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Morphine Reduces Social Cohesion in Rats

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PANKSEPP, J., N. NAJAM AND F. SOARES. *Morphine reduces social cohesion in rats.* PHARMAC. BIOCHEM. BEHAV. 11(2) 131–134, 1979.—The effect of low (1 mg/kg) doses of morphine on maintenance of physical proximity were evaluated in paired rats observed in a 4 square foot test arena. Morphine reliably reduced proximity maintenance time, and this was apparently not due to sedation, since the effect was unmodified by doses of amphetamine which substantially increased motor activity. The effects of naloxone were inconsistent on this measure of social motivation. In general, the results are consistent with the theoretical proposition that a brain neurochemical change which might lead to social attraction is the activation of endogenous opioid systems. When opiate activity is exogenously sustained, animals exhibit a subnormal tendency to be gregarious.

Morphine Amphetamine Social proximity Brain opioids Autism

MANY kinds of animals desire company. For instance, two rats placed together in a large chamber spend substantially more time together than would be expected by chance [9,10]. The biological basis for such interanimal attractions is not known, but our recent work on social affect has led us to consider that part of the incentive value of interanimal proximity might be elaborated by activation of brain opioid systems [13]. In previous work we have evaluated the role of brain opioid systems in controlling the intensity of emotions which arise from social separation, and have found that opiates are very powerful in reducing isolation induced distress vocalizations in young puppies [13], guinea pigs [7] and chicks [14]. We have interpreted this to mean that activation of brain opioid systems simulates a central affective state which is the feeling of comfort which animals normally experience in a social context. If this is the case, we predict that injections of opiates should reduce the need for gregariousness. Accordingly, the aim of the following experiment was to determine whether morphine could reduce the urge of animals to seek social proximity.

GENERAL METHOD

All test animals in these experiments were male Long-Evans hooded rats. In Experiment 1 animals were between 60 and 80 days of age, and in Experiment 2 and 3, a single group of animals was tested between 40–46 and 51–57 days of age, respectively. Animals were housed in pairs in 24.5×17.5×19 cm suspended wire mesh cages, and had free access to food and water. Behavioral testing occurred in the light part of the 12–12 hr light-dark cycle, and animals were tested in the same pairings as they were housed.

Proximity maintenance time was measured by placing paired animals in a 2×2×1 ft high arena which was constructed of sheet aluminum, except for one Plexiglas wall and ceiling. The floor of the chamber was divided into 36 equal (4×4 in.) squares, and the field was illuminated with a 50 W incandescent bulb situated 3 feet above the floor of the chamber.

The main dependent measure of these experiments was proximity maintenance time which consisted of both animals having at least their two front paws in the same 8 inch square. In some experiments, additional measures were also recorded, namely, motor activity (number of 8 in. squares traversed and rearing), the frequency of together bouts, the number of times an animal followed the other animal, the total amount of time spent following, and the total amount of time spent in isolation (both animals sitting in different 8 in. squares with no exploratory activity). All measures were recorded manually on digital counters and timers.

All pairs received one 5–10 min adaptation session prior to testing. In each experiment, all pairs were tested under all conditions in a counterbalanced fashion with about 48 hrs between successive tests. All drugs were administered intraperitoneally (1 cc/kg) 20 min prior to testing—both animals receiving the same treatment. Test sessions were initiated by placing animals in diagonally opposite corners. Only experiments 2 and 3 employed blind testing procedures.

EXPERIMENT 1

Eighteen pairs of rats were tested for 5 minutes following treatment either with 0.9% saline carrier or 1 mg/kg morphine sulphate. The average (± SD) together time for control animals was 127 (± 52) secs while under morphine it was reliably lower at 94 (± 34) secs, $t(17)=3.7$, $p<0.001$. Activity was not different between the saline (44 ± 22 crosses) and morphine (47 ± 18) conditions. There were no apparent gross differences between animals in the two treatments in this experiment or in the subsequent ones.

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EXPERIMENT 2

The first experiment supported our initial hypothesis, but since it was not executed blind, the following replication used coded drugs tested by a blind experimenter, and several additional measures of behavior were collected.

Twenty pairs of rats were tested in a counterbalanced within-subject dose-response study employing 0.0, 0.25, 0.50, and 1.0 mg/kg morphine. The test session was lengthened to 10 min and additional dependent measures were recorded as indicated in Fig. 1. The relative changes summarized in Fig. 1 are from the following 100% control scores (± SD): together time 329 (± 100) secs, together frequency 12 (± 4), follow time 38 (± 35) secs, follow frequency 8 (± 6), isolation time 27 (± 38) sec, crossings 62 (± 26), rearings 41 (± 17).

Paired comparisons indicated that activity was reduced reliably at all doses of morphine, t's(19)=3.6–12.9, p's<0.01. Together time was reduced only at the 1.0 mg/kg dose of morphine, $t(19)=2.5$, $p<0.01$. All other social measures were reliably different under all morphine doses as compared to saline, t's(19)=2.4–7.5, p's<0.05. Since together frequency was reduced in parallel with together time, the reduced social cohesion produced by morphine was due primarily to a reduction in the frequency of together bouts rather than to a reduction in average bout duration.

Although morphine did not reduce activity of animals tested in Experiment 1, it did in this experiment. The only major differences between the two experiments was the age of the animals (60–80 vs. 40–46 days) and the test duration (5 vs 10 min).

EXPERIMENT 3

Although it is not clear how a reduction of activity should affect togetherness (animals should be as capable of exhibiting the behavior whether active or inactive), it is possible some subtle change in arousal level may have caused the effects. Accordingly, in the following experiment we determined whether increasing arousal would counteract the social isolation induced by morphine.

After a rest period of 4 days, the animals used in Experiment 2 were tested in a 2×2 repeated-measure, factorial design—1 mg/kg morphine being crossed with 1 mg/kg of d-amphetamine. Injections were administered 20 mins before testing.

The data, summarized in Fig. 2, indicate that amphetamine increased the activity of animals treated concurrently with morphine, $t(19)=2.5$, $p<0.05$. The fact that morphine by itself had no reliable effect on activity in this study suggests either a maturational or tolerance effect. Still, morphine by itself reduced together time, $t(19)=9.4$, $p<0.001$, while amphetamine alone had a very modest effect in the same direction, $t(19)=2.4$, $p<0.05$. The large morphine effect remained completely intact in the presence of the activating dose of amphetamine, $t(19)=11.5$, $p<0.001$. Although together frequency was reduced from 13 (± 6) to 8 (± 8) by morphine, $t(19)=2.9$, $p<0.01$, it was essentially normal (12 ± 10) in animals which had received amphetamine with the morphine. Accordingly, the amphetamine+morphine reduction in together time was due to a reduction in the duration of together bouts.

DISCUSSION

These results clearly indicate that morphine can reduce social cohesion. The effect is not readily explicable by reduced arousal, since the effect was apparent in the absence of decreased activity (Experiments 1 and 3) as well as during hyperactivity produced by concurrent treatment with amphetamine. The results are consistent with other work conducted concurrently which indicated that infant-mother proximity maintenance time is reduced by morphine in guinea pigs [7].

More evidence for the specificity of endogenous opioids in the mediation of social cohesion would be provided by the observation of opposite effects with naloxone. We have executed such studies with inconsistent findings. In a within-subject dose-response study with 24 pairs of rats (5 min sessions run as above), 0.5 mg/kg naloxone reliably increased proximity maintenance time from 77 (± 18) to 93 (± 21) secs, $t(23)=3.5$, $p<0.001$, while a higher 2.5 mg/kg dose

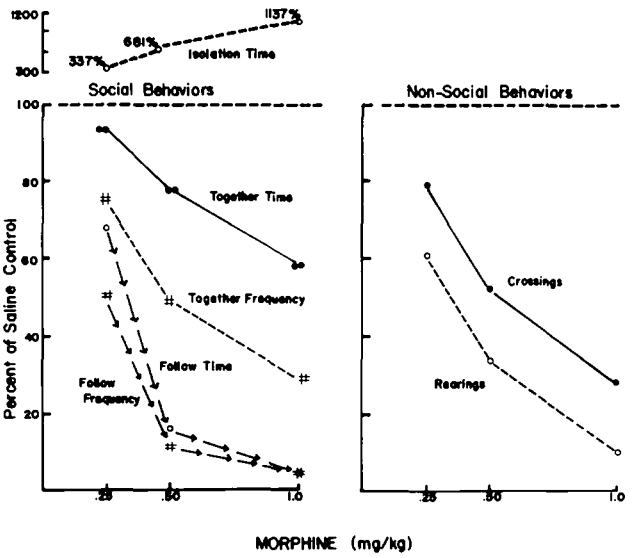

FIG. 1. Social and non-social behaviors of paired animals in an open field as a function of various morphine doses. Absolute scores for the 0 mg/kg condition are presented in the text.

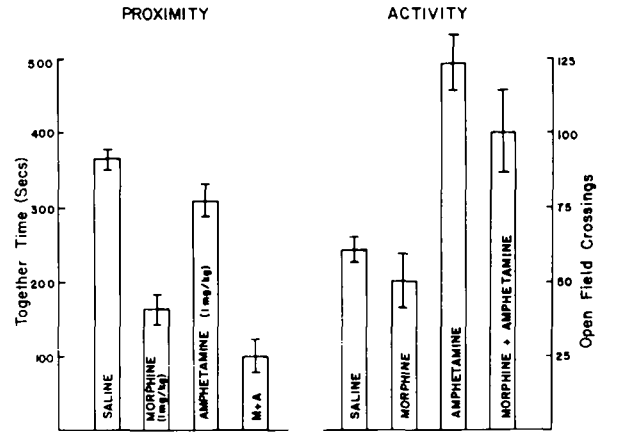

FIG. 2. Proximity maintenance time and activity (± SEM) for Experiment 3.

yielded a smaller effect in the same direction. In an attempted replication, 1 mg/kg naloxone yielded just the opposite effect, reducing together time from 125 to 95 sec $t(17)=2.3$, $p<0.05$. In another experiment using repeated injections of naloxone, effects were reliable on some days (reduced together time) but not others. Accordingly, we have not been able to obtain consistent directional evidence for opioid blockade and social cohesions. Indeed, in retrospect, it seems difficult to predict what effect naloxone should have. If social cohesion is due partially to animals receiving brain opiate mediated comfort from each other, should temporary blockade of the reward increase or decrease social solicitation? Certainly it would seem reasonable to expect that the reduced reward could lead to rapid extinction of solicitive behavior. On the other hand, from a congnitive perspective, we could expect that reduced reward would lead to increased effort to obtain the reward. There is a precedent for such an expectation in the facilitation of behavior (frustration effect) seen during early segments of extinction, and the facilitation of behavior which can be observed in certain situations when reward is reduced [19]. Perhaps such counteracting tendencies caused the inconsistent results obtained with naloxone. In any case, during the course of the present experiments we have been unable to elucidate the variables which are controlling the effects of naloxone. One untested possibility is that the naloxone variability may be due to time of daily testing. Frederickson, *et al.* [5] have found that naloxone could produce hyperalgesia only at certain times of the day. In some recent experiments (Scheuch, Bishop and Panksepp, 1979, Unpublished data) we have found such effects of naloxone on isolation induced distress vocalizations in chicks. At some points during the light phase of the illumination cycle (last few hours) we have found naloxone to reduce DV's even though at all other time points it increases these vocalizations.

In any case, our morphine results have remained consistent from experiment to experiment, and we believe they provide further evidence for the importance of opioid systems in the mediation of social affect. it is noteworthy that the increased social isolation caused by morphine in our rats is reminiscent of the social isolation which has been often observed to be a characteristic of human narcotic addicts [17]. Perhaps an underlying psychological reason for the attractiveness of opiate drugs is the capacity of narcotics to fulfill biological aspects of social needs in the absence of social interactions. From such a perspective, we predict that narcotic addiction should be capable of being increased by social isolation, and that social isolation will reduce the activity of brain opioid systems. This may explain why social variables modify the intensity of morphine analgesia and the density of brain opiate receptors. The lower analgesic efficacy of morphine in group-housed animals as opposed to isolated animals [3,8] may be due to the sustaining influence of social contacts on brain opioid activity. Group-housed animals may have a higher level of brain endorphin activity than isolated animals, and hence they may be more tolerant to the effects of exogenously administered opiates. Similarly, the capacity of social isolation to increase proliferation of opiate receptors [2] may reflect a regulatory attempt of brain endorphin systems to bring functional brain opioid activity back in line with the reduced activation by the environment.

The presence of high levels of opioids in somatosensory systems of the spinal cord and brainstem [16] .is certainly consistent with the possibility that opioids may participate in the mediation of contact comfort. Furthermore, skin receptors such as those on the nipples appear to be capable of activating brain endorphin systems, since opiates are among the most powerful agents to induce prolactin release [4,11]. Thus blockade of opioid systems with naloxone can markedly disrupt maternal behavior in BALB mice [18]. The facilitation of sexual behavior in sexually inactive males following naloxone [6] is also compatible with the present conceptualization, since, a reduction of brain opioid activity should increase care- and contact-soliciting behaviors. Indeed, from our theoretical perspective we were anticipating such a result, but we also anticipate that continuous opioid blockade through the pre- and post-pubertal phases of development might retard the onset of behavioral sexual competence, even though physiological readiness may be concurrently increased [1].

Beside having implications for the underlying dynamics of narcotic addiction, we think the results observed in this study may have implications for the etiology of childhood autism [12]. A prominent characteristic of autistic children is their failure to seek company, and this is the kind of social pattern that morphine induced in our rats. This, taken in conjunction with other data [15] indicating that low-doses of morphine can induce autistic-like symptoms in animals (namely, a lack of crying, a decrease in clinging behavior, and extreme resistance to extinction of learned habits, as well of course, a relative insensitivity to pain) suggest the possibility that autistic aloofness could be precipitated by endogenous overactivity of brain endorphin systems.

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