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Prenatal Exposure to Morphine Alters Analgesic Responses and Preference for Sweet Solutions in Adult Rats

R. GAGIN,* E. COHEN AND Y. SHAVIT[1]

Department of Psychology, The Hebrew University of Jerusalem, Jerusalem 91905, Israel

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GAGIN, R., E. COHEN AND Y. SHAVIT. *Prenatal exposure to morphine alters analgesic responses and preference for sweet solutions in adult rats.* PHARMACOL BIOCHEM BEHAV **55**(4) 629–634, 1996.—In the present study, we examined long-term effects of prenatal morphine on pain response and on preference for sweet solutions. Pregnant Fischer 344 rats were given increasing doses of morphine (0.75–12.0 mg/day) in slow-release emulsion, during gestational days 12–18. Control rats were injected with vehicle and were either pair-fed to morphine rats, or ad libitum fed. At birth, all litters were culled to 8–10 pups (half males and half females) and cross-fostered to naive, surrogate dams. Testing began when rats were 10–12 week old. Rats prenatally exposed to morphine exhibited higher analgesia in response to a morphine challenge, and a greater preference for saccharin solution as compared with both control groups. These findings indicate that prenatal morphine induces long-lasting alterations of systems involved in reward processes and in opiate analgesia, perhaps by modulating endogenous opiate systems. **Copyright © 1996 Elsevier Science Inc.**

Nociception Analgesia Opiates Morphine emulsion Palatability Saccharin Prenatal Delayed effects Reward Sweetness preference

OPIATES can adversely affect fetal development as is evident from reports of reduced birth weight and length (30), smaller head size (6), and higher mortality rates (13,15), observed in neonates exposed to opiates during gestation. Long-term effects of intrauterine opiate exposure have also been reported. For example, growth retardation (19) and impaired cognitive potential (48) were observed in preschool and school age children. In rodents, enhanced self-administration of cocaine and heroin (34), impaired female reproductive behavior (45), and long-term changes in opiate receptors (11,43,52) were reported following prenatal exposure to opiates.

Endogenous opiate systems play a pivotal role in pain perception. Therefore, alterations in nociception could be expected in offspring of dams treated with opiates during pregnancy. Prenatal exposure to opiates was shown to either increase (5,13,23,51,53), or decrease (20,33) the analgesic response to opiate challenge later in life.

Endogenous opiate systems also play an important role in neural circuits of reward. Opiate agonists increase the rewarding effect of brain stimulation (2), whereas opiate antagonists lower such effect (37). Opiate agonists are also involved in the rewarding effect of consummatory behavior (9) and in preference for sweet solutions (10).

In the present study, we sought to examine the long-lasting effects of prenatal opiate exposure on morphine analgesia and on sweetness preference. Pregnant dams were injected with increasing doses of morphine emulsion on days 12–18 of pregnancy. The offspring were examined, as adult rats, on two behavioral responses: Morphine-induced analgesia (measured by either the tail-flick or hot-plate tests) and preference for saccharin solutions.

METHODS

Prenatal treatments. Nulliparous Fischer 344 female rats (Harlan Laboratories, Jerusalem), 10–12 weeks old, weighing 230–250 g, were maintained under standard laboratory conditions (23 ± 1°C; 12-hr light-dark cycle, with light on between 19:00–7:00). Food and water were constantly available (unless otherwise specified). To determine the day of estrus, animals were placed with sexually vigorous studs for a brief observation. Estrus was defined by the occurrence of lordosis behavior. Estrous females were housed with Fischer 344 males for

[1] To whom requests for reprints should be addressed.

approximately 16 hours. The day of mating was considered day 0 of pregnancy. Females mated on the same day were housed in group cages until day 12 of gestation, after which they were separated into single cages until parturition. Morphine or vehicle were daily administered on days 12–18 of pregnancy, using subcutaneous (sc) injections (1 ml) of a slow-release emulsion, composed of saline (with or without morphine), light mineral oil and an emulsifying agent (Arlacel-A; Sigma, Israel) in ratios of 8:6:1, respectively (after 8,14). Pregnant rats were randomly assigned into 3 groups. The protocol of prenatal morphine administration was based on a pilot-study in which we have examined various increasing doses of morphine and several schedules of drug administration, including injections up to delivery day. The selected protocol yielded a survival rate of $\geq$ 80% of the newborns. For the experimental (Morphine) group, morphine HCl (Teva, Israel) was dissolved in the saline of the slow-release injection in increasing doses as follows: 0.75, 1.5, 1.5, 3.0, 6.0, 12.0, 12.0 mg/injection, corresponding to 7 injections during days 12–18 of pregnancy. Two control groups were used: Ad-Lib control animals received vehicle injections and ad libitum feeding; and Pair-Fed control animals received vehicle injections and restricted feeding, corresponding to the average food intake measured on the previous day in morphine-injected dams. Each litter was culled to 8–10 pups (half males-half females) 24 h after birth, and cross-fostered to naive dams for 3 weeks, after which offspring were weaned, housed in cages of 3–4 rats per cage, and maintained at standard conditions.

Postnatal testing. Postnatal testing began when rats were 10–12 week old. A different batch of rats was used for each of the following 3 experiments:

Tail-flick latency (TFL) was measured in males and females of the three prenatal treatment groups. Animals received 6 TFL tests, with at least 3 interval days between succeeding tests. On each testing day, each rat was placed in a plexiglass tube, allowed 30 min of adjustment to the restraint, and was then injected (sc) with a single dose of morphine (dissolved in saline). The following doses were used, in the specified order: 0.0, 0.5, 1.0, 2.0, 4.0, 8.0, and again, 0.0 mg/kg. Following the injection, the rat was returned to the plexiglass tube. Tail-flick measurements began 5 min later. The tail was placed over a source of radiant heat and the latency to tail-flick was measured. Cutoff latency was set at 9 seconds to prevent tissue damage. Measurements were taken every 5 min for 1 h.

Hot-plate latency (HPL) testing schedule was similar to that of the TFL test. Six tests were carried out in 3 day intervals. Each animal was injected (sc) with a single dose of morphine each testing day, at the following doses: 0.0, 0.25, 0.5, 2.0, 4.0, 8.0, and 16.0 mg/kg. Thirty min later, the animal was placed onto a hot-plate (20 $\times$ 20 cm) which was maintained at 53 $\pm$ 1°C, and covered by an insulating cardboard (the apparatus was surrounded by a 45 cm high plexiglass enclosure). Each rat was allowed 1 min of adjustment, following which the cardboard was removed and the rat exposed to the heated surface. HPL was defined as the latency from the time the cardboard was removed to the first incidence of hind paw licking or jumping. Cutoff latency was set at 45 s to prevent tissue damage.

Sweetness preference testing was carried out in two consecutive batches, one for each sex. Rats were housed in single cages and allowed 48 h of adjustment, following which they were each offered two drinking fluids: Deionized water and a solution of sodium saccharin (Sigma, Israel) dissolved in deionized water. Drinking fluids were presented in graded cylinders, which were attached to the front of the cage via

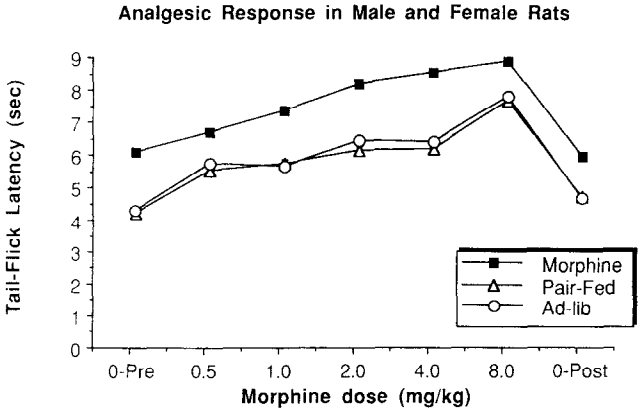

FIG. 1. (A) Tail-Flick Latency (TFL) across several morphine doses, in female rats prenatally treated with morphine (Morphine; n = 10), vehicle and pair-feeding (Pair-Fed; n = 10), or vehicle and ad libitum feeding (Ad-Lib; n = 8). (B) TFL in male rats of the same prenatal treatments: Morphine (n = 10), Pair-Fed (n = 10), and Ad-Lib (n = 8). All data are expressed as means $\pm$ SEM.

L-shaped spouts. Saccharin solutions, at concentrations of 1, 3, 10, or 30 mM, were each presented for 48 h, in ascending order, with the position of the water and saccharin cylinders switched every 24 h, to balance out position preferences. Fluid intake was recorded every 24 h, and fluids were then either replenished or replaced.

Data were analyzed using ANOVA procedures with repeated measures and post-hoc multiple comparisons. Significance level for all comparisons was set at $p < 0.05$.

RESULTS

Maternal/litter data. Food intake of morphine-injected dams was reduced to approximately 35% of food consumption by ad-lib dams, in accordance with previous reports (24). There was no difference in the number of newborns among the prenatal treatment groups. Newborns of morphine-treated dams had lower body weight at birth, but did not exhibit apparent malformations.

TFL. TFL scores were computed as the average of the 12 measures recorded over the 1 h period, following each dose of acute morphine. Rats prenatally exposed to morphine exhibited greater TFL baseline values compared with controls, and this effect was evident in both males and females $F(2,40)$ = 91.95 (point "0-Pre" in Fig. 1). Acute morphine induced a dose-related significant analgesia $F(6,40)$ = 115.00. TFL scores obtained following each of the doses of morphine were consistently greater in the prenatal morphine groups compared with the control groups $F(2,40)$ = 217.00 (Fig. 1). No significant differences were found between the control groups or between male and female rats within each of the three prenatal treatment groups.

HPL. Baseline values of HPL recorded in rats prenatally exposed to morphine, were not significantly different from those observed in controls (Fig. 2). Morphine induced a dose-related analgesia $F(6,65)$ = 143.46, which was significantly greater in rats prenatally exposed to morphine than in control rats $F(2,65)$ = 36.60 (Fig. 2). There was a significant main effect of sex: female rats exhibited an overall lower HPL compared to males $F(1,65)$ = 9.51. No significant differences were found between the control groups.

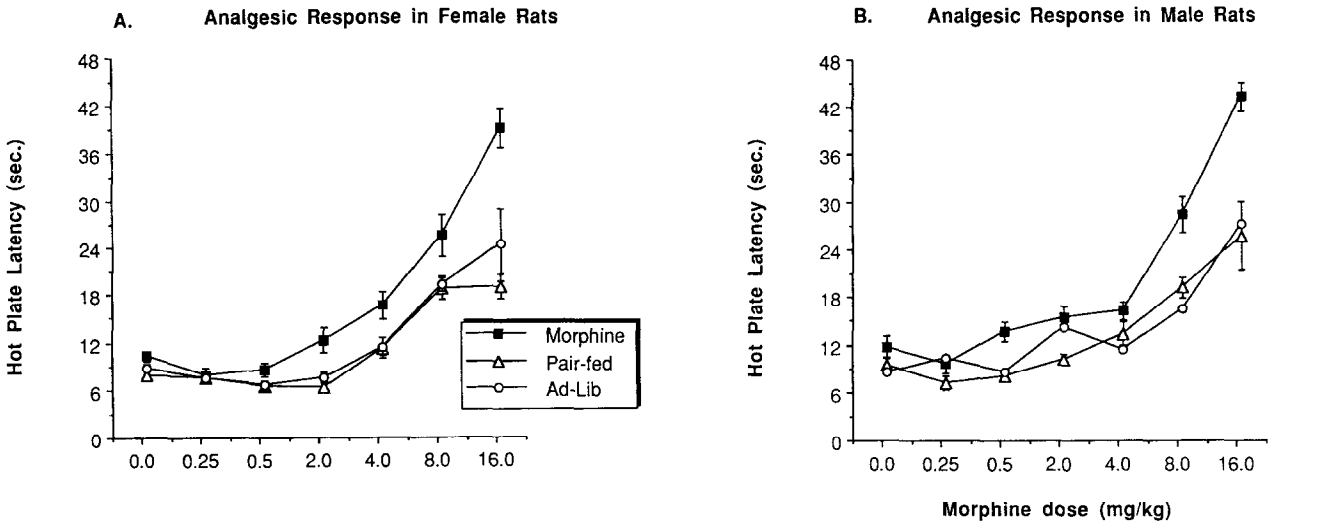

FIG. 2. (A) Hot-Plate Latency (HPL) across several morphine doses, in female rats of the three prenatal treatment groups: Morphine (n = 12), Pair-Fed (n = 12), and Ad-Lib (n = 12). (B) HPL in male rats of the same treatments: Morphine (n = 12), Pair-Fed (n = 11), and Ad-Lib (n = 12). All data are expressed as means ± SEM.

Saccharin preference. Saccharin preference scores were expressed as the percentage of daily consumption of each of the four saccharin solutions presented, over baseline consumption of deionized water (measured in days 1 and 2 of the experiment). Prenatal morphine markedly enhanced saccharin preference compared with the two control groups (Fig. 3). Preference was evident in prenatal morphine rats even at the lowest concentration of saccharin used (1 mM), which was sub-threshold for rats of the control groups. The effect of prenatal morphine was most prominent at the 10 mM solution (which was most preferred by all groups), and was clearly preserved at the 30 mM solution, despite the general decline in consumption of this concentration (due to its bitter taste). The two control groups did not significantly differ from each other. Water intake curves appeared as "mirror-image" of the sweet solution consumption curves. Water intake was decreased as a function of sweet solution consumption and was most decreased for prenatal morphine rats.

Female rats exhibited a significantly greater sweetness preference compared with their male counterparts. These findings agree with previous reports (44).

DISCUSSION

The present study examined the long-term effects of intrauterine exposure to morphine on two behavioral responses, pain sensitivity and preference for sweet solutions, previously shown to be mediated by endogenous opiate systems (31).

Prenatal morphine significantly elevated the analgesic response to acutely administered morphine in adult male and

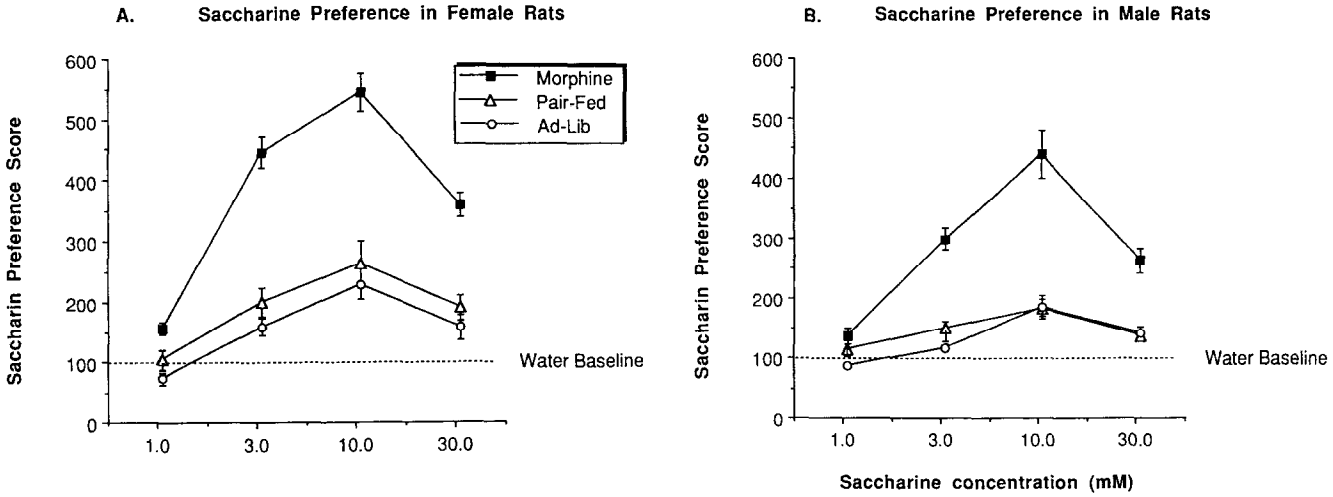

FIG. 3. (A) Saccharin preference scores across several saccharin concentrations, in females of the three prenatal treatment groups: Morphine (n = 12), Pair-Fed (n = 12), and Ad-Lib (n = 12). (B) Saccharin preference scores in males of the three prenatal treatment groups: Morphine (n = 10), Pair-Fed (n = 11), and Ad-Lib (n = 10). All data are expressed as means ± SEM.

female rats, as measured by the tail-flick and hot-plate tests. These findings agree with several previous reports (5,13,23,51, 53), but are inconsistent with others (20,33). Such inconsistency could be attributed to variance in the schedules of drug administration. For example, Kirby and colleagues reported (24) that an identical dose of morphine had different effects on the fetus, depending on whether it was given 2 vs. 4 times daily. Variations in the effects of prenatal morphine may also be attributed to drug withdrawal experienced by the fetus between injections (27). The method of morphine administration employed in the present study ensured continuous presence of the drug (8,14), which served to minimize the problem of daily withdrawal.

Differences in baseline pain responses were observed between the two nociception tests used in this study, the tail-flick and hot-plate tests. Average baseline latency of prenatal morphine rats was significantly higher (compared with their controls) in the tail-flick, but not in the hot-plate, test. This discrepancy could be attributed to known procedural differences between the two tests: The TFL test involves stressful confinement of animals in restraint tubes for 90 min, whereas HPL measurements involve placing the animal in an unfamiliar but non-restraining environment. It has been reported that restraint stress induces an opioid-mediated form of analgesia, that could be potentiated by prenatal morphine; this form of stress could also potentiate morphine-induced analgesia (for review see, 35). Therefore, the elevated baseline latency observed in prenatal morphine rats in the TFL test is most likely induced by restraint stress, suggesting that these rats are more sensitive to the analgesic effects of both morphine and stress. Because baseline measurements in the HPL test do not involve restraint stress, we suggest that they better reflect the baseline pain sensitivity of the rats, indicating no significant differences in baseline pain sensitivity among the three prenatal treatment groups.

Saccharin preference was greater in both male and female rats of the prenatal morphine group compared with control rats. Group differences were evident in each of the concentrations used, including the 1 mM solution, which was significantly preferred by prenatal morphine rats but not by others. The relationship between the endogenous opiate systems, reward, and saccharin preference is well documented. Acute administration of exogenous and endogenous opiates into several brain sites is rewarding by itself, and can enhance the rewarding effect of brain stimulation, whereas administration of opiate antagonists is aversive and can attenuate rewarding brain stimulation (4,49). Endogenous opiates also play an important role in the rewarding aspects of consummatory behavior, especially regarding intake of palatable food and fluid (9). Opiate antagonists reduce the preference for sweet solutions (31), whereas opiate agonists increase the intake of sweet solutions (10). There is evidence that consumption of palatable solutions can activate the endogenous opiate systems. For example, intake of a sweet solution increased the release of β-endorphin in the hypothalamus (12); chronic consumption of sweet solutions attenuated the analgesic effect of small doses of morphine (3,7,28); while chronic exposure to morphine attenuated the preference for sweet solutions (29). The apparent cross-tolerance between morphine and sweet solutions indicates that a common substrate is activated by both substances (28,29). Taken together, these findings led to the hypothesis that opiate antagonists render sweet solutions less palatable or rewarding, whereas agonists have the opposite effect (9). Consistent with this hypothesis, opiate-receptor-deficient mice exhibit a reduced preference for saccharin solutions (50). The present findings are also consistent with this hypothesis, indicating that prenatal morphine induces long-lasting alterations of the reward system, which render sweet soltions more palatable or rewarding.

Several mechanisms may account for the long-term effects of prenatal morphine. First, morphine could induce changes in various aspects of the developing opiate system, such as the density, affinity, or pattern of distribution of the opiate receptors. Increased activity and/or sensitivity have been reported following prenatal opiate exposure. For example, prenatal exposure to morphine or β-endorphin induces an increase in μ, but not σ, opiate receptors in the striatum and nucleus accumbens (18,22,52); increased proenkephalin mRNA levels and decreased met-enkephalin levels were observed in the striatum of newborns (42), and enhanced development of met-enkephalin containing neurons in the rat was observed following perinatal morphine (11). In contrast, others have shown transient increase (43) or decrease (25,41) in the activity or sensitivity of the endogenous opiate systems. Still others have reported long-term decrease in these systems (1,46,51). As described above, these discrepancies are most likely due to differences in prenatal drug treatment, including drug dose, chronicity of receptor occupation, and gestational days during which dams were exposed. Another important factor is the age of the offspring when tested, which is especially important for transient effects, that could be demonstrated in neonates, but diminish over time (42). Although no direct assessment of the endogenous opiate systems was carried out in the present study, its findings, including increased sensitivity to morphine-induced analgesia and increased preference for sweet solution, together with our findings of increased morphine-conditioned place preference (manuscript in preparation), suggest long-term increase in the activity/sensitivity of the endogenous opiate systems following prenatal morphine exposure.

The reward system is regulated by an interplay between the dopamine (DA) and the endogenous opiate systems. A tonically active μ opioidergic system in the VTA has been suggested (39), that increases basic DA release in the nucleus accumbens. Thus, it is possible that a long-term increase in μ-opiate receptor sensitivity induced by prenatal morphine would result in increased basal DA release in the nucleus accumbens, and a highly sensitive reward system. Corroborating this hypothesis, Stinus and colleagues (40) demonstrated potentiation of opiate-induced hyperactivity and increased opiate reinforcing effects, following lesioning of DA neurons in the VTA. These investigators attribute their findings to the development of compensatory supersensitivity of the opiate systems in the nucleus accumbens or at a higher brain level. Other investigators demonstrated the development of subsensitivity in the striatal DA system following fetal exposure to β-endorphin (36). It is plausible that similar subsensitivity may develop in the mesolimbic system following prenatal morphine, resulting in compensatory supersensitivity of the endogenous opiate systems. Indeed, several reports have shown reciprocal effects in which prenatal cocaine exposure resulted in increased sensitivity to μ-opiate receptor ligands, and prenatal exposure to opiates resulted in enhanced reactivity of the reward system to both opiates and cocaine (16,34).

Other possible mechanisms include changes in secondary messengers, such as G-protein-cAMP, in the nucleus accumbens, as has been demonstrated in opiate-dependent individuals (38); alternatively, upregulation/supersensitivity of NMDA receptors due to blockade of these receptors by morphine have been suggested (26).

The present findings suggest that prenatal exposure to mor-

phine induces changes in the reward system, such that a sweet solution is perceived more palatable and/or otherwise more rewarding. The same changes may also intensify the perceived reward derived from drug of abuse. Gosnell and colleagues have recently reported (17), that rats, genetically selected for high saccharin preference, exhibited a higher rate of intravenous morphine self-administration, compared with rats selected for low preference. Thus, the enhanced preference for sweet solutions observed in rats prenatally exposed to morphine, may be associated with a higher risk for drug abuse. Indeed, prenatal exposure to morphine has been reported to enhance self-administration of morphine (21), heroin and cocaine (35) in rats. In humans, craving for sweet substances is frequently reported by opiate addicts, accompanied by large intake of sweet food (32,47). The present results, together with other animal and human studies, suggest that measures of taste sensitivity and preference may prove useful as a means of identifying those at risk for drug abuse.

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