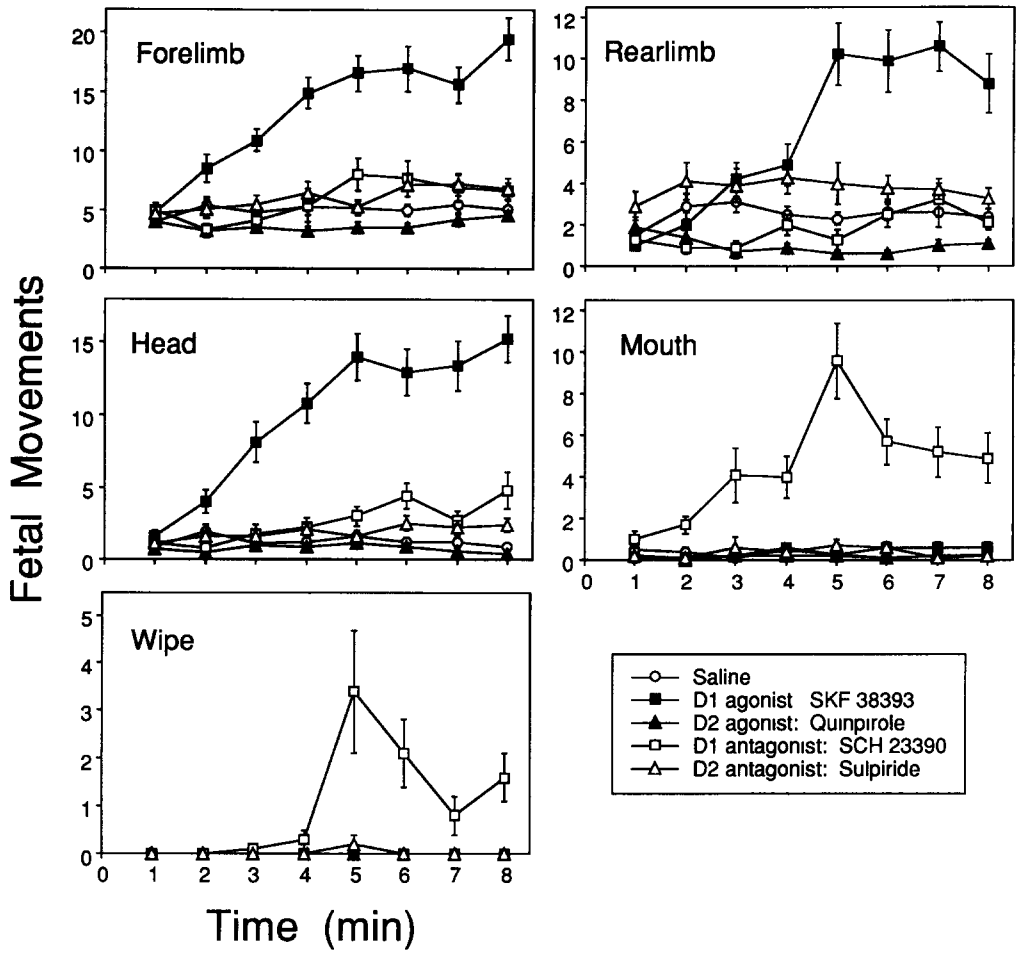

FIG. 2. Mean activity (±SEM) in five specific categories of fetal behavior in Experiment 1.

quinpirole (n = 20), SK&F + sulpiride (n = 20), quinpirole (n = 20), or SCH + sulpiride (n = 20). Except for the high dose of quinpirole (5.0 mg/kg), dosages for each drug were the same as reported in Experiment 1. Coadministration was accomplished by a single injection of a mixture of the two drugs. Immediately following IP injection of the drugs or saline vehicle, fetuses were observed for 8 min and their behavior continuously recorded.

TABLE 1

RESULTS OF PLANNED COMPARISONS OF DRUG TREATMENT GROUPS WITH SALINE VEHICLE-INJECTED CONTROLS IN EXPERIMENT 1

	Overall Activity	Forelimb	Rearlimb	Head	Mouth	Wipe
SK&F38393 (D_1 agonist)	+	+	+	+	NS	
Quinpirole (D_2 agonist)	−	−	−	NS	NS	
SCH23390 (D_1 antagonist)	+	NS	NS	NS	+	+
Sulpiride (D_2 antagonist)	NS	NS	NS	NS	NS	

+, significant ($p < 0.01$) increase in movement in drug-treated fetuses; −, significant decrease in movement in drug-treated fetuses; NS, no significant difference ($p > 0.01$).

RESULTS AND DISCUSSION

The two-factor ANOVAs comparing various measures of fetal behavior all indicated significant interactions of drug treatment with time after injection, $F(28, 588) = 5.8$, $p < 0.001$ (overall activity), $F = 3.1$, $p < 0.001$ (forelimb), $F = 2.8$, $p < 0.001$ (rearlimb), $F = 3.7$, $p < 0.001$ (head), $F = 4.4$, $p < 0.001$ (mouth), and $F = 2.5$, $p < 0.001$ (facial wiping) (Figs. 3 and 4). Subjects in the saline control group did not exhibit a change in activity over the 8-min observation session. The results of the planned comparison of each drug treatment with the saline control group are presented in Table 2. Coadministration of SK&F + quinpirole did not result in a change in overall activity but produced a small but significant reduction in head and mouth movements. Coadministration of SK&F + sulpiride produced a modest increase in overall activity, which resulted from the small but nonsignificant increase in movement in each of the specific behavioral categories. The higher dosage of the D_1 agonist (quinpirole) produced a significant decrease in overall fetal activity, which was evident in the virtual elimination in rearlimb movements and significant reduction in head movements. Coadministration of SCH + sulpiride resulted in a twofold increase in overall fetal activity, which comprised increases in forelimb, head, mouth, and facial wiping behavior.

There was no evidence that fetal rats exhibit the form of synergism following simultaneous stimulation of D_1 and D_2 receptors that has been described in postnatal subjects (2,24). Coadministration of D_1 and D_2 agonists resulted in little change in fetal behavior, unlike administration of the D_1 agonist alone. Similarly, coadministration of the D_1 agonist and D_2 antagonist resulted in fetal activity that was diminished relative to subjects treated with the D_1 agonist alone. These findings imply that some optimal level of D_2 activity is necessary for the D_1 manipulations to exert behavioral effects in the fetus, with either blockade or stimulation of the D_2 receptor attenuating D_1 agonist responding. The high dose of the D_2 agonist quinpirole suppressed fetal activity, suggesting that the reduced activity seen in response to the lower dose of quinpirole (Experiment 1) is not attributable to stimulation of D_2 autoreceptors. Blockade of dopamine receptors by coadministration of D_1 and D_2 antagonists resulted in similar behavioral effects to administration of the D_1 antagonist alone. Specifically, both treatments promoted mouthing and facial wiping activity, which were rare or absent in fetuses exposed to saline injection or other drug treatments.

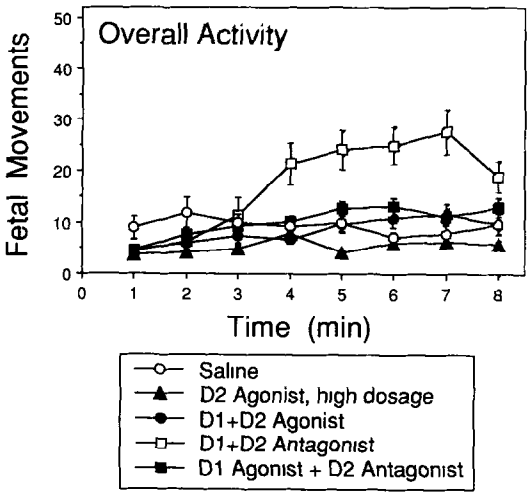

FIG. 3. Mean overall activity expressed by fetuses in Experiment 2.

GENERAL DISCUSSION

The findings of these experiments provide the first direct evidence that pharmacological manipulations of the dopamine system can produce effects on fetal motor behavior. Stimulation of D_1 receptors with a receptor-specific agonist induces a general increase in fetal activity, including forelimb, rearlimb, and head movements. D_2 agonist administration, however, results in a general suppression of all categories of fetal movement at both moderate and high dosages. While the D_1 agonist-induced increase in forelimb, rearlimb, and head movements may be related in a general way to locomotor effects described in neonatal rat pups following D_1 agonist (24) or L-DOPA administration (17), fetal rats showed no evidence of organized, rhythmic stepping behavior (36). In contrast to the behavioral activation promoted by D_2 receptor stimulation in rat pups, D_2 agonist administration resulted in a suppression in fetal activity. Because this effect was evident at both moderate and high dosages, it is unlikely to be autoreceptor mediated (7).

Blockade of D_1 receptors with SCH induces mouthing activity and spontaneous facial wiping behavior, while administration of the D_2 antagonist sulpiride produces no observable behavioral effect. These antagonist-induced effects on fetal behavior appear to differ from the catalepsy reported following D_1 or D_2 blockade in postnatal preweanling to adult rats (3,8,18). Given the fairly high dose of SCH23390 used in the present experiments, nonspecific effects of this D_1 antagonist potentially could account for the different pattern of behavioral effects. However, ontogenetic differences in the effects of D_1 and D_2 manipulations also may account for the observed pattern of results. The expression of facial wiping following D_1 antagonist administration was consistent: More than 85% of the fetal subjects treated with SCH23390 exhibited wiping behavior. This finding contrasts sharply with virtually all previous studies of nonevoked behavior in both unmanipulated and drug-treated fetal rats (30,35), where fetuses have been observed to rarely exhibit facial wiping in the absence of explicit tactile or chemosensory stimulation (33). The ability of D_1 receptor blockade to promote wiping behavior, as well as a pronounced increase in mouthing, also stands in contrast to reports of grooming (21) and oral activity (24) promoted by D_1 stimulation in the early postnatal period. One interpretation is that reversal in DA mediation of these behavior patterns occurs between the pre- and postnatal periods, with mouthing and facial wiping being inhibited by endogenous activity at the D_2 receptor in the fetus.

The results from these experiments also suggest that D_1 and D_2 receptors are functionally coupled during the prenatal period. The marked activational effect of the D_1 receptor agonist appears to be inhibited by simultaneous administration of either a D_2 agonist or antagonist. This finding suggests that a moderate level of D_2 receptor activity, provided by endogenous DA release, is necessary to potentiate D_1-mediated behavioral effects in the rat fetus. The specific behavioral effects promoted by D_1 receptor manipulation, and the modulation of D_1 effects by D_2 manipulation, provide evidence that D_1 and D_2 receptors are functional and coupled during the prenatal period. This coupling differs from that observed after birth, where synergistic responding is typically observed fol-

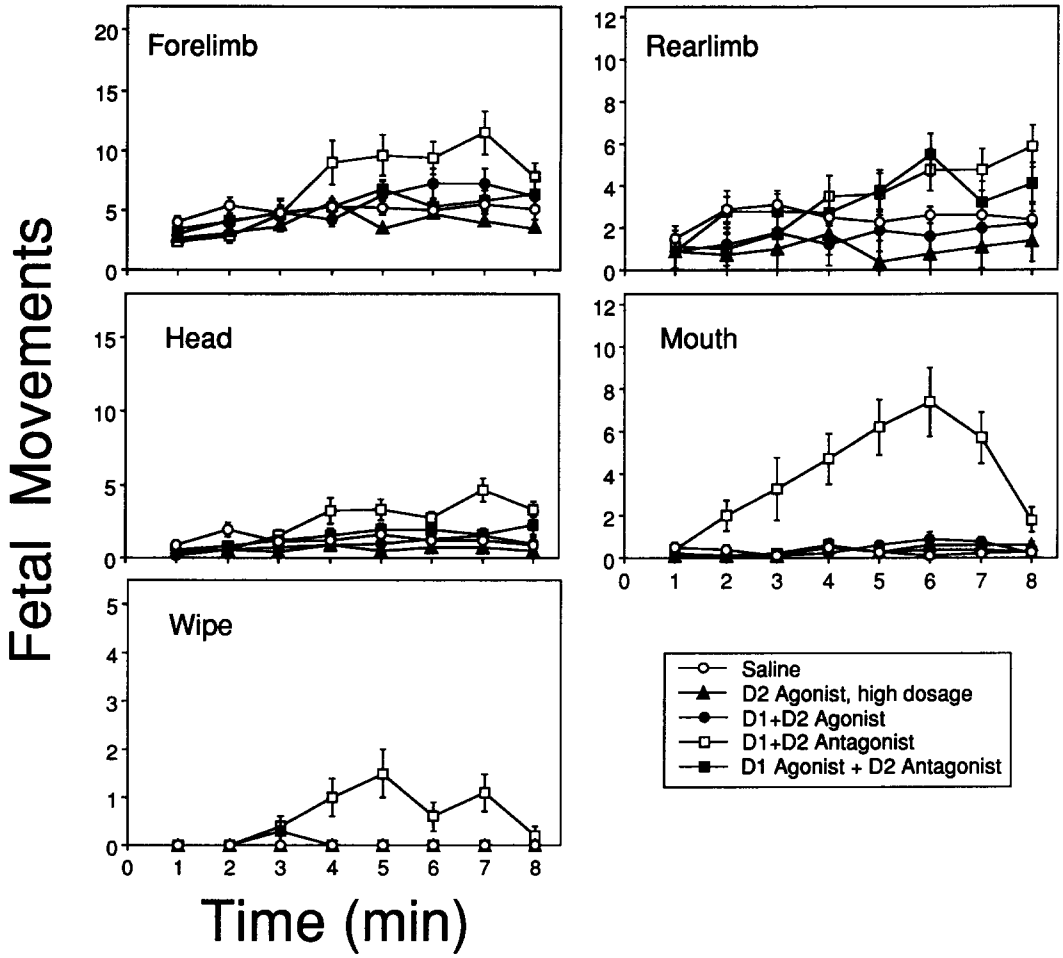

FIG. 4. Mean activity in five behavioral categories in Experiment 2.

lowing combined administration of D_1 and D_2 agonists (2,24,37,38). Inhibition of specific D_1 agonist effects by either a D_2 agonist or depletion of endogenous dopamine has occasionally been observed postnatally (24,25). Such findings are similar to the behavior of fetal subjects in the present study.

The effectiveness of these pharmacological manipulations to alter fetal behavior suggests that drugs of abuse that affect the dopamine system, such as cocaine, may cause profound changes in fetal behavior in utero and thereby alter the subsequent course of behavioral and CNS development. For in-

TABLE 2

RESULTS OF PLANNED COMPARISONS OF DRUG TREATMENT GROUPS WITH SALINE VEHICLE-INJECTED CONTROLS IN EXPERIMENT 2

	Overall Activity	Forelimb	Rearlimb	Head	Mouth	Wipe
Quinpirole (D_2 agonist, high dose)	–	NS	–	–	NS	
SK&F38393 + quinpirole (D_1 + D_2 agonist)	NS	NS	NS	–	–	
SK&F38393 + sulpiride (D_1 agonist + D_2 antagonist)	+	NS	NS	NS	NS	
SCH23390 + sulpiride (D_1 + D_2 antagonist)	+	+	NS	+	+	+

+, significant ($p < 0.01$) increase in movement in drug-treated fetuses; –, significant decrease in movement in drug-treated fetuses; NS, no significant difference ($p > 0.01$).

stance, cocaine exerts its effects through interference with dopamine reuptake. Prenatal cocaine exposure alters functioning of the dopamine system, which in turn promotes lasting changes in postnatal responsiveness to dopaminergic drugs (23,29). Because functional activity in neural systems is an important determinant in their development (14,26), fetal exposure to drugs such as cocaine and amphetamine that alter dopamine regulation during the late prenatal period may alter the course of development of the endogenous dopamine system.

ACKNOWLEDGEMENTS

This research is supported by NICH&HD (NIH) Grants HD 16102 and HD 00719 to W.P.S., HD 28231 to W.P.S. and S.R.R., and Grants DA 00140 and DA 04478 to L.P.S. The authors also thank Eli Lilly and Company for their generous gift of quinpirole.

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