



0031-9384(94)00358-0

Development of Responses to an Artificial Nipple in the Rat Fetus: Involvement of Mu and Kappa Opioid Systems

SCOTT R. ROBINSON, THOMAS C. M. HOELTZEL AND WILLIAM P. SMOTHERMAN¹

Laboratory of Perinatal Neuroethology, Center for Developmental Psychobiology, Department of Psychology, P. O. Box 6000, Binghamton University, Binghamton, NY 13902-6000

Received 13 April 1994

ROBINSON, S. R., T. C. M. HOELTZEL AND W. P. SMOTHERMAN. *Development of responses to an artificial nipple in the rat fetus: Involvement of mu and kappa opioid systems.* *PHYSIOL BEHAV* 57(5) 953–957, 1995.—Presentation of an artificial nipple to the rat fetus on E19, E20, or E21 of gestation promotes the expression of organized behavioral responses. Fetal responses include mouthing, licking, head-turning, and oral grasping of the nipple. Fetuses on E21 were more successful at grasping the nipple. Because all subjects were naive at the time of testing, this improved performance occurred in the absence of explicit experience with the nipple or specific practice (grasping the nipple). Manipulation of kappa and mu opioid activity with selective agonist drugs (U50,488 and DAMGO, respectively) altered fetal responsiveness to the nipple. U50,488 generally disrupted appetitive responses and promoted aversive reactions to the artificial nipple, whereas DAMGO increased responsiveness (licking and oral grasping), especially on E21. These findings suggest that both the mu and kappa systems may play functional roles in regulating neonatal behavior at the nipple by initiating and terminating a suckling bout.

Rat fetus Artificial nipple Suckling Opioids

EXPERIMENTS conducted with developing rats have suggested a role for the endogenous opioid system in early experiences at the nipple. For instance, infusion of milk into the mouth of the infant rat results in endogenous opioid activity that can modify infant behavior, including responsiveness to other forms of sensory stimulation (2,4,17). The ability of milk to elicit activity in the endogenous opioid system develops without explicit suckling experience during the prenatal period. Exposure to milk in the fetal rat on E20 or E21 of gestation consistently evokes activity in the kappa opioid system, which results in a cascade of effects on motor behavior and sensory responsiveness (21,22). Further, experiments with fetal subjects have suggested that milk-induced opioid activity can support associative learning. Three paired presentations of an artificial nipple with milk infusion results in the expression of a conditioned opioid response upon reexposure to the artificial nipple. But presentation of the artificial nipple alone, or explicitly unpaired presentations of milk and the artificial nipple, are not effective in promoting conditioned opioid responses (13). Although the unconditioned stimulus in these experiments (milk) ordinarily evokes activity in the kappa opioid system alone, the conditioned response involves activity in the mu opioid system. The finding that a single pairing of the nipple with milk is sufficient to promote a conditioned

opioid response suggests that classical conditioning can occur rapidly in the context of the first few suckling episodes (24).

Experimental demonstration of conditioned opioid responses in fetal subjects has provided general support to the hypothesis that sensory stimuli present in the early suckling environment can quickly come to evoke conditioned activity in the endogenous opioid system in advance of milk letdown (5,23). Subsequent to the initial suckling episode and ingestion of milk, infant rats may experience sensory cues that consistently predict the proximity of the nipple and availability of milk. If so, then infant rats are likely to experience conditioned activity in the endogenous opioid system during early experiences at the nipple. To assess the potential ramifications of such opioid activation on suckling behavior in general, it will be informative to assess the effects of opioid activity on developing responses to suckling stimuli. Previous reports have documented how selective agonists of mu and kappa opioid receptors can influence fetal responses to intraoral infusion of milk (1,22,25). The aim of this study was to provide data on the influence of opioid activity on responses to an artificial nipple in developing fetal subjects that lack prior experience with the nipple, milk, or other suckling stimuli.

Published descriptions have suggested that rat fetuses begin to exhibit responsiveness to an artificial nipple on E18 of the

¹ To whom requests for reprints should be addressed.

21.5 day gestation, and are capable of actively grasping the nipple with the mouth from E19 through term (14). By E21, oral contact with the nipple also evokes other behavioral responses, including appetitive responses (such as mouthing and licking) and rejection responses (such as head aversion) (5). In this experiment, the behavioral responses of rat fetuses to an artificial nipple were recorded on videotape on E19, E20, or E21 of gestation after treatment with a mu-selective opioid agonist (DAMGO) or a kappa-selective agonist (U50,488). Because conditioned responses to milk and the artificial nipple involve activity in the mu opioid system, our expectation was that DAMGO would facilitate appetitive responses directed at the artificial nipple. Conversely, because kappa opioid activity is evoked by milk and results in terminal behaviors in the suckling sequence (e.g., behavioral activation and the stretch response (15)), it was predicted that U50,488 would interfere with fetal responses to the artificial nipple.

METHOD

Subjects

A total of 54 rat fetuses from 20 pregnancies served as subjects in this study. Fetuses were the progeny of Sprague-Dawley rats (Charles River Laboratories, Wilmington, MA) time-mated in our laboratory. Breeding females were housed in groups of three in plastic breeding cages (36 × 47 × 20 cm) under constant room temperature (22°C) and 12:12-h light/dark cycle (lights on at 0700), with food and water freely available. Vaginal smears were collected daily during a 4-day breeding period, with the first date of detectable sperm designated as the date of conception (E0). Animals were maintained and treated following guidelines of the National Institutes of Health (PHS publication 86-23), International Society for Developmental Psychobiology, and Society for Neuroscience. To avoid confounding litter effects with treatment effects in testing multiple offspring (7), different experimental conditions were represented only once in each pregnant female.

Prenatal Preparation

Pregnant rats were prepared for fetal testing on E19, E20, or E21 of the 21.5 day gestation. Under brief ether anesthesia, the pregnant rat received a 100 μ l injection of 100% ethanol into the spinal cord between the first and second lumbar vertebrae. This procedure produces an irreversible spinal blockade at the low thoracic level and eliminates sensation in the lower half of the rat's body. The prepared rat was placed in a plexiglas holding apparatus and immersed to chest depth in an isotonic saline bath maintained at body temperature (37.5°C). The condition of the prepared rat was monitored throughout the period of fetal observation. The prepared rat was allowed to acclimate to the bath environment for 20 min before fetal observation. To gain direct visual access to fetuses, the uterus was externalized through a low midline laparotomy, and individual fetal subjects were delivered from the uterus and amniotic sac into the saline bath, taking care to maintain the integrity of the umbilical cord and placental attachment to the uterus. Coloration of the fetus and umbilical cord was used to judge fetal oxygenation; only fetuses that remained pink throughout the observation session were included in the study (20).

Administration of Opioid Agonists and Antagonists

Selective agonists of mu or kappa opioid receptors were administered to manipulate the opioid system of fetal subjects. (D-Ala²,NMe-Phe⁴,Gly⁵-ol)-enkephalin (DAMGO; Sigma Chemical

Co., St Louis, MO) is a selective mu opioid agonist; U50,488 (U50; Research Biochemicals Inc., Natick, MA) is a selective kappa opioid agonist. These drugs, or the isotonic saline vehicle, were administered by IP injection into the midabdominal cavity of the fetal subject using a 30-ga hypodermic needle. During the injection, the fetus remained submerged within the saline bath. A fixed volume of the drug solution (50 μ l) was administered to each fetal subject, with the dosage adjusted for the mean body weight of rat fetuses on Days 19–21 (18). This study involved administration of a single dosage of each opioid agonist, which was selected based on dose response studies previously reported in rat fetuses. DAMGO has been administered in dosages of 0.5 to 5.0 mg/kg, with all dosages effective in reducing fetal responsiveness to aversive cutaneous stimuli applied to the perioral region (25). The dosage of DAMGO employed in this study (1.0 mg/kg) has no effect on motor activity. U50,488 has been administered in dosages of 0.1 to 5.0 mg/kg, with dosages of 1.0 or greater also reducing fetal responsiveness to a perioral stimulus (19). The dosage of U50,488 employed in this study (1.0 mg/kg) results in a 3-fold increase in motor activity, which predominantly involves rearlimb movements (22). Behavioral evidence has confirmed that both drugs exert their maximum effects within 5 min after IP injection; in this study, the opioid agonist or saline vehicle injection was administered to the fetal subject 8 min before behavioral testing.

Nipple Presentation

The artificial nipple (AN) was fashioned from soft vinyl to approximate the dimensions of a lactating nipple in a recently parturient rat. The AN tapered to a diameter of 1 mm at the rounded tip. The base of the AN was attached to a handle to facilitate manual presentation by the experimenter. Presentation consisted of gently holding the tip of the AN in contact with the mouth of the fetus, without forcing the tip into the mouth, during a 3-min test session. The total duration of contact with the AN (determined from examination of videotape records) was 111.5 ± 2.4 s (mean ± SEM), which did not vary systematically among Age or Drug groups.

Behavioral Observation

Test sessions were videotaped to permit detailed analysis of fetal responses to the AN. A video camera (Panasonic, model AF-X8) was positioned vertically over the subject fetus during recordings (VHS format, 33.35 mm/s recording speed). To facilitate creation of videotape records and subsequent analysis of fetal movements, subjects were placed on a high-contrast vinyl substrate below the surface of the water bath during the observation session. The subject was illuminated from two sides with cool light directed from fiber-optic lightguides (Schott KL1500-Z). Videotape records were time-stamped with a video timer (FOR-A, model VTG-33A) to uniquely label each video frame, and analyzed frame by frame (30 frames/s) on a video playback system (Sony SLV-676UC).

Analysis of fetal responses from videotape records focussed on oral and head movements. Contact with the AN evokes oral grasping responses, which involve an active movement of the head of the fetus that results in the tip of the AN entering the mouth, which closes around the AN. Grasp responses can be expressed by rat fetuses at each of the ages tested in this study (E19–E21) (14). Oral responses included mouthing movements (opening and closing of the mouth immediately after physical contact of the nipple with the oral area), and licking movements (protrusion of the tongue, with or without mouthing activity). Lateral movement of the head, which resulted in movement of

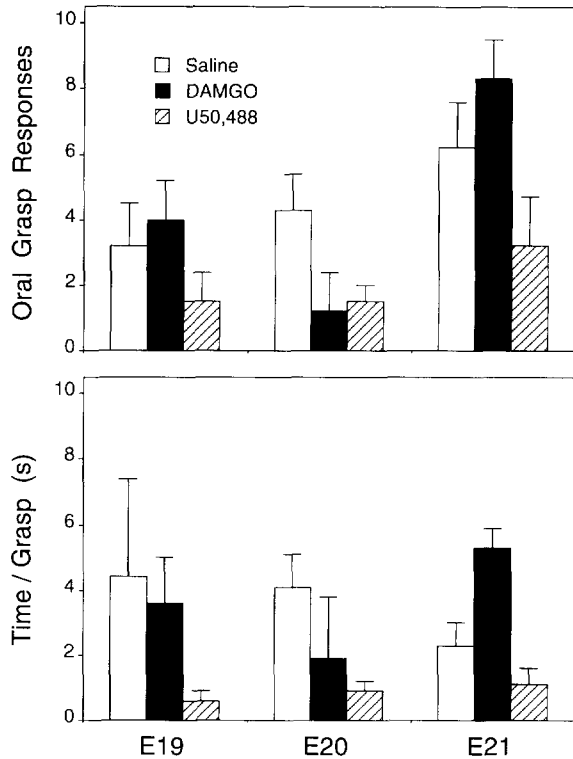


FIG. 1. Number of oral grasp responses (top) and duration of each grasp response (bottom) directed toward the artificial nipple by fetuses in the three drug groups at three gestational ages. Bars represent group means; vertical lines depict SEM.

the mouth away from the tip of the AN, also were scored as head-turning responses. The observer who scored these response measures from videotape records was blind to the opioid treatment received by each fetal subject. Time measurements with this protocol for scoring from video records were accurate to ± 0.03 s.

Experimental Design and Analysis

The AN was presented to a total of 54 fetal subjects, distributed equally among three drug groups (SAL, DAM, U50) at three gestational ages (E19, E20, E21; $N = 6$ subjects per Age \times Drug group). Duration or frequency measures of different behavioral categories were analyzed by two-factor (Age \times Drug) between-subjects analysis of variance (ANOVA). Where the overall ANOVA indicated significant main or interaction effects, additional analyses were conducted to assess simple main effects and pairwise comparison of individual group means (Fisher PLSD).

RESULTS

Oral Grasping of AN

A two-factor (3 Ages \times 3 Drug treatments) ANOVA comparing the number of oral grasping responses evoked by the AN indicated the significant main effects of Age, $F(2, 45) = 7.9$, $p < 0.01$, and Drug treatment, $F(2, 45) = 4.4$, $p < 0.05$ (Fig. 1, top). The interaction between Age \times Drug was not significant ($p > 0.10$). Posthoc comparisons indicated that grasping of the AN was expressed more frequently by fetuses on E21 (5.9 ± 0.9) than at earlier ages (E19: 2.9 ± 0.7 ; E20: 2.3 ± 0.6). Fetuses treated with U50,488 expressed fewer oral grasping responses (2.1 ± 0.6) than fetuses injected with DAMGO (4.5 ± 1.0) or

saline (4.6 ± 0.7). The average duration of each grasp response was compared in a second ANOVA, which indicated the significant main effect of Drug treatment, $F(2, 45) = 3.9$, $p < 0.05$ (Fig. 1, bottom). The main effect of Age and the Age \times Drug interaction were not significant (p -values > 0.40). Posthoc comparisons indicated that average grasp duration was shorter in fetuses treated with U50,488 (0.9 ± 0.2 s) than in subjects injected with DAMGO (3.6 ± 0.8 s) or saline (3.6 ± 1.0 s). In an earlier experiment, we reported that morphine (a nonselective mu agonist) facilitated fetal grasping of the AN on E21 of gestation, and specifically increased the amount of time spent on the AN after grasping (14). A planned comparison of E21 fetuses in this study was conducted to confirm this mu influence on grasp duration. The one-way ANOVA indicated the significant effect of Drug treatment on E21, $F(2, 15) = 13.0$, $p < 0.001$. Pairwise comparison of groups indicated that the duration of grasping was significantly longer in fetuses treated with DAMGO at this age than either saline or U50,488 (p -values < 0.05).

Oral Responses to AN

Mouthing activity, which involved opening and closing of the mouth, was commonly expressed during periods of AN presentation. The number of mouthing responses evoked by the AN was compared in a two-factor ANOVA. Mouthing did not differ as a function of either Age or Drug treatment, or the interaction of these factors (p -values > 0.10). However, a subset of all mouthing responses were followed immediately by oral grasping of the nipple. (Across all Age and Drug conditions, these pregrasp Mouth responses resulted in 59% of all observed Grasp responses). Pregrasp Mouth responses, expressed as a percentage of the total number of mouthing responses evoked by the AN, varied as a function of Age and Drug treatment, as indicated by the significant interaction, $F(4, 45) = 3.0$, $p < 0.05$ (Fig. 2). The simple main effect of Age was evident in the saline control group, $F(2, 15) = 7.0$, $p < 0.01$. Among control subjects, pregrasp Mouthing was greater on E20 and E21 than on E19 (p -values < 0.05). The simple main effect of Age also was evident for fetuses treated with DAMGO, $F(2, 15) = 5.5$, $p < 0.05$). Among DAMGO treated subjects, pregrasp Mouthing was higher on E21 than on E20 or E19 (p -values < 0.05). The simple main effect of Age was not significant among subjects treated with U50,488 ($p > 0.25$).

Licking activity, as distinct from mouthing, also was expressed during periods of AN presentation. The two-way

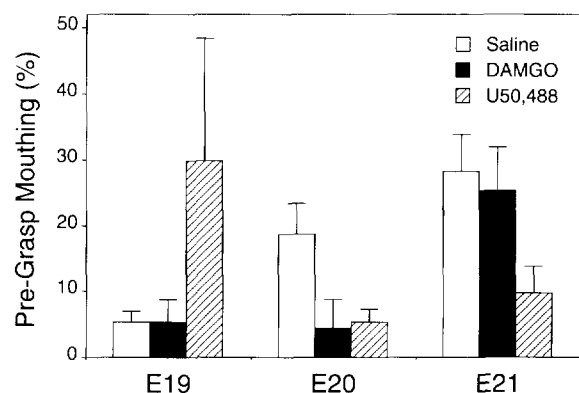


FIG. 2. The percentage of mouthing responses that resulted in oral grasping of the artificial nipple (pregrasp mouthing). Bars represent group means; vertical lines depict SEM.

ANOVA comparing the total number of licking movements indicated the significant main effects of Age, $F(2, 45) = 5.1, p < 0.01$, and Drug treatment, $F(2, 45) = 15.2, p < 0.001$ (Fig. 3). No interaction between Age \times Drug was evident ($p > 0.20$). Posthoc comparisons indicated that licking behavior was expressed more often by fetuses in the DAMGO group than by subjects treated with U50,488 or saline (p -values < 0.05). Licking movements on E21 were significantly more frequent than on E20 ($p < 0.05$), but did not differ from the intermediate levels of this behavior on E19.

Head Aversion Responses to AN

The two-way ANOVA comparing head-turning responses evoked by the AN indicated the main effect of Drug treatment, $F(2, 45) = 29.8, p < 0.001$. The main or interaction effects involving the Age factor were not significant (p -values > 0.15). Posthoc comparisons indicated that head-turning responses were expressed more often by fetuses treated with U50,488 (35.9 ± 24.1 movements) than by fetuses in the DAMGO (7.7 ± 1.3) or saline groups (13.2 ± 2.1), (p -values < 0.05).

DISCUSSION

During the first three weeks after birth, infant rats receive virtually all of their nutrition and fluids through suckling from a lactating mother. Although behavior directed toward the nipple is an important focus of neonatal behavior, infant rats are reluctant to show typical suckling responses to surrogate nipples (8,14). By necessity, alternative methods of delivering milk to the neonatal rat have been employed to study the development of suckling and feeding behavior (12). The responsiveness of the rat fetus to an artificial nipple stands in sharp contrast to the behavior of pups after birth. Presentation of a soft artificial nipple to the fetus over the last three days of gestation (E19–E21) elicits a complex assortment of behavioral responses, including the expression of rare patterns such as oral grasping and licking, and increases in common patterns such as mouthing and head movement. This study illustrates how presentation of a stimulus that mimics features of the postnatal suckling environment—the artificial nipple—can reveal behavioral competence in the fetus, which lacks any experience in the context of suckling.

The behavior of fetuses treated by injection of isotonic saline in this experiment provides information about age-related changes in responsiveness to the artificial nipple. The number of oral grasping responses to the artificial nipple increased with fetal age. Although mouthing responses to the artificial nipple did not change per se, the percentage of mouthing movements that were followed by oral grasping (pregrasp mouthing) increased steadily with age. This finding indicated that a higher percentage of oral responses in older fetuses resulted in grasping the nipple (28% on E21 compared to 5% on E19). If mouthing responses are indicative of attempts to seize the nipple, changes in the percentage of pregrasp mouth responses imply general improvement in the success rate of grasping the nipple with advancing age. Because the between-subjects experimental design in this study involved presenting the artificial nipple to each subject at only one age, the apparent improvement in grasp success rate was not due to experience with the artificial nipple. Similar age-related improvement in reaching toward, pecking, or grasping an object have been reported in developmental studies of young birds and mammals (e.g., 6,16,26) and generally have been interpreted as the consequence of accruing experience. However, it is important to note that all studies to date of postnatal subjects have necessarily confounded age-related improvement in performance with experience. The findings from the fetal subjects in this study

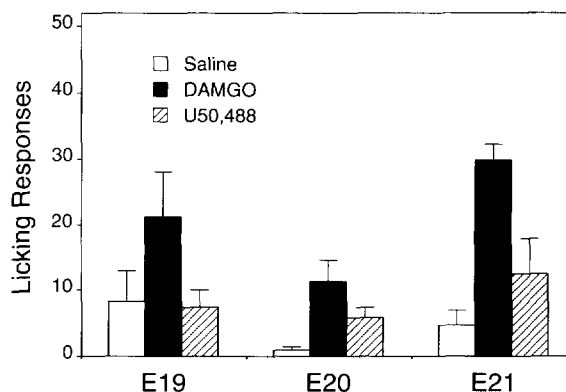


FIG. 3. Mean number of licking responses (+ SEM) during presentation of the artificial nipple.

provide evidence that improved performance can occur in the absence of explicit experience with the target (the artificial nipple) or specific practice (grasping the nipple).

The responses of fetal rats to the artificial nipple also are influenced by selective agonists of the mu or kappa opioid systems. The kappa opioid agonist U50,488 appeared to diminish appetitive responses to the nipple, including oral grasping and pregrasp mouthing, all of which resemble functional behavioral responses expressed by infant rats during suckling. At the same time, U50,488 promoted the rejection response of head-turning away from the nipple. U50,488 effects generally were evident on E20 and E21 of gestation. Kappa opioid agonists such as U50,488 or U69,593 have been shown to increase overall motor activity in the fetal rat, and specifically to increase movement in caudal portions of the body, including rear limbs, lower body trunk, and tail (1,11). Kappa agonists also reduce fetal responsiveness to perioral cutaneous stimulation on E20 and E21 (25). These findings appear to present a consistent picture of the behavioral effects of kappa opioid activity, namely, to shift the focus of motor activity and responsiveness away from the head and mouth and toward the caudal half of the body. In contrast, the mu opioid agonist DAMGO had varying effects on different categories of fetal behavior. DAMGO appeared to increase some appetitive responses, such as licking behavior evoked by the artificial nipple. Other responses, including mouthing behavior, appeared to be little influenced by DAMGO, even though the same dose of DAMGO has been shown to be highly effective in reducing fetal responsiveness to other forms of perioral stimulation (25). The effects of this highly specific mu agonist broadly agree with previously reported effects of a less selective opioid agonist on nipple-evoked behavior: morphine increased the duration of grasp responses and decreased rejection responses (head-turning and facial wiping) in E21 rat fetuses (14). The facilitatory effect of a mu agonist was confirmed in this study, with DAMGO increasing the duration of grasp responses on E21. In general, it appears that activity at mu opioid receptors may facilitate some aspects of appetitive responses to the artificial nipple and suppress aversive responses that interfere with nipple attachment.

During the first 3 weeks after birth, infant rats receive virtually all of their nutrition and fluids through suckling from a lactating mother. Although behavior directed toward the nipple is an important focus of neonatal behavior, infant rats are reluctant to show typical suckling responses to surrogate nipples (8,14). By necessity, alternative methods of delivering milk to the neonatal rat have been employed to study the development of suckling and feeding behavior (12). The lack of response of the neonatal rat to an artificial

nipple stands in sharp contrast to the behavior of the rat fetus. Presentation of a soft artificial nipple to the fetus over the last three days of gestation (E19-E21) elicits a complex assortment of behavioral responses, including the expression of rare patterns such as oral grasping and licking, and increases in common patterns such as mouthing and head movement. Differences in the responsiveness of fetal and neonatal rats to the artificial nipple may be due to subtle changes in the sensory cues that direct and elicit suckling behavior. Before birth, simple contact with an object of appropriate size and shape is sufficient to evoke an oral grasp response (14). After birth, however, pups are attracted to the maternal ventrum and nipples by olfactory stimuli, including amniotic fluid that is deposited on nip-

ples during parturition (10), and pup saliva deposited during subsequent suckling episodes (9). Removing these postnatal odor cues by lavage markedly reduces attachment even to natural, lactating nipples (3). This study thus illustrates how presentation of a stimulus that mimics key features of the postnatal suckling environment—the artificial nipple—can reveal behavioral competence in the fetus, which lacks any experience with postnatal cues associated with suckling.

ACKNOWLEDGEMENTS

WPS is supported by MERIT Award HD 16102. WPS and SRR are supported by NICHD Grants HD 28231 and 28014.

REFERENCES

- Andersen, S. L.; Robinson, S. R.; Smotherman, W. P. Ontogeny of the stretch response in the rat fetus: Kappa opioid involvement. *Behav. Neurosci.* 107:370–376; 1993.
- Arnold, H. M.; Robinson, S. R.; Spear, N. E.; Smotherman, W. P. Conditioned opioid activity in the rat fetus. *Behav. Neurosci.* 107:963–969; 1993.
- Blass, E. M.; Teicher, M. H. Suckling. *Science* 210:15–22; 1980.
- Blass, E. M.; Jackson, A. M.; Smotherman, W. P. Milk-induced opioid-mediated antinociception in rats at the time of cesarean delivery. *Behav. Neurosci.* 105:677–686; 1991.
- Browne, J. B.; Robinson, S. R.; Smotherman, W. P. Fetal experience with milk or an artificial nipple alters appetitive and aversive responses to perioral cutaneous stimuli. *Behav. Neurosci.* 108:606–613; 1994.
- Hailman, J. P. The ontogeny of an instinct. *Behav. Suppl.* 15:1–159; 1967.
- Holson, R. R.; Pearce, B. Principles and pitfalls in the analysis of prenatal treatment effects in multiparous species. *Neurotoxicol. Teratol.* 14:221–228; 1992.
- Hoshiba, J. An automatic feeder for infant rats. *Lab. Anim. Sci.* 36:682–685; 1986.
- Pedersen, P. E.; Blass, E. M. Olfactory control over suckling in albino rats. In: Aslin, R. N.; Alberts, J. R.; Peterson, M. R., eds. *The development of perception: Psychobiological perspectives*. San Diego, CA: Academic Press; 1981:359–381.
- Pedersen, P. E.; Blass, E. M. Prenatal and postnatal determinants of the 1st suckling episode in albino rats. *Dev. Psychobiol.* 26:375–387; 1982.
- Petrov, E. S.; Varlinskaya, E. I.; Robinson, S. R.; Smotherman, W. P. Kappa opioid effects on fetal behavior: Central administration of U50,488. *Physiol. Behav.* 56:175–182; 1994.
- Phifer, C. B. The study of early feeding and drinking behaviors. In: Shair, H.; Barr, G. A.; Hofer, M. A., eds. *Developmental psychobiology: New methods and changing concepts*. Cambridge: Oxford University Press; 1991:189–205.
- Robinson, S. R.; Arnold, H. M.; Spear, N. E.; Smotherman, W. P. Experience with milk and an artificial nipple promotes conditioned opioid activity in the rat fetus. *Dev. Psychobiol.* 26:375–387; 1993.
- Robinson, S. R.; Hoeltzel, T. C. M.; Cooke, K. M.; Umphress, S. M.; Smotherman, W. P. Oral capture and grasping of an artificial nipple by rat fetuses. *Dev. Psychobiol.* 25:543–555; 1992.
- Robinson, S. R.; Smotherman, W. P. Organization of the stretch response to milk in the rat fetus. *Dev. Psychobiol.* 25:33–49; 1992.
- Rochat, P. Object manipulation and exploration in 2- to 5-month-old infants. *Dev. Psychol.* 25:871–884; 1989.
- Shide, D. J.; Blass, E. M. Opioid mediation of odor preferences induced by sugar and fat in 6-day-old rats. *Physiol. Behav.* 50:961–966; 1991.
- Simonik, D. K.; Robinson, S. R.; Smotherman, W. P. Cocaine alters behavior in the rat fetus. *Behav. Neurosci.* 107:867–875.
- Smotherman, W. P.; Moody, C. A.; Spear, L. P.; Robinson, S. R. Fetal behavior and the dopamine system: D₁ receptor interaction with the kappa opioid system. *Physiol. Behav.* 53:191–197; 1993.
- Smotherman, W. P.; Robinson, S. R. Accessibility of the rat fetus for psychobiological investigation. In: Shair, H.; Barr, G. A.; Hofer, M. A., eds. *Developmental psychobiology: New methods and changing concepts*. Cambridge: Oxford University Press; 1991:148–164.
- Smotherman, W. P.; Robinson, S. R. Kappa opioid mediation of fetal responses to milk. *Behav. Neurosci.* 106:396–407; 1992.
- Smotherman, W. P.; Robinson, S. R. Opioid control of the fetal stretch response: Implications for the first suckling episode. *Behav. Neurosci.* 106:866–873; 1992.
- Smotherman, W. P.; Robinson, S. R. Prenatal experience with milk: Fetal behavior and endogenous opioid systems. *Neurosci. Biobehav. Rev.* 16:351–364; 1992.
- Smotherman, W. P.; Robinson, S. R. Classical conditioning of opioid activity in the fetal rat. *Behav. Neurosci.* 108:951–961; 1994.
- Smotherman, W. P.; Simonik, D. K.; Andersen, S. L.; Robinson, S. R. Mu and kappa opioid systems modulate fetal responses to cutaneous perioral stimulation. *Physiol. Behav.* 53:751–756; 1993.
- Thelen, E.; Corbetta, D.; Kamm, K.; Spencer, J. P. The transition to reaching: Mapping intention and intrinsic dynamics. *Child Dev.* 64:1058–1098; 1993.