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Modulation of Dopamine Binding in the Fetal Rat: Effects of Milk and Exogenous Opioid Manipulation

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ANDERSEN, S. L., S. M. UMPHRESS, S. R. ROBINSON, W. P. SMOTHERMAN, K. M. WARD AND P. KEHOE. *Modulation of dopamine binding in the fetal rat: Effects of milk and exogenous opioid manipulation.* PHARMACOL BIOCHEM BEHAV 46(2) 377–381, 1993.—Presentation of milk to the newborn rat promotes changes in sensory and motor behavior and concomitant changes in both endogenous opioid and dopamine systems. The present study employed an in vivo binding technique with a tritiated ligand for the D_2 receptor ([^{3}H]raclopride) to examine the effects of intraoral milk infusion and opioid manipulations on dopamine activity in the term rat fetus (E21). In Experiment 1, fetuses received a series of milk infusions, which resulted in decreased occupancy at D_2 receptors by the endogenous ligand, dopamine, in striatal, septal, and hypothalamic brain regions. In Experiment 2, fetuses were pretreated with morphine, the μ-agonist [D-Ala^2,NMe-Phe^4,Gly^5-ol]-enkephalin (DAMGO), the κ-agonist U50,488, or saline. Opioid manipulations had no effect on binding at D_2 receptors. These results confirm that intraoral milk infusion can modulate activity in the dopamine system of the near-term fetal rat.

Rat fetus In vivo receptor binding [^{3}H]Raclopride Endogenous opioids μ κ

THE behavior of perinatal rats can be markedly altered by brief exposure to milk delivered into the mouth. Specifically, behavioral responsiveness to cutaneous or thermal stimulation following an intraoral milk infusion is significantly attenuated in both newborn pups (5) and rat fetuses on the last 2 days of gestation (26). Fetal rats demonstrate a characteristic facial wiping response to cutaneous stimulation of the facial region. The wiping response is eliminated by an intraoral infusion of milk, but not by infusion of saline or other chemosensory stimuli (27), suggesting that milk reduces fetal responsiveness to cutaneous stimulation. The ability of milk to effect changes in fetal behavior is present upon the fetus's first exposure to milk. Administration of selective agonists and antagonists of opioid receptors indicates that milk-induced changes in fetal behavior are mediated by the κ-opioid system (3,26). For example, facial wiping in response to cutaneous stimulation is diminished by administration of either μ- or κ-opioid agonists, and milk-induced changes in fetal sensory responsiveness are blocked by a κ-antagonist, but not by a μ-antagonist. Thus, while μ- or κ-opioid activity can promote changes in fetal behavior and sensory responsiveness, the κ-system is implicated in the behavioral effects produced by milk.

The dopamine system also plays a role in regulating motor behavior in the fetus. Both D_1 and D_2 receptors are present early in development (6,8,21). Drugs that alter endogenous dopamine activity, such as cocaine (23), promote changes in independent measures of fetal behavior, including levels of overall motor activity and expression of facial wiping behavior in a bioassay of cutaneous sensitivity. SK&F38393, a selective agonist of D_1 receptors, promotes a three- to fourfold increase in fetal activity (18) and reduces the facial wiping response to cutaneous stimulation (19). Endogenous changes in dopamine activity, or drugs that alter dopamine regulation, thus promote changes in fetal motor behavior that parallel some of the effects of milk infusion and opioid manipulations. Evidence from neonatal rats further suggests that the dopamine system plays a role in mediating the behavioral effects of milk. Blockade of dopamine receptors with haloperidol eliminates milk-induced increases in motor activity in 6-day-old rat pups (7). Extracellular dopamine in the striatum of caesarean-

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derived newborn rats is reduced following multiple infusions of milk, as demonstrated by in vivo microdialysis (2). Presentation of milk to the fetus therefore should result in changes in dopamine activity.

Milk-induced changes in fetal behavior result from an interaction between the dopamine and opioid systems. The selective D_1 antagonist SCH23390 blocks the effects of milk on facial wiping behavior in the fetal rat. The effects of the D_1 agonist SK&F38393 on fetal activity and facial wiping are blocked with coadministration of the κ-opioid antagonist norbinaltorphimine (BNI); fetuses given this combination of drugs express reduced levels of overall motor activity (24) and high levels of the wiping response to cutaneous stimulation (19). However, SCH23390 does not alter the effect of the κ-agonist U50,488 on either fetal motor activity or facial wiping; fetuses receiving the D_1 antagonist and κ-agonist exhibit elevated motor activity and reduced facial wiping to cutaneous stimulation. Thus, blockade of κ-opioid receptors reverses the effect of D_1 stimulation, but blockade of D_1 receptors has no effect on κ-induced changes in fetal behavior (19,24). These data indicate that the pattern of interaction between the κ-opioid and dopamine systems in the rat fetus is sequential, with milk first modulating activity in the dopamine system, which subsequently leads to changes in activity at κ-opioid receptors.

More detailed information concerning the neurochemical effects of milk in the fetus is not available. The purpose of the present study was to determine the effectiveness of intraoral milk infusion to promote regional changes in prenatal dopamine activity. The strategy in these experiments was to employ the technique of in vivo receptor binding to measure changes in D_2 receptor occupancy by endogenous dopamine in the striatum, septum, and hypothalamus of the term rat fetus (E21). In vivo binding at D_2 receptors, using tritiated raclopride, has been used as an assay of dopamine release in humans (22), mice (1), and rats (16,29). Potential interactions between the dopamine and opioid systems were examined by treating fetuses with a κ-opioid antagonist (BNI) before milk infusion (Experiment 1) or with various μ- and κ-opioid agonists (Experiment 2) prior to measurement of activity in the dopamine system as indicated by dopamine receptor-specific binding.

METHOD

Subjects

Female Sprague–Dawley rats (Charles River Laboratories, Wilmington, MA) were housed under constant room temperature (22°C) and 12 L : 12 D cycle in groups of three with Sprague–Dawley male rats in plastic breeding cages (36 × 47 × 20 cm). Food and water were available ad lib. The date of conception (E0) was considered to be the day that the vaginal smear indicated the presence of sperm. Throughout the course of this experiment, animal subjects were maintained and treated in accordance with guidelines established by the National Institutes of Health (PHS Publication 86-23).

Prenatal Preparation

Pregnant rats were prepared following well-established procedures that permit experimental manipulation of individual fetal subjects on E21 of gestation (25). The pregnant rat was anesthetized briefly with ether and 100 μl ethanol was injected into the spinal cord between the first and second lumbar vertebrae, rendering the lower body insensate. The prepared dam was placed in a plastic holding device, immersed in a water bath containing buffered saline maintained at 37°C, and the uterus externalized into the bath through a low midline laparotomy. Pregnant rats prepared in this way quickly adapt to the testing situation and provide access to fetal subjects that can be observed for periods up to 60–90 min. These procedures circumvent the need to administer a general anesthetic to the pregnant rat, which eliminates motor behavior in fetuses. Experimental procedures were conducted after a 20-min period to allow the dam to acclimate.

Drug Administration

To administer experimental treatments, individual fetal subjects were carefully delivered from the uterus and the embryonic membranes removed. Care was taken to ensure that the placenta remained attached to the dam and that umbilical circulation was unimpaired (25). Opioid antagonists, agonists, and vehicle controls were administered to fetal subjects via IP injection. The selective antagonist norbinaltorphimine diHCl (BNI; 9.2 mg/kg; Research Biochemicals Inc., Natick, MA) was used to block activity at κ-opioid receptors. Opioid activity was promoted with the nonspecific agonist morphine sulfate (MOR; 0.5 mg/kg; Sigma Chemical Co., St. Louis, MO), the μ-receptor agonist [D-Ala^2,NMe-Phe^4,Gly^5-*ol*]-enkephalin (DAMGO; 1.0 mg/kg; Sigma), and the κ-receptor agonist U50,488 (U50; 1.0 mg/kg; Research Biochemicals). Binding at dopamine receptors was assessed by administering a tritiated or nontritiated form of the highly selective D_2 antagonist raclopride (1,11,15). Nontritiated raclopride (3.0 mg/kg; Astra Labs, Sweden) was administered to some subjects to saturate D_2 receptors and thereby provide a measure of nonspecific binding of the radiolabeled ligand (30). [^{3}H]Raclopride (New England Nuclear, Boston, MA) was used as the radiolabeled ligand in this study and was administered to each fetal subject in an IP injection of 0.6 μCi. All drug solutions were prepared in an isotonic saline vehicle (SAL) and administered in a volume of 50 μl.

Fetal Chemosensory Manipulation

Fetal subjects that received chemosensory stimulation (Experiment 1) were fitted with an intraoral cannula immediately following opioid drug manipulation. The cannula was constructed from PE-10 polyethylene tubing (outer diameter = 0.61 mm) and was inserted through the lower jaw at the midline, with a terminal flange resting on the dorsal surface of the tongue in a mid-anterior position (13). Cannulated subjects received a series of five 20-μl infusions of milk (bovine light cream) or isotonic saline, delivered at 5-min intervals by a micrometer syringe pump (12).

Receptor Binding Preparation

Drug injections, intraoral infusions, and collection of fetal brain samples occurred during a 25-min period (Fig. 1). [^{3}H]Raclopride was injected 5 min after administration of opioid agonists or antagonists, with brain samples collected 20 min after administration of [^{3}H]raclopride. The umbilical cord of the subject fetus was clamped and cut and the subject sacrificed by decapitation. The brain was rapidly dissected on ice and divided into striatal, septal, hypothalamic, and cerebellar brain regions. Each individual brain region was placed into a preweighed scintillation vial containing 750 μl tissue solubilizer and reweighed to determine the weight of each brain tissue sample. After the tissue was digested over-

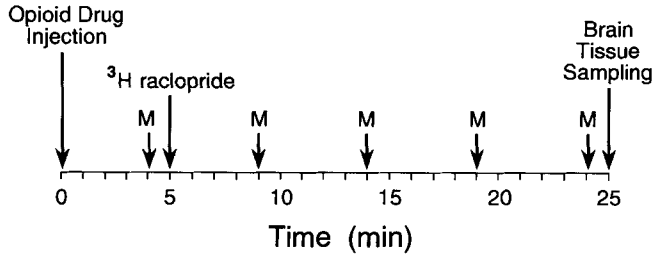

FIG. 1. Timeline for in vivo binding experiments. Fetuses received an IP injection of opioid drugs {morphine, [D-Ala^2,NMe-Phe^4,Gly^5-ol]-enkephalin (DAMGO), U50,488, norbinaltorphimine (BNI)} or nontritiated raclopride at min 0. A series of five intraoral infusions of saline or milk (M) were delivered at 5-min intervals beginning at min 4. The radiolabeled ligand [^{3}H raclopride] was administered at min 5 and brain tissue samples collected 20 min later.

night at 40°C, 15 ml Flour-989 was added to the vial containing the dissolved tissue. The amount of radioactivity was measured by an LKB Wallac 1219 Rackbeta liquid scintillation counter and the counts corrected with a previously established quench curve.

Prior to this study, techniques for measuring receptor-specific binding in vivo have not been applied to fetal subjects. Radioactivity data were subjected to two manipulations to correct for nonspecific binding in different brain regions and general physiological effects of sensory or pharmacological treatments on availability of the radiolabeled ligand. Within each brain region, receptor-specific binding was calculated as the total radioactivity (dpm/mg) in an experimental subject minus the radioactivity in control subjects receiving nonradioactive raclopride (30). To control for differential availability of raclopride to the fetal brain, radioactivity counts in the cerebellum, a brain region that has a low density of D_2 receptors in adult rats (17), were subtracted from measures of specific binding in the striatum, septum, and hypothalamus.

Data Analysis

In each experiment, measures of receptor-specific binding, adjusted for activity in the cerebellum, were compared in a two-factor analysis of variance (ANOVA), with different brain regions (striatum, septum, and hypothalamus) treated as a repeated measure. Where significant main effects were evident, posthoc comparisons of individual treatment means were conducted by the method of Fisher LSD. An alpha level of $p < 0.05$ was used to judge significance in all statistical tests.

RESULTS

Experiment 1: Effect of Milk Infusion on D_2 Receptor Occupancy

A total of 25 fetal subjects from 8 pregnant rats provided data in three experimental conditions in Experiment 1. Two groups received an initial IP injection of SAL and subsequently received a series of five intraoral infusions of isotonic saline (SAL; $n = 8$) or milk (milk; $n = 8$). The third group was pretreated by injection of the κ-opioid antagonist BNI and then received five infusions of milk (BNI + milk; $n = 9$). Eight additional fetuses, one from each pregnancy, were pretreated with nontritiated raclopride and received no infusion. Receptor-specific binding, corrected for radioactivity in the cerebellum, provided a measure inversely related to occupancy of the D_2 receptor by dopamine. This measure thus provided information about relative activity of the dopamine system following chemosensory stimulation.

Receptor-specific binding was compared in a two-factor (three infusion condition × three brain regions) ANOVA, with the brain regions factor treated as a repeated measure. This analysis revealed the significant main effect of infusion, $F(2, 22) = 4.6$, $p < 0.05$, and the significant main effect of brain region, $F(2, 44) = 8.0$, $p < 0.001$, but no interaction between infusion and brain region. Posthoc comparisons indicated that fetuses in the milk group exhibited significantly higher levels of [^{3}H]raclopride binding than the SAL group ($p < 0.05$), suggesting a decrease in receptor occupancy by the endogenous ligand, dopamine (Fig. 2). Further, the effect of milk infusion on specific binding was not affected by pretreatment with BNI ($p > 0.05$). Elevated specific binding following milk infusions indicated that fetal exposure to this chemosensory fluid decreased endogenous D_2 receptor occupancy. However, milk-induced changes in dopamine activity were not affected by antagonism of the κ-opioid system.

The main effect of brain region and posthoc comparisons suggested that receptor-specific binding was greater in the septum than in the hypothalamus and striatum ($p < 0.05$). However, the effect of milk infusion to suppress endogenous dopamine activity was evident in all three brain regions, and the influence of intraoral infusion per se (as indicated by the saline infusion group) appeared to differ among regions. To further explore possible differences in milk effects in the three brain regions, the mean level of receptor-specific binding in the saline infusion group was subtracted from binding in the milk and BNI + milk conditions. A two-factor (two infusion condition × three brain regions) ANOVA indicated no significant main or interaction effects ($p > 0.40$). This analysis revealed that milk did not exert a differential effect on receptor-specific D_2 binding in the striatum, septum, and hypothalamus and that the κ-opioid antagonist norbinaltorphimine did not influence the effect of milk infusion on D_2 binding. The findings of Experiment 1 confirm that the fetal rat's initial experiences with milk produce changes in dopamine activity in the striatum, septum, and hypothalamus.

Experiment 2: Effect of Opioid Drug Manipulation on D_2 Receptor Occupancy

A total of 31 fetal subjects from 10 pregnant rats provided data in 4 experimental conditions in Experiment 2. Fetuses in the four groups received an initial IP injection of SAL ($n = 10$), MOR ($n = 7$), DAMGO ($n = 8$), or U50 ($n = 7$). Ten additional fetuses, 1 from each pregnancy, were pretreated with nontritiated raclopride. All subjects received the injection of ^{3}H raclopride 5 min after the initial drug administration, with fetal brain samples collected 20 min later (Fig. 1). The brain was rapidly dissected on ice into striatal, septal, hypothalamic, and cerebellar brain regions for measurement of D_2 receptor-specific binding.

Receptor-specific binding, corrected for radioactivity in the cerebellum, was compared in a two-factor (four drug treatments × three brain regions) ANOVA, with the brain regions factor treated as a repeated measure. This analysis revealed the significant main effect of brain region, $F(2, 54) = 4.4$, $p < 0.05$. Specific binding was greater in the striatum (4.1 ± 5.0 dpm/mg) and septum (6.3 ± 4.2) than in the hypothalamus (−0.3 ± 4.2). No significant main or interaction effects

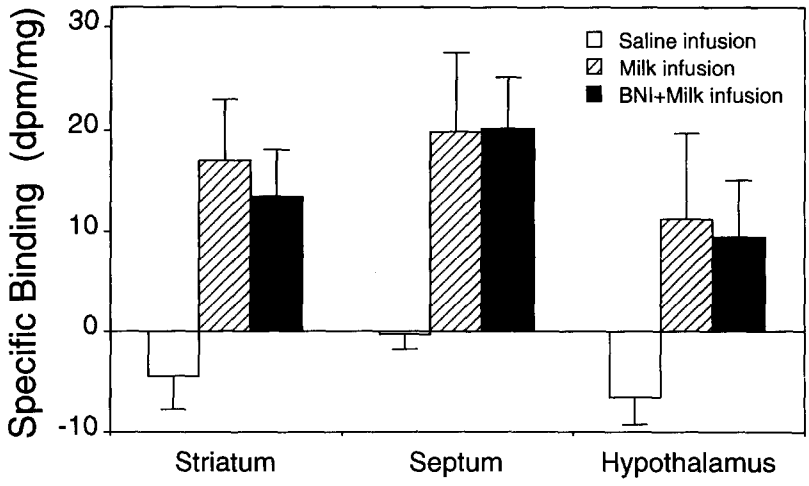

FIG. 2. Specific binding at D_2 receptors, expressed in disintegrations per min per mg of brain tissue (after subtracting radioactivity in the cerebellum) in Experiment 1. Fetuses were assigned to one of three infusion conditions, which involved intraoral infusion of saline, infusion of milk, or infusion of milk after pretreatment with 9.2 mg/kg of the κ-opioid antagonist norbinaltorphimine (BNI). Bars depict mean specific binding of [^{3}H]raclopride measured in three different regions of the fetal brain (striatum, septum, and hypothalamus); vertical lines show SEM.

involving the drug treatments factor were found. There was no evidence that manipulations of either μ- or κ-opioid receptors influenced occupancy of D_2 receptors in the fetal rat.

DISCUSSION

The results of the current study confirm that intraoral milk infusions can alter activity within the dopamine system of the fetal rat. Specifically, binding of [^{3}H]raclopride at D_2 receptors in vivo increased following intraoral infusion of milk in the E21 fetus. The increased binding of the radiolabeled ligand following milk infusion implies a decrease in dopamine release in three brain regions. These findings are consistent with neurochemical data obtained by in vivo microdialysis in newborn rats (2). Levels of extracellular dopamine in the neonatal striatum decreased when newborn pups received multiple intraoral infusions of milk. Both the in vivo binding and microdialysis findings were evident upon the perinatal rat's first exposures to milk.

The results of the present study provide no evidence that manipulations of the κ-opioid system alter activity in the dopamine system. The κ-opioid antagonist BNI had no effect on the decrease in dopamine release promoted by intraoral milk infusion. Further, fetuses treated with the κ-agonist U50,488 showed the same levels of dopamine activity as saline-injected controls. These findings, obtained from manipulations of intact fetuses in vivo, contrast with experiments on opioid–dopamine interactions in fetal and neonatal brain slice preparations. From E17 through P21, κ- stimulation with U50,488 was found to decrease dopamine release in the striatum following electrical stimulation (9). In the intact fetus, either the κ-opioid system does not interact with the dopamine system on E21 or the two systems interact in the opposite direction, with dopamine activity promoting changes at κ-opioid receptors. Evidence obtained from pharmacological manipulations of both opioid and dopamine receptors and measurement of fetal behavior suggests that the latter possibility is more likely. κ-Opioid antagonists have been shown to be effective in reversing the behavioral effects of D_1 dopamine agonists, but D_1 antagonists have little influence on the effects of κ-opioid agonists on fetal behavior (19,24).

Stimulation of μ-opioid receptors with morphine or DAMGO similarly failed to produce effects on dopamine activity. This finding is consistent with in vitro studies of opioid–dopamine interactions in adult and developing rats. In vivo microdialysis of adult rats has indicated that morphine increases levels of dopamine release in the striatum (10). DAMGO has been reported to decrease release of norepinephrine, but not dopamine, in striatal slice preparations (9). Morphine has been found to increase levels of dopamine turnover in whole striata of rats from P6 to adult. However, morphine-induced changes in dopamine turnover are not evident in younger rat pups (P3) (20). Because the μ-opioid system undergoes rapid development during the first week after birth (4), interaction between the μ-opioid system and the dopamine system may not be evident until well after birth.

Measurement of receptor-specific binding in vivo is an effective method for assessing activity in the dopamine system in developing rats. Unlike in vitro techniques, in vivo binding permits measurement of functional receptor occupancy under physiological conditions following behavioral manipulation of the animal (30). Use of this technique in the present study confirms that dopamine activity can be modulated by a sensory event—intraoral infusion of milk—during the prenatal period. This finding complements other approaches for assessing function in the developing dopamine system, including chromatographic assay of neurotransmitter utilization in whole-brain regions (20), direct collection of extracellular dopamine by in vivo microdialysis (2), and measurement of functional consequences of receptor activation or blockade with pharmacological manipulations and behavioral observation (14,28). It is curious that milk appears to result in a decrease

in dopamine release in fetal and neonatal rats [(2); this study], but dopamine agonists mimic the behavioral effects of milk infusion in the rat fetus (19,24). It is beyond the scope of the present study to resolve this paradox. However, because the available evidence suggests ontogenetic differences in the pattern of interaction between opioid and dopamine systems it is imperative to adopt a developmental perspective in understanding the interaction between neurotransmitter systems and the functional consequences of such interactions in the fetus, infant, and adult.

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