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Opiate Effects on Isolation Stress in Domestic Fowl

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SUFKA, K. J., R. A. HUGHES, T. M. McCORMICK AND J. L. BORLAND. *Opiate effects on isolation stress in domestic fowl.* PHARMACOL BIOCHEM BEHAV **49**(4) 1011-1015, 1994.—In an attempt to examine the role of opioid system functioning in social attachment and isolation stress in young domestic fowl, the effects of morphine (5.0 mg/kg) and naloxone (5.0 mg/kg) were evaluated on distress vocalizations, thermal nociception, thermoregulation, and respiration following 15 min of isolation in 7-day-old White-Leghorn cockerels. Morphine decreased and naloxone increased distress vocalizations in isolated chicks. Isolation produced an increase in jump response latencies (i.e., hypoalgesia) on a standard hot-plate test. In general, morphine decreased and naloxone increased mean jump latencies in both isolated and nonisolated chicks. Isolation produced an increase in core body temperature (i.e., hyperthermia); morphine decreased and naloxone increased core body temperatures independent of the isolation manipulation. Social isolation did not affect respiration. However, morphine depressed respiration in both isolated and nonisolated chicks. These results support the notion that opioid systems modulate social attachment and isolation stress.

Domestic fowl Chicks Thermal nociception Pain Distress vocalizations Thermoregulation Respiration Isolation stress Morphine Naloxone Opioid

CONSIDERABLE research has examined the stress of social separation in a variety of animal models including domestic fowl (28,35,37), ducks (8), mice (31), rats (5,6,19), guinea pigs (10), and dogs (26). Among the behavioral consequences of this isolation experience are increased distress calling (1,6, 28,32,35,37) and hypoalgesia (18,35,37) in both rats and domestic fowl and hyperthermia in domestic fowl (7,35,37). These response measures provide converging indices of the stress that accompanies social isolation (37).

An extensive literature documents the biochemical substrates of stress [for reviews, see (22,38)] and the biochemical substrates of social attachment (1,3-5,16,20,21,26,27,29,39). From these research efforts, alternative models on the role of opioid system functioning in social attachment and isolation stress have emerged. One model proposes that isolation stress evokes the release of endogenous opioids. Support for this model is provided by observations that isolation-induced hypoalgesia in rats (1,19,31) is reversed by administration of the opiate antagonist naltrexone. Further support for this model is provided by reports that stress increases β-endorphin levels in rats (17).

The alternative model of isolation stress and opioid system functioning suggests that social contact maintains opioid system activity and separation from conspecifics places an animal into a state of opioid withdrawal (26,28,29). Evidence that isolation-induced distress vocalizations in rats and chicks are decreased by administration of the opiate agonist morphine (13,19,28) and increased by administration of the opiate antagonist naloxone (10,13,28) support this opioid withdrawal model. Additional support for this model is provided by the demonstration that morphine reverses isolation-induced hyperthermia in domestic fowl (7).

Much of the evidence about the biochemical basis of social attachment and isolation effects has been derived from measuring distress vocalizations in rat pups or young domestic fowl. Recent research has demonstrated that nociceptive and thermal regulatory systems are also sensitive to isolation manipulations (1,7,15,35-37). Examination of these multiple be-

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haviors following opioid manipulations may further define the role of opioid system functioning in social attachment and isolation stress. The present study, therefore, examined the effects of morphine and naloxone on isolation-induced vocalizations, hypoalgesia, and hyperthermia in young domestic fowl. Respiration was also monitored as an additional index of opiate effects (36).

METHOD

Subjects

Cockerels (TK-Line, Hy-Line International, Dallas Center, IA) were obtained several hours after hatch and were housed in pairs in chambers (described below) that allowed for visual and auditory access to other animal pairs. Chicks were maintained under 24-h overhead fluorescent lighting, and room temperature was maintained at 32°C. Chicks were permitted food (Wayne Pullet Starter) and water ad lib.

Apparatus

Housing. Two separate 125 × 56 × 30 cm housing units were constructed of 2 × 2 hardware cloth. Each unit was divided into 10 25 × 28 × 30 cm cells with attached hardware cloth lids. The outer perimeter of each unit was draped with white fabric.

Isolation. The isolation apparatus consisted of a 38 × 21 × 16 cm hardware cloth cage located in a sound-attenuating chamber (LVE). Illumination was provided by a 7.5 W light and masking noise by the LVE ventilation fan. Vocalizations were monitored by a microphone connected to a sound-activated relay (Gerbrands 1341I; sensitivity setting 5.5) that triggered an electromechanical counter.

Hot plate. The hot-plate apparatus consisted of a 16 × 29 × 30 cm Plexiglas chamber with a hinged lid. The walls of the chamber were covered with white paper, except for a 5 cm opening near the floor to permit observation. The chamber floor was a grid-like surface composed of eight 1 cm diameter glass tubes spaced 2 cm center to center, and mounted to the side walls of the chamber. One end of the test chamber was occupied by a 12.5 × 15.5 × 7 cm wooden platform. The grid-like floor was heated by a Nichrome wire heating element (Eagle Glocoil Incubator) that was threaded through the glass tubing of the floor chamber. Grid temperature was regulated by a variable transformer (Standard Electric Company, Model 300 BU) and monitored by a thermister located inside the center glass tube interfaced with a digital thermometer (Fluke, Model 52). Response latencies were measured to the nearest 0.1 s by an electronic timer (Hunter, Model 120A).

Procedure

Animals were briefly handled, once daily, on days 1-7 posthatch. This handling manipulation is an effective means of reducing experimenter-related stress in chicks (35). Animal pairs were removed from the housing apparatus, held for approximately 30 s, and then placed into a chamber of an identical empty housing unit. When all 10 animal pairs were handled, they were returned to their original home cage.

The groups in this study formed a 2 × 3 factorial design (n = 10 per group). Factors were isolation (15 min isolation or no isolation) and drug (saline, morphine, or naloxone). Animals were randomly assigned to one of six independent groups using a random block procedure. On day 7 posthatch, chicks were removed from their home cages, weighed, and given intramuscular (IM) injections of either saline, 5.0 mg/kg morphine, or 5.0 mg/kg naloxone in a volume of 1.0 ml/kg. Although lower doses of morphine (e.g., 2..5 mg/kg) have been shown to affect vocalizations (28), the 5.0 mg/kg dose of morphine used in the present study was chosen on the basis of earlier work demonstrating that this dose produced significant changes in thermal nociception (34) and respiration (36). As well, the naloxone dose was chosen on the basis of earlier work demonstrating that this naloxone dose significantly reversed morphine algesic and respiratory effects (12,15) in domestic fowl. Drug injections were administered 30 min before hot-plate tests. Chicks were returned to their home cage for this period. Chicks assigned to the isolation treatment condition were placed in the isolation apparatus 15 min before hot-plate tests; vocalization measures were taken during this isolation period in these groups only. Nonisolated animals did not receive this explicit manipulation and were tested within 1 min upon removal from their home cage. All chicks were transported to and from the isolation chamber and/or hot-plate apparatus in vented opaque plastic containers.

Following these experimental manipulations, the following dependent measures were taken from each animal: hot-plate latency, body temperature, and respiration. The hot-plate test, modified for use with young domestic fowl (12,14,33-35) involved placing the chick onto the heated grid (79.5°C) facing away from the raised platform. Latency to perform a jump response (i.e., upward thrust of the animal with both feet leaving the grid floor) or move to the raised platform served as an index of nociception. A chick that did not perform a jump response within 90 s was removed from the apparatus and assigned a latency score of 90 s. Although most animals performed a jump response on the hot-plate test, chicks that attained a cutoff score of 90 s did not exhibit any discernible signs of tissue injury. Immediately following the hot-plate test, body temperature and respiration measures were concomitantly assessed; core body temperature was recorded 60 s after insertion of a thermister (YSI, Model 702) 2 cm into the cloaca. Respiration was assessed during the entire 60 s interval by counting rhythmic chest movements (i.e., respirations per min). These procedures were approved by the Institutional Animal Care and Use Committee, Iowa State University and

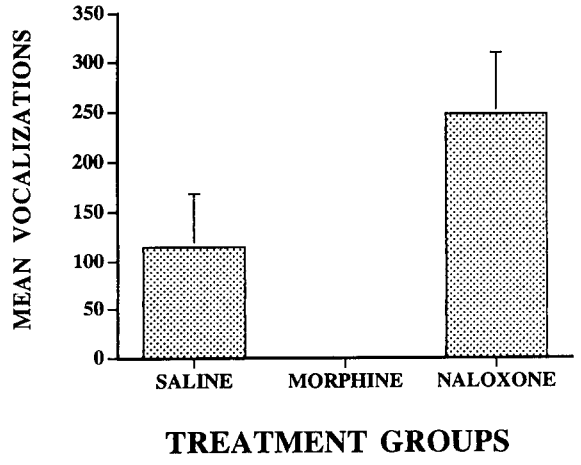

FIG. 1. Mean vocalizations + standard error of the mean during the 15-min isolation period in chicks that received IM injections of either saline, 5.0 mg/kg morphine, or 5.0 mg/kg naloxone in a volume of 1.0 ml/kg (n = 10).

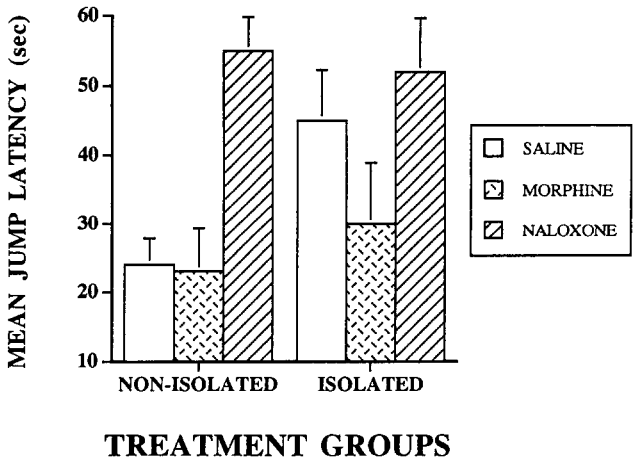

FIG. 2. The effects of saline, morphine 5.0 mg/kg, and naloxone 5.0 mg/kg (IM, 1.0 ml/kg) on thermal nociception in nonisolated and isolated (15 min) chicks. Bars represent mean jump latency (+ standard error of the mean, $n = 10$).

were conducted under the ethical guidelines of the American Psychological Association.

Data were analyzed using one- or two-way analysis of variance (ANOVA). Planned comparisons were analyzed using power-adjusted t-tests (23).

RESULTS

As is evident in Fig. 1, morphine attenuated and naloxone enhanced distress calling in the isolated chicks. A one-way ANOVA of these data revealed a significant treatment effect, $F(2, 27) = 7.12$, $p < 0.005$. Further analyses demonstrated that morphine significantly decreased and naloxone significantly increased vocalizations compared to the saline-treated chicks, $t(27) = 1.74$ and 2.03, $p < 0.05$. Morphine-treated chicks typically adopt a ventral recumbent posture with head down and eyes closed. This suggests that decreased vocalizations may be due to morphine sedative effects. However, that animals are capable of vocalizations is provided by the observation that morphine-treated chicks exhibit robust vocalizations during handling by the experimenter.

The effects of morphine and naloxone on thermal nociception in isolated and nonisolated chicks are summarized in Fig. 2. A two-way ANOVA of the jump latency data revealed a significant drug effect, $F(2, 54) = 8.29$, $p < 0.001$. The isolation, $F(1, 54) = 2.24$, $p = 0.14$, and drug × isolation interaction, $F(2, 54) = 1.52$, $p = 0.22$, terms were not significant. Planned comparisons demonstrated that in the saline-treated groups, isolated chicks had significantly longer mean jump latencies than nonisolated chicks, $t(54) = 2.17$, $p < 0.05$. In addition, nonisolated naloxone-treated chicks exhibited significantly longer jump latencies than the nonisolated saline- and morphine-treated chicks, $t(54) = 3.21$ and 3.28, respectively, $p < 0.001$. Finally, in the isolated chicks, the mean jump latency of the naloxone group was significantly longer than that of the morphine group, $t(54) = 2.31$, $p < 0.05$.

The body temperature results are summarized in Fig. 3. In general, isolated chicks exhibited an increase in core body temperature compared to the nonisolated chicks. Morphine uniformly decreased and naloxone uniformly increased core body temperature in both isolated and nonisolated chicks. A two-way ANOVA of the body temperature data revealed a significant effect of drug, $F(2, 54) = 21.56$, $p < 0.001$, and isolation, $F(1, 54) = 12.64$, $p < 0.001$. The drug × isolation interaction term was not significant, $F(2, 54) = 0.29$, $p = 0.75$. Further analyses demonstrated that for the saline animals, isolated chicks exhibited a marginally significant increase in core body temperature than nonisolated chicks, $t(54) = 1.58$, $p < 0.06$. Morphine significantly decreased body temperatures in both nonisolated and isolated groups, $t(54) = 2.55$ and 2.21, respectively, $p < 0.05$. As well, naloxone significantly increased body temperatures in both nonisolated and isolated groups, $t(54) = 1.73$ and 2.79, respectively, $p < 0.05$.

A summary of the respiration data is provided in Fig. 4. A two-way ANOVA of these data revealed a significant drug effect, $F(2, 54) = 41.02$, $p < 0.001$. The isolation, $F(1, 54) = 2.04$, $p = 0.16$, and drug × isolation, $F(2, 54) = 0.40$, $p = 0.67$, terms were not significant. Further analyses of these data demonstrated that morphine-treated chicks exhibited significantly lower respiration than the saline controls in both the nonisolated and isolated groups, $t(54) = 5.13$ and 5.27, respectively, $p < 0.001$. In addition, these morphine-treated chicks exhibited significantly lower respiration than the naloxone-treated chicks in both the nonisolated and isolated groups, $t(54) = 5.26$ and 6.43, respectively, $p < 0.001$. All other relevant comparisons were not statistically significant, $p > 0.05$.

DISCUSSION

The results of earlier research on the role of the opioid system functioning that subserves social attachment and isolation stress has yielded two competing theories. One theory (social separation-opioid stimulation) suggests that opioid system activity is stimulated by stress experiences such as social separation (1,19). The second theory (social separation-opioid withdrawal) suggests that social attachment maintains opioid system functioning and that social isolation places the animal into a state similar to opioid withdrawal (26,27,29). Much of the support for these two theoretical viewpoints was derived from analysis of vocalization rate and/or nociceptive thresh-

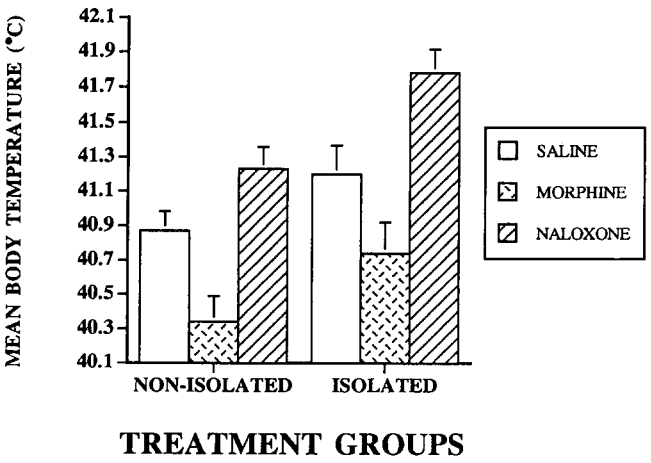

FIG. 3. The effects of saline, morphine 5.0 mg/kg, and naloxone 5.0 mg/kg (IM, 1.0 ml/kg) on thermoregulation in nonisolated and isolated (15 min) chicks. Bars represent mean core body temperature (± standard error of the mean, $n = 10$).

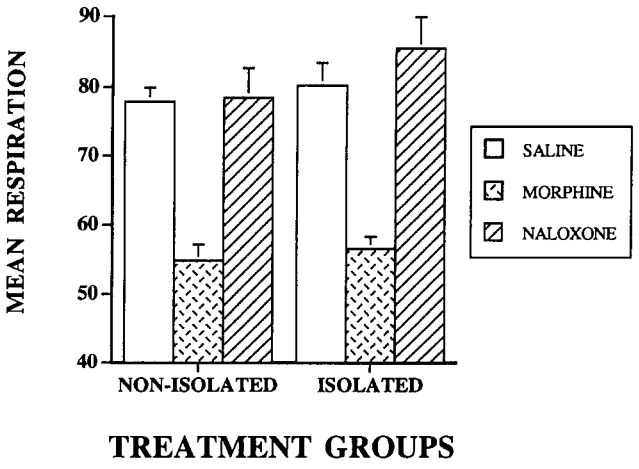

FIG. 4. The effects of saline, morphine 5.0 mg/kg, and naloxone 5.0 mg/kg (IM, 1.0 ml/kg) on respiration in nonisolated and isolated (15 min) chicks. Bars represent mean respiration (+ standard error of the mean, $n = 10$) for a 1-min interval.

old and/or body temperature in response to social isolation. Like rats (1,2,11), domestic fowl exhibit multiple behavioral indices (i.e., vocalizations, nociception, thermoregulation, and respiration) of the isolation experience and/or are sensitive to opioid manipulations (35,37). By examining the effects of morphine and naloxone on isolation-induced distress vocalizations, hypoalgesia, and hyperthermia in young domestic fowl, the present study sought to more fully describe the relationship between opioid system functioning in social attachment and isolation stress in this precocial species.

Although contrary evidence exists [see (2)], isolation-induced calling is often used to index stress in rats and chicks (5,6,26,35,37). In the present study, isolation-induced distress calling in young domestic fowl was decreased by morphine and increased by naloxone (see Fig. 1). These results are consistent with earlier research demonstrating that separation from conspecifics elicits distress calling (35,37) and that these distress vocalizations are decreased by opiate agonists and increased by opiate antagonists (28). These vocalization data demonstrate that the effects of social separation on distress calling can be attenuated by stimulating or exacerbated by blocking opioid system activity and support the social separation-opioid withdrawal theory.

In the present research, saline-treated chicks that were isolated exhibited longer mean jump latencies than saline-treated nonisolated chicks (see Fig. 2). This hypoalgesic effect is consistent with earlier work demonstrating isolation-induced hypoalgesia in young domestic fowl (35,37). The pattern of opiate effects on thermal nociception, although not statistically significant, was characterized by decreased (i.e., hyperalgesia) and increased (i.e., hypoalgesia) mean jump latencies in morphine- and naloxone-treated chicks, respectively. Although morphine hyperalgesia and naloxone hypoalgesia seem paradoxical, previous reports have demonstrated that this atypical effect is replicable, strain dependent, and naloxone sensitive on both thermal and chemoinflammatory nociceptive tests (12,15). The pattern of opiate effects, on the nociceptive data herein and elsewhere (12,15), demonstrates that isolation-induced changes in nociceptive systems are attenuated by stimulating opioid activity and exacerbated by blocking opioid activity.

Isolated animals exhibited an increase in core body temperature compared to nonisolated animals (see Fig. 3). These results are consistent with reports of isolation-induced hyperthermia in chicks (7,35,37) and stress-induced hyperthermia in other species (30). In the present study, morphine attenuated and naloxone enhanced these isolation-induced changes in thermoregulatory functioning. This pattern of opiate effects, like that of vocalizations and nociception, demonstrates that changes in thermoregulation induced by social separation are attenuated by stimulating opioid activity and exacerbated by blocking opioid activity.

Morphine and naloxone effects on respiration were also evaluated. Respiration was not affected by the isolation manipulation or naloxone administration. However, morphine significantly decreased respiration (see Fig. 4). The observation that morphine produced respiratory depression is consistent with other reports that opiate agonists decrease respiration in fowl (36) and other species (9,25). Although respiration appears to be less sensitive to isolation and naloxone effects, the overall pattern of isolation and opiate effects obtained for respiration is similar to the pattern of isolation and opiate effects for nociception and thermoregulation (see Figs. 2 and 3). The possibility that morphine sedative effects account for the decrease in body temperature and respiration effects was not evaluated in the present study. Moreover, it is unlikely that morphine sedative effects can account for the decrease in body temperature and respiration as all treatment groups tend to be inactive during the 30 min injection-to-test interval.

The effects of isolation on vocalizations in chicks (see Fig. 1) (26,28,35,37) and rat pups (1,4,5,19) are consistent: isolation increases vocalizations and this increase is attenuated by the opiate agonist morphine and exacerbated by the opiate antagonist naloxone. These vocalization data are consistent with the view that isolation induces an opioid withdrawal state (26,28,29). The data on isolation effects on nociception in chicks (see Fig. 2) (35,37) and rat pups (1) are also consistent: isolation induces hypoalgesia in both species. This outcome is consistent with the view that isolation engages (1) rather than disengages (26,28,29) an opioid system. Thus, opiate effects on isolation-induced vocalizations tend to support the view that isolation disengages an opioid-based social comfort system and produces distress, whereas the effects on nociception tend to support the view that an opioid system is engaged and produces hypoalgesia.

We suggest that the two views just described are not mutually exclusive but rather reflect separate albeit pharmacologically overlapping systems. According to this interpretation, isolation, indeed, disengages an opioid-based social comfort system that produces concomitant distress. This distress is alleviated by morphine (14,19,28) and exacerbated by naloxone (10,13,28). We further suggest that such isolation is, in fact, stressful and engages an opioid portion of the nociceptive system that produces hypoalgesia. This hypoalgesia is enhanced by morphine (24) and attenuated by naloxone (1,24). Thus, the initial effect of social isolation is to disengage the opioid system subserving social comfort and this, in turn, engages an opioid mechanism that subserves nociception. The systemic administration of opioid agonists and antagonists in most animal models acts on both the social comfort and nociceptive systems and effects on the two systems are not readily separable.

That the present interpretation is more than mere speculation derives from the unusual opiate effects on nociception in domestic fowl reported herein and elsewhere (12,13,15,33, 34,36). Morphine and naloxone decrease and increase hypoalgesia, respectively, in chicks (13,15,36). We have suggested in

an earlier report (14) that, in chicks, these unusual opiate effects reflect strain-dependent tolerance at hatching to opiate effects on nociception. Accordingly, morphine should influence the social comfort system but have little effect on nociception. Thus, morphine should prevent stress hypoalgesia by maintaining opioid activity in the social comfort system and produce an apparent hyperalgesic effect relative to saline-injected controls. Naloxone should enhance the distress of social isolation, and this stress may engage nonopioid hypoalgesic mechanisms (24). These apparently unusual opiate effects are supported by the present study as well as by a variety of earlier reports (12,13,15,33,34,36).

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