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# Opioid Mediation of Odor Preferences Induced by Sugar and Fat in 6-Day-Old Rats

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SHIDE, D. J. AND E. M. BLASS. *Opioid mediation of odor preferences induced by sugar and fat in 6-day-old rats.* PHYSIOL BEHAV **50**(5) 961–966, 1991.—Intraoral infusions of sucrose, fat or polycose reduce ultrasonic vocalizations during isolation, and increase pain threshold in infant rats. These effects are naltrexone reversible. The present study determined whether these substances, when paired with an odor, caused a change in preference for that odor. In 6-day-old rats, pairing orange odor with intraoral infusions of sucrose or corn oil, but not polycose, water, mineral oil or 0.01% quinine hydrochloride, caused a substantial increase in preference for orange. Preference formation was blocked by systemic injection of naltrexone (0.25 mg/kg) prior to pairing orange with either sucrose or corn oil. Moreover, preference expression was prevented by naltrexone injection prior to testing. Thus certain substances thought to reduce stress in infant rats via endogenous opioid release can also cause preference for substances that predict their occurrence. Preference formation depends upon the availability of endogenous opioids. Preference expression reflects the conditioned stimulus causing opioid release.

Sucrose Fat Opioids Naltrexone Preference

A substantial literature on conditioning and motivation in rats during the antenatal period has demonstrated that, at birth (13,25), classes of natural stimuli that either sustain or abbreviate ongoing behavior (5, 9, 14, 15, 19, 24) can come under the control of events that predict the occurrence of these stimuli. For example, an odor that predicted intraoral milk infusion in 6-day-old rats elicited the stereotypical pattern of movements when presented alone two days later. These movements are otherwise expressed only under conditions of excitement caused by milk infusions, for example, in deprived neonates (14,16).

The capacity of an odor to influence the expression of an available behavior during development is not limited to behaviors elicited by oral stimulation. Alberts and May (1) reported increased incidence of huddling with a substrate scented with an odor made familiar to the rat through previous exposure during huddling in the litter, and increased preference for an odor previously experienced while in contact with the dam. Furthermore, odors that predict and are associated with anogenital stimulation, such as normally provided by the dam prior to nursing, become preferred (24,25). Pairing odor with stimulation also allows the odor to elicit suckling of washed nipples that otherwise would not be suckled by infant rats. Thus pairing an odor with an event that causes a measurable change in the infant's behavior has two demonstrated consequences. First, the odor elicits the behavioral pattern in the absence of the normally eliciting stimulation (19). Second, animals spend more time in the odor's proximity than they otherwise would (24,25).

The mechanisms underlying these changes are not known and are the source of the present investigation. We use as a point of departure some recent findings in 10-day-old rats concerning quieting and antinociceptive effects of intraoral infusions. The findings were of two kinds. First, maternally isolated 10-day-old rats that received intraoral infusions of sucrose (3), milk (4) fats or polysaccharide (21) markedly reduced their levels of ultrasonic vocalizations. Moreover, these intraoral infusions also caused a significant elevation in pain threshold. Both of these substantial changes were reversed by low doses (0.25–0.50 mg/kg) of the opioid mu receptor antagonist naltrexone.

Second, Kehoe and Blass (17) showed that pairing morphine with an otherwise nonpreferred orange odor established a preference for that odor, one that could be prevented by naltrexone administration at the time of pairing. Moreover, naltrexone injections at the time of choice expression, i.e., 5 days later, eliminated preference for the odor (18).

The present study capitalizes on these findings to address the broader issue of change underlying formation and expression of preference. We focus on a class of stimulation, intraoral infusions of palatable fluids that, on behavioral grounds, appears to cause release of endogenous opioids. The present studies determine: a) if pairing an odor with certain intraoral infusions will cause later behavioral change upon exposure to that odor, b) if that change can be prevented from occurring by making functionally unavailable endogenous opioids to the mu receptor either at the time of odor-flavor association, or c) at the time of odor choice.

The substances evaluated in these studies, sucrose, corn oil,

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and the polysaccharide Polycose, all reduce isolation-induced vocalizations and increase pain threshold in 10-day-old rats (3, 4, 21). These effects were reversible with naltrexone, making them good candidates for blockade of preference formation and expression by naltrexone.

## GENERAL METHOD

### *Subjects*

Primiparous and multiparous Sprague-Dawley rats (Camm Laboratory, Wayne, NJ) were mated in our colony and their litters served as subjects. Females and their litters were individually housed in plastic tubs (38 × 30 × 27 cm) with stainless steel wire lids. Litters found at 1100 h were designated as born on that day (Day 0) and adjusted to 10 pups on Day 1. The dam had Purina Lab Chow and tap water continuously available in the cage top. Lights in the colony were maintained on a reversed light-dark cycle and were on from 2100 to 1100 h. Room temperature ranged from 23° to 25°C, humidity, 50–60%.

Six-day-old pups that weighed between 11–16 g were studied. Animals were simultaneously exposed to odors and tastes as below, and later tested under red illumination. Only one pup per treatment condition came from any given litter. In all experiments, subjects were tested only once.

### *Surgical Procedures*

Surgical implantation of a jaw cannula (11,12) occurred 4–6 h prior to testing. A 9-cm long cannula was constructed from PE-10 Intramedic Polyethylene Tubing (Clay-Adams) with a small flange (1.5 mm in diameter) formed at the tip by heating and then gently pressing the tip against a cool smooth surface. The surgical procedure was achieved by passing an 8 cm length of curved wire (0.255 mm in diameter) beneath the animal's tongue and out the ventral surface of the jaw. The distal end of the wire was then drawn through the jaw with the friction-fit cannula. The surgical procedure was complete in about 20 s.

### *Substance Delivery*

Six substances were used in these experiments: 7.5% sucrose solution, 32% (w/v) Polycose solution, corn oil (Mazola Corn Oil is a long chain unsaturated fat similar in structure to that found in rat milk), 0.1% quinine solution, mineral oil, and distilled water. All solutions were infused at 36°C.

The designated substances were delivered via infusion pump (Sage Instruments) at a rate of 0.04 cc/min, via a 5-cc hypodermic syringe attached to a length of PE-50 Intramedic Polyethylene Tubing (Clay-Adams), that, in turn, engaged the individual pup's cannula. Each rat received a total of 0.4 cc of fluid.

### *Experimental Treatment*

Five-day-old pups were separated from their mother and deprived as a group in a plastic tub (12.5 cm diam × 12.5 cm h) containing 200 cc of fresh bedding chips, in an environmental chamber (Forma Scientific, model BF-88M) with temperature set to 32°C, humidity at 55%. Nineteen to 20 hours later, the pups were weighed, numbered, received the jaw cannula as described above and were returned to the environmental chamber as a group. Four to five hours later, each subject was connected to the infusion apparatus, and then placed individually for 30 min in a styrofoam cup (310 ml) that contained fresh cedar bedding chips (20 cc) mixed with 0.3 ml orange extract (McCormick Co.). The free end of the jaw cannula was connected by silastic tubing (Clay Adams) to a 5-cc syringe (Becton Dickinson and Co.) that contained the solution to be infused. During the initial 10-min period of odor exposure, no infusion was made. This was immediately followed by twenty infusions that were delivered in a 30-s-on/30-s-off pulsatile fashion. After completion of the training session, the jaw cannula was removed. Pups were housed as a group for 1 h in the environmental chamber before being returned to their dam in the colony room.

### *Test Procedure*

Forty-eight hours later, subjects were removed from the colony, reweighed, remarked and housed as described above. After 3–5 h, each pup was placed in a test arena, a plastic tub (13 × 18 × 29 cm). The arena was divided into 3 parts: a side (7.5 cm) containing 75 cc fresh bedding sprinkled with 0.12 ml orange extract, a central no-bedding area (3 cm), and the other side (7.5 cm) containing 75 cc plain bedding. A wood-frame nylon screen was seated in the tub 2 cm above the chips, allowing the rats the freedom to move about the arena without contacting the chips (10). Order of experimental group testing was counterbalanced among litters to avoid differences in overall duration of deprivation.

At the start of the 10-min test, a rat was placed on the screen over the neutral area and allowed to freely ambulate. After 5 min, the rat was removed from the arena, and 10 s later, placed again on the screen over the neutral area, but facing the direction opposite the initial placement, for the second 5-min period. The amount of time that a subject spent on each portion of the arena was recorded by an experimenter unaware of the pup's treatment history. Clean containers, screens and fresh bedding were used for each rat.

### *Statistical Analysis*

Group means were compared by analysis of variance with post hoc *t*-tests. Data from Experiment 1 were analyzed by one-way ANOVA; two-way ANOVA was used for Experiment 1a (infusion × odor), and Experiment 2 (infusion × injection).

## EXPERIMENT 1

This experiment determined whether odors that predicted and accompanied infusions of various solutions would become preferred by infant rats. To assess specificity of effect, a number of solutions with distinctly different tastes and flavors were associated in a constant manner to a constant olfactory stimulus. The prediction, based on increased pain limen and reduced vocalization in isolated rats, was straightforward; sucrose, corn oil, or Polycose associated with a novel odor should cause a preference for that odor; water, quinine or mineral oil should not.

### METHOD

### *Subjects*

Eighty-two pups from 12 litters were studied, with only 1 pup from each litter contributing to each of seven substance conditions: 7.5% sucrose (S); 32% Polycose (P); corn oil (CO); 0.1% quinine (Q); mineral oil (MO); distilled water (W); or no substance (NS). Mineral oil was infused as a control for the viscosity of the corn oil infusion; distilled water and quinine served as controls for the passage of different, novel fluids through the oropharyngeal tract.

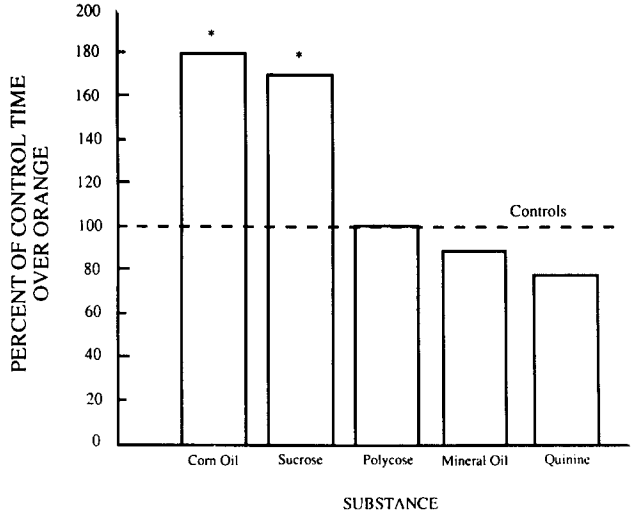


FIG. 1. Ratio of time spent over orange odor by rats in the four experimental conditions relative to control subjects when 8 days of age. The amount of time spent over orange by control rats receiving either no infusion or an intraoral infusion of distilled water at 6 days of age was 2 min 30 s.

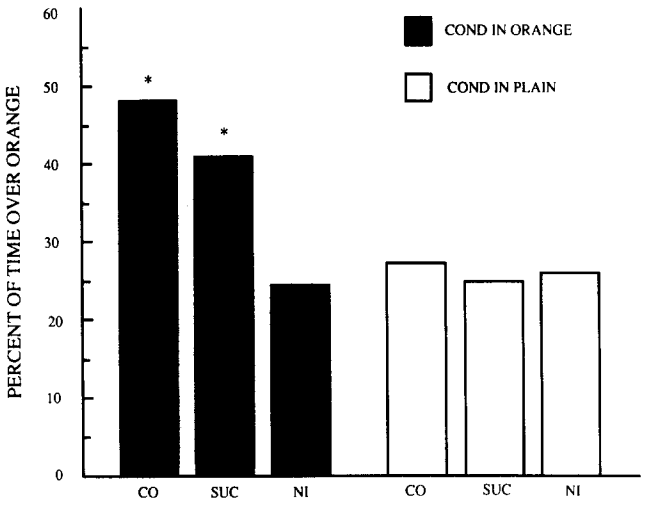


FIG. 2. Percentage of time spent over orange odor by 8-day-old rats that had received their experimental treatment while in the presence of orange odor (filled histograms) or in the presence of standard unscented bedding (clear histograms).

*Training and Testing*

Privation, surgical implantation, training and testing occurred as described above.

*Statistical Analysis*

The time that pups from different groups spent over the orange-scented bedding (in s) was compared by one-way ANOVA.

RESULTS AND DISCUSSION

Time (in s) spent over the orange-scented bedding on Day 8 differed according to Day 6 treatment, $F(6,81)=4.18$, $p<0.01$. Pups that had received intraoral infusions of 7.5% sucrose or corn oil preceded by and in conjunction with orange odor spent 43% and 45% respectively of the 10-min test over the orange-scented bedding (Fig. 1). In contrast, control pups that received either no infusion or a distilled water infusion spent 22% and 25% respectively of the time over the orange-scented area. Pups that received an infusion of 32% Polycose, 0.1% quinine, or mineral oil did not differ significantly from control rats with respect to their choice behavior (25, 20, and 21% of the time over orange). That Polycose infusion did not alter choice behavior was unexpected, given its effects in Day 10 rats. It is possible that Day 6 pups do not detect or taste Polycose; this is supported by Vigorito and Sclafani (26), who showed that infant rats responded differentially to Polycose, as compared to water, only after 9 days of age. These findings speak to a specificity of effect. Not all substances associated with the odor caused a statistically significant shift in choice behavior. Failure of these substances to alter choice behavior will be discussed below.

## EXPERIMENT 1A

Experiment 1a was undertaken to evaluate whether the increased time spent over the orange odor reflected changes caused by 1) a specific contingency between orange and sucrose or corn oil, 2) exposure to orange per se, which might diminish the aversive quality of the odor (although evidence against the latter was presented in Experiment 1), or 3) the potential sensitization caused by intraoral infusions of sucrose or corn oil. Accordingly, subjects were either exposed to orange-scented chips or to fresh untreated chips and received either no infusion, or using the same parameters as above, corn oil or sucrose infusions.

METHOD

*Subjects*

Seventy two pups from 12 litters were studied, with 2 pups from each litter contributing to each of 3 substance conditions: 7.5% sucrose (S); corn oil (CO); or no substance (NS). One pup in each pair received its experimental treatment in the presence of orange scent, the other in unscented chips.

On Day 5, pups were separated from the dam and placed in an environmental chamber for 19–20 h. The pups received intraoral jaw cannulae 4–5 h before conditioning. Conditioning took place as described in the General Method section, with the exception that one-half of the pups received their designated infusion in plain, unscented chips. Then, one h after the infusion, these pups were exposed to orange-scented bedding for 30 min. This procedure evaluated both familiarity, sensitization and the order in which the predictive sequence unfolded.

*Testing*

Testing took place on Day 8 as described in the General Method section.

RESULTS AND DISCUSSION

The amount of time spent over the orange-scented bedding on Day 8 differed according to Day 6 treatment (Fig. 2). Two-way ANOVA revealed a significant main effect for infusion, $F(2,71)=8.12$, $p<0.01$, and for odor $F(1,71)=23.36$, $p<0.01$. The conditioning effect was specific to pairing orange with corn oil or sucrose. Neither the presentation of orange alone, nor of sucrose or corn oil alone in the absence of the conditioned stimulus, caused a change in preference behavior.

TABLE 1

| Group | Infused Substance | Injection Training | Injection Testing |
|---|---|---|---|
| 1 | No Infusion | Saline | — |
| 2 | No Infusion | Naltrexone | — |
| 3 | Corn Oil | Saline | — |
| 4 | Corn Oil | Naltrexone | — |
| 5 | Sucrose | Saline | — |
| 6 | Sucrose | Naltrexone | — |
| 7 | Corn Oil | — | Saline |
| 8 | Corn Oil | — | Naltrexone |
| 9 | Sucrose | — | Saline |
| 10 | Sucrose | — | Naltrexone |

## EXPERIMENT 2

Experiment 1 revealed that an intraoral infusion of 7.5% sucrose or corn oil paired with a novel odor altered subsequent responsivity to that odor. Based on naltrexone reversibility of quieting and elevated pain threshold, it was suggested (4,21) that the tastes of sugar and corn oil engage endogenous opioid systems. This suggestion provides direction for identifying a possible mechanism for preference formation under the present circumstances. It predicts that linking the taste of sucrose or the flavor of fat with orange changes preference for the odor because of the endogenous opioids released by the infusion. Thus orange gains significance through linkage with the released opioid rather than through taste per se.

Blocking the change in preference behavior by administering a mu receptor blocker at the time of conditioning has an additional implication: orange at the time of testing becomes effective because it now either causes the release of endogenous opioids or, at some level, it sensitizes the system that detects ongoing fluctuations in opioid level. In either case, a clear prediction is made, namely, that naltrexone administered at the time of testing should prevent the manifestation of orange preference because it successfully competes with endogenous opioids at the receptor. Blockade effectiveness is not predicted by a theory that asserts that preference, reflects anticipation of a sucrose or corn oil infusion. Accordingly, to evaluate these predictions, naltrexone was administered either just prior to taste-odor association or just prior to testing.

### *Conditioning*

Conditioning took place as described in the General Method section with the exception that 6 of 10 pups in each litter received a naltrexone (0.5 mg/kg) or saline injection 30 min before the conditioning experience.

### *Testing*

Testing took place exactly as described in the General Method section with the exception that the 4 pups in each litter that had not been injected prior to conditioning now received either a naltrexone (0.5 mg/kg) or saline injection 30 min before the testing session.

### METHOD

### *Subjects*

One hundred twenty-two pups from 14 litters were studied.

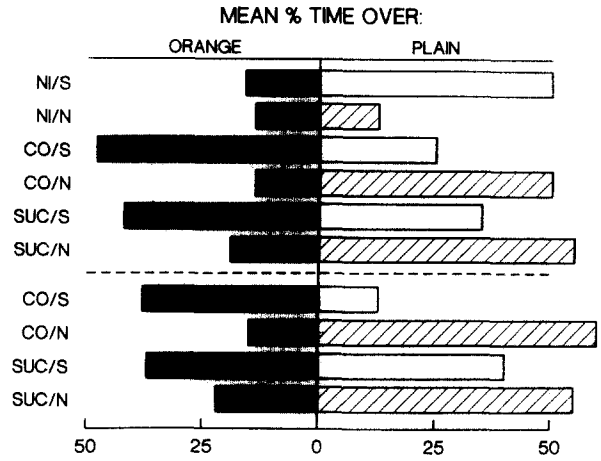


FIG. 3. Mean percentage of time that Day 8 pups spent over orange-scented (filled histograms) or plain (open histograms) bedding. Pups on Day 6 received either no infusions or intraoral infusions of corn oil (CO) or 7.5% sucrose (SUC). Treatment groups above the dotted line received saline (S) or naltrexone (N) before conditioning on Day 6; treatment groups below the dotted line received saline or naltrexone before testing on Day 8 (total mean percent time does not equal 100 as time over the no bedding area was not included in this figure).

The 10 groups of rats that comprised this study are depicted in Table 1.

### RESULTS AND DISCUSSION

Figures 3 and 4 confirm that saline-pretreated pups receiving an infusion of sucrose or corn oil demonstrate a marked shift in responsivity to orange odor, in both the mean time spent over the orange-scented portion of the arena (Fig. 3), and in the number of rats preferring the odor (Fig. 4). Two-way ANOVA revealed significant main effects for substance infused, $F(2,121) = 5.21$, $p<0.01$, and for injection, $F(1,121) = 26.78$, $p<0.01$.

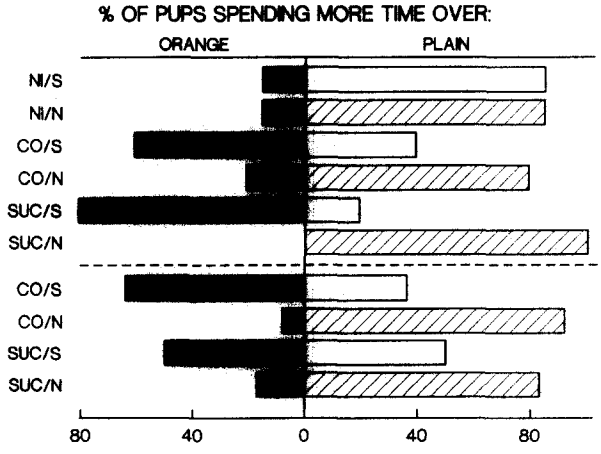


FIG. 4. Mean percentage of Day 8 pups that spent more time over orange-scented (filled histograms) or plain (open histograms) bedding. Pups on Day 6 received intraoral infusions of corn oil (CO) or 7.5% sucrose (SUC). Treatment groups above the dotted line received saline (S) or naltrexone (N) before conditioning on Day 6; treatment groups below the dotted line received saline or naltrexone before testing on Day 8 (NI = noninfused controls).

Naltrexone pretreatment either at the time of conditioning or testing prevented the formation and expression respectively of orange preference by rats that had orange paired with infusions of sucrose or corn oil. Blockade of formation is presented above the dashed line in both Figs. 3 and 4. Whereas pairing corn oil or sucrose with orange caused a shift in preference from the 20% spent by control rats over orange to 48% and 44% respectively, preceding these pairings with naltrexone returned performance to baseline levels. A comparable profile is obtained when the percentage of pups that expressed the preference is used as the measure. Specifically, naltrexone preceded conditioning reduced the percentage of rats preferring orange to 25% and 0% for corn oil and sucrose respectively, values comparable to the 10% in control rats that received naltrexone prior to odor exposure alone that was not followed by infusion. These findings support the view that intraoral infusions of corn oil or sucrose gained control over preference behavior by virtue of their causing opioid release, presumably of a central origin. It is interesting in this regard that taste alone (assuming that taste perception was not altered by naltrexone treatment) did not gain control over odor preference.

Naltrexone administration 30 min prior to testing in rats that had received the standard conditioning procedure eliminated orange preference, reducing the time from 36 to 22% and 38 to 14% for sucrose-treated and corn oil-treated pups respectively. The fact that these percentage times are well within the range of control rats that (had or had not experienced naltrexone at the time of conditioning) were drug free at test time argues against naltrexone effectiveness at test time by virtue of increased irritability to orange odor.

## GENERAL DISCUSSION

Pairing orange odor with intraoral infusions of either 7.5% sucrose or corn oil changed the hedonic value of that odor. Significantly more time was spent over orange by rats for whom orange predicted and was paired with sucrose or corn oil than by rats that either received no infusion, or water, QHCl, mineral oil or Polycose infusions with orange. Thus simple exposure to orange odor did not cause a significant change in preference behavior nor did pairing the odor with an intraoral infusion of other novel substances. Shift in preference also did not reflect a sensitization to orange as a result of the infusion because identical infusions of sucrose or corn oil in the absence of pairing with orange did not cause a change in preference (Experiment 1a).

Altered preference behavior cannot be explained by recourse to taste novelty, texture (mineral oil was not effective), infusion rate, experimental novelty per se or the general experience of fluid passing through the oropharynx. The change in preference occurred only in rats that received sucrose or corn oil and not simply any tastant. Failure to establish preference was expected, of course, when water, quinine, or mineral oil (none of these substances elevate pain threshold or reduce vocalizations) was the unconditioned stimulus, but not for Polycose, which substantially reduced ultrasonic vocalizations in isolated Day 10 rat pups, and elevated pain limen. The Polycose infusion may not have been effective due to immature gustatory afferents in Day 6 pups. According to Vigorito and Sclafani (26), Polycose only starts to be an effective gustatory stimulus in rats by about Day 10.

Blocking preference formation by naltrexone administration prior to conditioning indicates that sucrose and corn oil, at the concentration and infusion parameters utilized in the present studies, either: 1) caused the release of endogenous opioids that became available to motivational systems subserving preference formation or 2) sensitized these systems without causing an increase in opioid release or uptake. Saturating the receptor with morphine injections prior to conditioning with fat or sucrose then allowing rats to choose between orange and plain bedding might help decide between these alternatives. If the former is true, there should be no orange preference formation because, in principal, the putative release of endogenous opioids would not be detected against the already very high background of exogenous opiate levels. If the latter holds, then orange should be preferred because, in principal, the system(s) mediating change in preference, at some level, should be more responsive to the circulating exogenous opiates.

Much the same can be said conceptually for the shifting valence towards an odor dependent upon its relationship with (at present) sucrose and corn oil. Prevention of preference expression by naltrexone at the time of testing provides indirect evidence that, within the parameters of the present study, orange odor is causing the release of endogenous opioids or sensitizing the motivational and neural systems subserving preference. It would be of theoretical interest in this regard both for understanding mechanisms underlying conditioning and performance and mother-infant interactions to determine if naltrexone administration at the time of testing would also block the manifestation of a preference established by pairing an odor with a stimulus that does not rely upon opioid systems for its effectiveness.

The issue of an odor gaining control over later choice behaviors is important in establishing principles of behavioral development. Odors experienced in the nest influence behavior in rats from infancy through adulthood. Rosenblatt (20) has proposed that olfactory cues, particularly those from the nest and mother, become established as incentives during early development because they have been associated with stimulation provided by the mother. An implication of Rosenblatt's proposal within the context of the present study is that the taste of rat milk should cause a similar pattern of events, i.e., an odor associated with milk delivery should become preferred, formation should be blocked by an opioid antagonist, likewise so should expression.

The present studies have identified an additional characteristic of opioid system engagement, namely that in addition to calming isolated animals and elevating pain limen, they participate in preference acquisition. This implies that exposure to the conditioned odor engages the endogenous opioid systems and the effector, perceptual and motivational systems that they subserve.

It is of interest in this regard that exposure to the conditioned odor causes preference and not aversion. This seems to be at variance with predictions based on the work of Siegel (23). In adult rats, even after a single pairing of morphine with a stimulus, subsequent exposure to that stimulus causes a reaction opposite to that of the morphine injection (23). A potential resolution between this prediction and the current findings originates from the fact that rats do not become tolerant to or show withdrawal symptoms from morphine injections until after 18–19 days of age (8).

Finally, it is necessary to demarcate the limitations of the present findings. Although they reflect certain aspects of infant motivation capacities in terms of experience causing a behavioral change and the mechanisms underlying this change, they do not address whether this system is actually engaged under normal circumstances in which the received fluid is milk delivered to the back of the mouth. Nor do they establish the generality of opioid release or opioid system sensitization as participants in ongoing behaviors during or following the period of early devel-

opment. These issues must be resolved for a more satisfactory understanding of how mothers influence their young. We have already established that quieting (2) [although see Carden and Hofer (6,7) for a differing view] and antinociception (22) caused by maternal contact is not opioid mediated. The synergy between these two classes of systems is currently being explored (1a).

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