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Effect of Chronic Neonatal Morphine and Naloxone on Sensorimotor and Social Development of Young Rats[1]

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NAJAM, N. AND J. PANKSEPP. *Effect of chronic neonatal morphine and naloxone on sensorimotor and social development of young rats.* PHARMACOL BIOCHEM BEHAV **33**(3) 539–544, 1989.—Chronic morphine treatment of newborn Long-Evans rat pups between 3–26 days of age (thrice daily starting with 0.5 mg/kg, increased daily by 0.5 mg/kg to 10 mg/kg) led to lags of 1 to 3 days in physical development (body weights and eye opening times) and motor coordination (catalepsy test, grasping, swimming). Chronic naloxone treatment (5 mg/kg administered thrice daily from day 3–26), in contrast, led to modest gains in development on a number of measures (body weights, vaginal opening). Morphine animals also lagged behind controls and naloxone-tested animals in social behaviors, such as homing and play. Chronic naloxone did not block or retard social development; in fact naloxone-treated animals exhibited more rapid acquisition of homing behavior than controls.

Morphine Naloxone Development Social behavior Play Homing Rats

EXTENSIVE deficits in physiological development of young animals result from chronic neonatal narcotic exposure (34), including decreased growth (10, 16, 27), delayed developmental milestones (fur covering, eye and ear opening), sexual maturity (e.g., vaginal opening), reflexive behaviors (righting, startle), and sensorimotor competence (10, 26, 30, 31, 34). Young animals treated chronically with opiates also exhibit decreased brain weights and deficits in synaptosomal uptake of major neurochemicals (25,29). Early studies indicated that chronic treatment with opiate receptor antagonists has little effect on physiological and behavioral development (8,21), except perhaps for changes in sensitivity to morphine in adulthood (8, 9, 12, 20). However, recent work by Zagon and McLaughlin (32,33) demonstrates that high doses of naltrexone (50 mg/kg), which block opiate receptors for 24 hours, can facilitate many of the developmental processes summarized above. In addition, earlier work by Vorhees (29), where pregnant dams which had been treated twice daily with 20 mg/kg naloxone during the last two weeks of gestation, had pups which grew faster and exhibited faster development according to several behavioral indices (righting, olfactory orientation and auditory startle).

Although many basic processes have been studied following chronic opiate agonist and antagonist exposure (34), there is relatively little work on the overall behavioral and social competence of such animals during later life. Because prior work from this laboratory has implicated endogenous opioids in the elaboration of various social processes [for reviews see (18,19)], the aim of this work was to determine whether the development of social motivation and social behavior is adversely affected by chronic exposure of young animals to either narcotic agonist (morphine) or antagonist (naloxone) during the first four weeks of life. The specific social behaviors observed were homing (17) and play behavior (16). Our homing task measures the competence of young rats to learn a spatial discrimination (T-maze) to return to the vicinity of their home, and play behavior is an easily quantified measure of the intensity of spontaneous social interaction among young rats. In addition, we also re-evaluated the development of sensorimotor competence. Most of the tasks designed to evaluate the motor development of the rat pups were adapted from Almli and Fisher (1) and administered from days 4–14. Swimming tests adapted from Shapiro *et al.* (24) and Salas (23) and spontaneous alternation tests adapted from Egger (6) were also studied.

METHOD

Housing

Pregnant Long-Evans female rats derived from BGSU breeding stock were housed individually in 24 × 40 × 19 cm cages with

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wood chip bedding. Illumination was maintained on a 12-hour light/dark cycle, and throughout testing animals had free access to food and water. The room temperature was maintained at 70 ± 2°F. Upon birth, pups within each litter were distributed and counterbalanced for sex among three groups: morphine, saline and naloxone. (For counterbalancing purposes, all litters selected for study in this experiment had 12 pups.) Pups were ear punched for individual identification. On day 3, the mother and the pups were transferred to new home cages (48 × 28.5 × 14 cm) designed for use in homing experiments. These home cages were divided lengthwise into two sections by a wire mesh partition. The mother and the pups were housed in the larger section (48 × 17.5 × 14 cm). The smaller section into which animals had no access from the home were 48 × 11 × 14 cm, and had two doors on each end (4 × 7 cm). It was used later for homing tests [see (17) for more extensive description of this apparatus].

Drug Treatment

Chronic drug treatment of the neonates was initiated on their third day of life. Morphine animals were started on 0.5 mg/kg morphine, naloxone animals on 5 mg/kg naloxone, and control animals on an equivalent volume of saline, all injected intraperitoneally (1 cc/kg) thrice daily at 8-hour intervals throughout the treatment period (day 3–26). The drug dosage for the morphine condition was increased daily by 0.5 mg/kg until 10 mg/kg per injection was achieved; this dosage was then maintained until day 26. All pups were weighed, injected, and returned to the mother. Throughout each testing procedure, the whole litter was taken away from the mother for testing and returned after testing was over (duration of separation was approximately 10–15 minutes). The litters were weaned on day 21 and all pups housed singly in wire mesh cages (25 × 18 × 18 cm).

Testing Procedure

Because the morphine doses employed caused marked catalepsy in these young animals, behavioral testing of morphine-treated animals (except for the catalepsy tests) was conducted approximately halfway between the injections administered during the daylight hours. Testing of naloxone and saline animals was conducted half an hour after the injections. All testing (except for swimming, spontaneous alternation, homing and play behaviors) was conducted under a 250-watt incandescent light placed at a distance sufficient to maintain the testing surface at 23 ± 2°C. All drug treatments were continued until day 26. Posttreatment testing continued until puberty.

Sixty subjects were studied (n = 20 per drug treatment, with subsets as indicated tested on the various dependent measures). Interobserver reliability for the various dependent measures ranged between .80–.92.

MOTOR TESTS

General Procedure

Pups were tested on the following tasks every other day between 4–14 days of age. Each pup was selected at random from the litter and tested for one minute on each task. After the completion of each task the pups were returned to the litter. The following sensorimotor tasks were administered in the same order throughout the experiment.

Catalepsy test (n = 20 per group). For the catalepsy test, animals were individually placed on a table, with their hind limbs resting on a 1.4-cm high platform. The time taken to climb off or onto the platform was recorded. If no response occurred within one minute, the subject was given a maximal score of 60. This test was administered 30 min following morphine injections.

Grasping (n = 20 per group). For the grasping test, each rat was placed in the center of the testing surface and then gently picked up under the forelimbs. A wooden stick (cir. 2.5 cm) was placed simultaneously on the ventral surface of both forepaws. If the paws curled around the pencil, a positive grasping response was recorded.

Swimming (n = 10 per group). Daily swimming tests were conducted from days 10–22. Each pup was dropped gently into a filled 50 × 31 × 31 cm aquarium (water temperature 27 ± 2°C). Swimming ability was rated on two scales [adapted from Shapiro *et al.* (24) and Salas (23)]: head position and leg activity. Head position was rated as 0 if the pup was unable to keep its nose out of water. It was rated as 3.0 if pup had its nose out of the water and head tilted at an angle. Leg activity was rated from 0–3, 0 being the uncoordinated use of both legs and 3 being inhibition of forepaw movement. After testing the animals were placed under a heat lamp to dry before being returned home.

Spontaneous alteration (n = 12 per group). Spontaneous alteration tests were run daily, from day 16 to criterion (two consecutive days of spontaneous alternation response). An open-bottom T-maze placed on a smooth surface was used for this test. The dimensions of the start arm and goal arms were 46 × 11.5 × 12 cm and 33 × 11 × 12 cm respectively. The animals were placed in the starting section (15 × 11.5 × 12 cm) for 15 seconds. The acrylic door was lifted and the latency of the subject's response to move forward and to turn into a goal arm was recorded. Each subject was given two successive trials. The running surface was cleaned between subjects to remove odor cues. Testing was terminated when subjects acquired the criterion.

Developmental Signs

In addition to the above, body weights were recorded daily, and eye and vaginal openings were monitored.

SOCIAL COMPETENCE TESTS

General Procedure

Homing (n = 19 per group). The homing test began when rats were 21 days of age and continued until subjects achieved criterion performance (2 consecutive days of 80% successful trials). The home cage was attached to the T-maze in such a manner that the doors of both juxtaposed [for detailed description, see Panksepp and DeEskinazi (17)]. At the start of testing, the pups were removed and kept isolated in separate "intertrial-interval" boxes.

At the start of a trial, a pup was placed in the start arm of the T-maze and latency to make a choice was recorded. The reward for making the correct response was contact with and visual/olfactory access to the home cage, mother, and litter mates. If a subject made an incorrect choice it could not achieve access to the home cage area. Without being permitted to retrace, the subject was removed from the maze and placed in isolation till the next trial 60 seconds later. Each subject was given 10 trials daily until criterion was achieved.

Play behaviors (N = 16 per group). The testing chamber was an acrylic box (31 × 31 × 31 cm) with wooden chip bedding on the floor. A chamber was housed in a larger sound-attenuating box illuminated within by a 25-watt red bulb. Pairs of animals of the same sex were placed in the acrylic box for 5-min test sessions, during which the frequency of pinning was recorded for each animal. Pinning was determined as physical dominance assumed by one animal with the other on its back.

The play tests were initiated at 21 days of age and were

TABLE 1

MEAN (±SD) EYE OPENING TIME AND ONSET OF VAGINAL OPENING IN DAYS, OF RATS CHRONICALLY EXPOSED TO MORPHINE, NALOXONE AND SALINE DURING EARLY DEVELOPMENT

Treatment	N	Eye Opening	N	Onset of Vaginal Opening
Morphine	20	15.3 ± 0.67†	8	40.0 ± 2.6‡
Naloxone	20	14.3 ± 0.65	8	37.0 ± 1.9*
Saline	20	14.7 ± 0.61	8	39.0 ± 3.0

*Different from controls at $p<0.10$.
†Significantly different from controls at $p<0.05$.
‡Significantly different from naloxone at $p<0.01$.

conducted on the same pairs every alternate day up to day 34, except for days 26, 27, and 28. On these latter days, daily tests were run to assess the effect of treatment withdrawal in the three groups. Play sessions were initiated 30–45 minutes after the injections.

RESULTS

Physical Characteristics

Delays in the development of physical characteristics in the morphine-treated groups and moderate precocity in the naloxone-treated groups were observed (Table 1). Overall, there was a 16-hour lag in the eye opening time of the morphine-treated groups and acceleration of 8 hours in the naloxone-treated subjects, with the difference among groups being reliable, $F(2,57)=14.32$, $p<0.002$.

Morphine-treated females exhibited a nonsignificant delay in vaginal opening (by 1 day), whereas naloxone-treated animals exhibited a reliable precocity (by 2 days), $F(2,21)=4.21$, $p<0.05$.

Body weights. As summarized in Fig. 1, by day 25, morphine-exposed animals were lighter than controls, $F(1,38)=12.28$, $p<0.01$; whereas by the end of treatment, naloxone animals were heavier than controls, $F(1,38)=6.18$, $p<0.05$. These differences were apparent by 8 days of age and were maintained for the duration of testing.

Motor Behaviors

Catalepsy. As summarized in Fig. 2, naloxone- and saline-treated groups did not differ in the time taken to step down from the test platform, whereas morphine-treated animals exhibited marked catalepsy until 14 days of age. There were significant differences between morphine and other groups [morphine and naloxone, $F(1,38)=149.3$, $p<0.001$, and morphine and saline, $F(1,38)=161.4$, $p<0.001$].

Grasping. The morphine-exposed animals exhibited a modest lag in the development of grasping, obtaining on the average 80% positive responses as compared to the 93% positive responses in saline-tested and 97% positive responses in naloxone-treated subjects at 6 days of age (Fig. 3). The difference between morphine and other two groups was significant [morphine and naloxone, $F(1,38)=5.70$, $p<0.05$, morphine and saline, $F(1,38)=3.34$, $p<0.10$, $p>0.05$]. By day 10 all groups were identical, exhibiting positive responses on practically all trials.

Swimming. Morphine-treated animals lagged slightly behind the other two treatment groups in the maturity of swimming patterns, reaching criterion of front paw inhibition on day 20, whereas all naloxone-treated animals had reached criterion by day 18. The swimming of saline-treated animals fell approximately midway between that of the other two groups throughout the testing period, but reached criterion on the same day as the morphine subjects. Individual F tests revealed significant differences between morphine and naloxone groups, $F(1,18)=9.51$, $p<0.01$, but not between morphine and saline groups, $F(1,18)=3.42$, $p<0.10->0.05$.

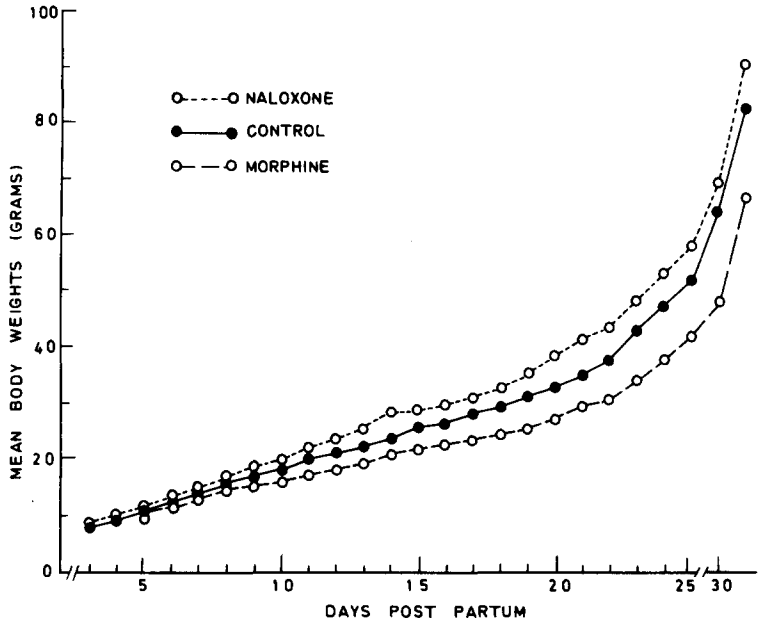

FIG. 1. Mean body weights of young rat pups chronically treated with morphine, naloxone and saline. At 8 days of age, body weights were 18.3, 16.7 and 15.1 g respectively for naloxone, saline and morphine animals p's<0.05 for all comparisons, and all differences remained reliable at $p<0.05$ for the duration of testing.

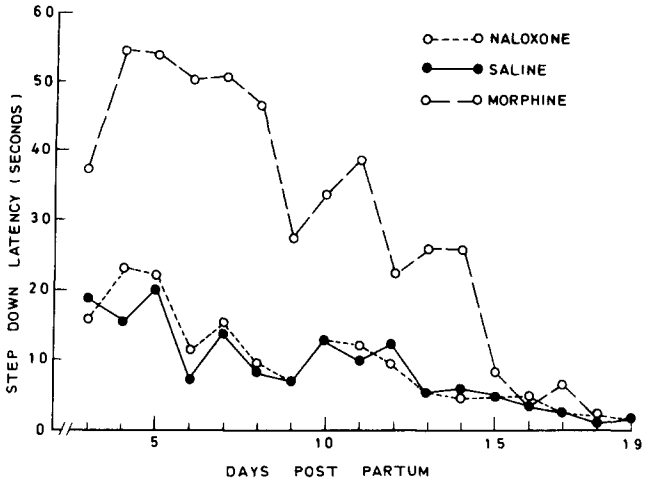

FIG. 2. Mean step down latencies of young rats chronically treated with morphine, naloxone and saline during days 3–26 postpartum. This test was conducted daily at 30 minutes after injection. The overall difference between the three groups was significant, $F(2,57) = 103.65$, $p<0.001$, which was accounted for by morphine animals which were reliably slower to step down for all of the first 12 days of testing (p's<0.01).

The morphine-treated animals exhibited a modest lag in the development of adult head posture, reaching criterion on day 20 as compared to day 17 for the naloxone- and saline-treated animals. Head posture development of the saline-treated group fell in between that of two treatment groups on days 10–17, but reached criterion on the same day as the naloxone subjects. The difference between morphine and naloxone groups was significant, $F(1,18) = 6.10$, $p<0.05$.

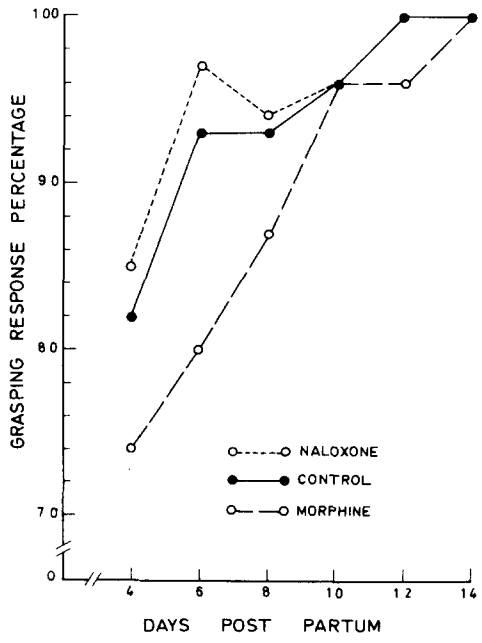

FIG. 3. Mean percentage grasping responses to a round stick placed under the front paws of young rats treated chronically with morphine, naloxone or saline. The only reliable differences were between morphine animals and other groups on the first three days of testing (p's<0.05).

TABLE 2

MEAN (± SD) PERFORMANCE IN A HOMING TEST FOR RATS CHRONICALLY TREATED WITH MORPHINE, NALOXONE OR SALINE DURING EARLY DEVELOPMENT

Treatment	N	Trials to Criterion	Age at Acquisition
Morphine	19	60.0 ± 18.5*	26.0 ± 1.8*
Naloxone	19	40.0 ± 8.9*	24.0 ± 0.9*
Saline	19	52.2 ± 16.3	25.0 ± 0.4

*Reliably different from controls at $p<0.05$.
Trials to criterion and age at acquisition of homing response.

Spontaneous alternation. Both naloxone- and saline-treated animals acquired spontaneous alternation behavior at 18 days of age, whereas morphine-treated animals achieved criterion 24 hours later. The differences among groups was not reliable, however, $F(2,33) = 1.80$.

Social Behaviors

The homing and play results suggest that development of social behaviors was modestly retarded by morphine and facilitated by naloxone.

Homing. In Table 2 the mean homing criterion and the average day of acquisition of the homing response indicate a lag in the acquisition of homing in the morphine group and acceleration in the naloxone group. The morphine animals took on the average 60 trials to reach criterion as compared to 40 and 52 trials for the naloxone and saline animals respectively, $F(2,54) = 7.42$, $p<0.001$. Post hoc comparisons yielded significant differences from controls for both morphine and naloxone animals.

Play behaviors. The results indicate differential effect of drug treatments on pinning behavior [Overall, $F(2,45) = 19.9$, $p<0.001$]. As summarized in Fig. 4, morphine-treated animals played reliably less than either naloxone and saline animals during the initial three days of drug treatment, $F(1,30) = 26.1$, $p<0.001$, and, $F(1,30) = 31.14$, $p<0.001$, respectively. During the withdrawal and postwithdrawal phases, there were no reliable differences among groups.

DISCUSSION

The results of the motor tests replicate earlier studies in which maturational delays were observed in young animals after chronic morphine exposure (10, 26, 27, 31, 34). Morphine-treated animals lag behind normals in physical development as indicated by body weights, and eye and vaginal opening time (35). Morphine animals also lagged in motor development, reaching criterion responses on motor tasks such as grasping, swimming, and spontaneous alternation 1–3 days later than normals. The step down latencies for morphine animals were longer than controls up to day 19, after which the responses were indistinguishable from controls. In the swimming test, morphine-treated animals lagged behind naloxone by 2–3 days in reaching criterion on forepaw inhibition and adult head posture development. Naloxone-treated animals, on the other hand, appeared to be precocious, maturing 1–3 days earlier than controls. In addition, naloxone treatment led to a sustained increase in body weights.

The present study does not replicate earlier work on chronic naloxone treatment of the young. Several investigations (9,12) evaluating the development of young rats chronically exposed to naloxone report no difference between the normals and the naloxone-treated animals on developmental measures (eye and

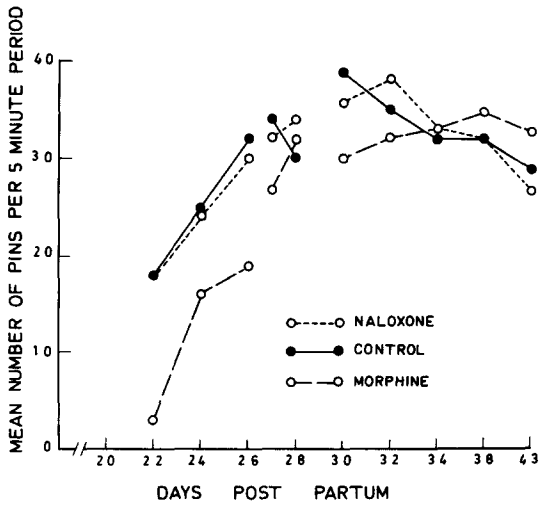

FIG. 4. Mean number of pins occurring during a five-minute play session. Days 22–26 were tests during the end of the drug treatment period, days 27–28 reflect the first two days following drug termination, and days 30–43 represent tests during the protracted postdrug withdrawal period. The only reliable differences were between morphine animals and the other groups during the first three days of testing (p's<0.05).

vaginal opening times), but the naloxone regimen in all of these studies was substantially less sustained than the one used here. However, Voorhees (29) using twice daily injections of 20 mg/kg of naloxone did observe a variety of accelerations in postweaning growth and behavior development.

In light of the present evidence, and the study of Voorhees (29), it appears that chronic naloxone treatment advances the process of overall physiological development. These findings affirm the recent series of reports by Zagon and McLaughlin (32,33) that a daily high dose of naltrexone produces the same pattern of increased development. The reason prior naloxone studies did not observe similar effects may be that opiate receptor blockade was not sustained for a sufficiently long period of time. The Zagon work indicates that low doses of naltrexone, which do not yield 24-hr blockade, actually retard development, perhaps because of compensatory influences of endogenous opioids during periods when low-dose naltrexone effects are diminishing.

Presently the mechanism(s) via which opiate receptor blockade accelerates normal development remains unknown. One influence may be the increase in rates of protein synthesis that have been observed following naloxone treatment (7). Another may be the retardation in protein synthesis observed following morphine treatment (4, 5, 7). Although these effects may be secondarily due to nutritional changes or to endogenous opioid modulation of anabolic hormone secretion [for review see (11)] such as increased growth hormone release (2), there are cogent arguments against such routes of action (33). As emphasized by Zagon and McLaughlin (33), opiate blockade may have a more direct effect on growth processes.

Regarding social behaviors, morphine did not block, but did modestly delay development of both homing and play behavior. Although naloxone had no apparent effect on the development of play, it did decrease time to learn the homing behavior. Naloxone-treated animals reached criterion on day 24, as compared to day 25 and 26 for the saline and morphine subjects respectively. Whether these results are due to general effects on memory, or to underlying social motivational processes cannot be specified from the present data. Even though chronic treatment with these drugs did have modest effects, it is as important to emphasize that all animals eventually developed what appeared to be normal social interactions and motivation. It is also noteworthy in the present context that following acute treatment, low doses of morphine tend to increase play, whereas naloxone reduces play (15,19).

In summary, although the present data affirm modest effects of opiate receptor agonists and antagonists on various aspects of physiological and behavioral development, repeated and persistent modification of opioid activity during early development did not have an especially severe or robust effect on the apparent social competence of our animals. Thus, we would provisionally conclude that environmentally-modulated activity within brain opioid systems, at least of the receptor varieties affected by naloxone (35), are not essential for the development of social behaviors. Of course, such a conclusion must be tempered by the absence of any clear knowledge of how the present manipulations actually affected brain opioid activity across the course of treatment. Though administered at a denser injection schedule (i.e., three times a day) than in most previous work, the pharmacological effects surely waned markedly during the eight-hour periods between successive injections. Accordingly, all animals may have had substantial experience with normal social stimuli in their home cages during various levels of brain opioid activity, and it is known that very small amounts of social experience during development suffice for progress of normal socialization. Accordingly, more work is needed in this area of inquiry before definitive conclusions can be drawn.

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