

BRIEF REPORT

Hypophysectomy Reduces Behavioral Activation to Morphine in the Rat

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Chronically maintained (2-4 weeks) hypophysectomized or sham-operated adult male Sprague-Dawley rats were injected with vehicle or one of two doses of morphine. Motor activity was remotely recorded for 100 min after injection. Activity was markedly reduced by prior pituitary removal. This finding is consistent with previous studies utilizing other models of pituitary-opiate interactions and may shed light on findings from other paradigms.

The pituitary gland and pituitary hormones and hormone fragments are known to affect numerous opiate or endorphin-mediated behaviors, including analgesia (Gispén, Buitelaar, Wiegant, Terenius, & DeWied, 1976; Pomeranz, Cheng, & Lau, 1977), self-administration (Van Ree & Niesink, 1978; Ziskind & Amit, 1976), pharmacologically induced grooming (Wiegant, Gispén, Terenius, & DeWied, 1977), and motor activity (Katz, 1979).

The activation response of rats to morphine is a highly quantifiable behavioral assay which might further aid in elucidating hypophyseal-opiate interactions. The response is specific to low doses of drug, and involves a period of behavioral activity of short duration (30-90 min). We examined the response in normal and hypophysectomized rats to determine if this form of motor stimulation is dependent upon the pituitary for its expression.

Materials and methods. Adult male Sprague-Dawley rats, each 70 days at the time of testing were obtained locally (Charles River, Portage, Mich.) and maintained in group housing with food (Teklad, 4.0% fat rodent diet S-0836) and tap water continuously available. Hypophysectomized rats ($n = 8$) were given a daily supplement of 0.9% sodium chloride in their water and a fruit supplement of one-fourth orange per rat to maintain normal health. Sham-operated rats ($n = 8$) were also given the fruit sup-

plement to avoid unduly biasing the experimental design. All surgery was carried out by the supplier two weeks prior to testing, with rats subjected to parapharyngeal hypophysectomy or sham operation under ether anesthesia.

The testing apparatus has been described in detail elsewhere (see Katz, 1979) and consisted of four commercially available (Stoelting, Chicago, Ill.) tuned oscillators adjusted and filtered to detect gross body movement. The monitors were located immediately below the experimental cages and recorded activity by remote sensing.

Rats were initially placed in $50 \times 40 \times 22$ cm while polypropylene experimental cages (Scientific Products) with a fresh pine chip bedding, and were extensively habituated (4 hr) prior to the injection of drug or vehicle. Experimental procedure involved briefly removing the animal and injecting one of two doses of morphine sulfate or vehicle. All injections were administered 2 ml/kg using 0.9% sodium chloride solution as the injection medium. Activity was recorded in 10-min intervals for the 100 min after injection. Care was taken to administer all treatments in a counterbalanced fashion and to systematically vary placement upon individual monitors across treatments. An interval of 72 hr or more separated all tests.

For purpose of histology 10 rats (5 each, experimental and control) were sacrificed at the close of testing. To further assess the completeness of the surgery the remaining three hypophysectomized rats were then deprived of their sodium chloride supplement.

Results. Control subjects showed elevated activity to both doses of drug, in comparison with vehicle. The activation was slightly prolonged with the higher dose. On the other hand hypophysectomy produced a virtual elimination of any drug-induced motor activation. These data are presented in Figs. 1 (for sham-operated performance) and 2 (for the hypophysectomized rats). All data are presented as means and standard errors. Analysis by a three-factor analysis of variance upon groups (sham vs hypophysectomy), dosage (vehicle vs drug), and time course, corrected for repeated measures, indicated all main effects were significant ($F(1, 14)$ groups = 28.9; $F(2, 28)$ dose = 7.2; $F(9, 126)$ time = 4.4; $F(18, 256)$ dose \times time = 3.7; $F(2, 28)$ dose \times groups = 11.3; $F(9, 126)$ groups \times time = 4.9; $F(18, 256)$ three-way interaction = 3.8). In all cases the probability of these findings occurring by chance was less than .01. The facts that the groups differed and that they differed specifically with respect to drug response support the major hypothesis, that hypophysectomized rats are less responsive to morphine.

Necropsy of five hypophysectomized subjects and five normal rats at the close of testing indicated complete absence of pituitary tissue in experimental subjects. (Only five of eight rats were examined histologically—sampling was random and the histological profile should

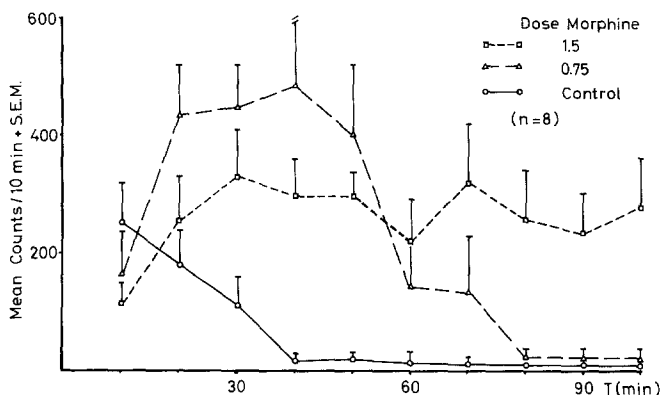


FIG. 1. Response of sham-operated rats to vehicle or two doses of morphine (mean and standard error). Behavioral activity is recorded based upon remote sensing. Extensive habituation precedes all injections.

therefore be representative). This was further confirmed by measures of body weight (median group score = 140 g for experimental vs 185 g for control), and by the death, within 3 weeks of the final test, of the remaining three hypophysectomized rats.

We have had occasion to test an additional group of four otherwise naive hypophysectomized rats after one week's exposure to the synthetic glucocorticoid dexamethasone (1 mg/liter in drinking water resulting in an effective daily dose of 30–50 g); they showed an intermediate level of response to 1.5 mg/kg of morphine (average 10-min count = 188; range = 75–280, compare to Fig. 1). These results suggest it may be possible to

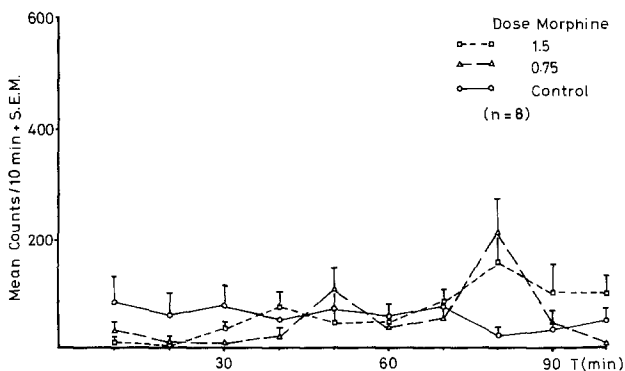


FIG. 2. Response of hypophysectomized rats to vehicle or two doses of morphine (mean and standard error). Behavioral activity is recorded based upon remote sensing. Extensive habituation precedes all injections.

partially reverse the behavioral deficit. At the present time the limitations of sample size restrict this to a suggestive finding.

Discussion. Hypophysectomy profoundly inhibited the normal response to opiates using activity as a dependent variable. It may be questioned whether this represented a general debilitation due to hypophysectomy or a specific failure to respond to the drug treatment. Since the animals all were extensively habituated it was possible to examine their behavioral baselines during this initial exposure to the apparatus. If the hypophysectomized rats were generally debilitated it would be predicted that they would also be initially less mobile in their exploratory activity during habituation. In fact this did not occur. The control animals had 4678 + 742 counts on the average while the hypophysectomized animals had 6377 + 1036 counts (mean and standard error). This represents a nonsignificant ($t(14) = 1.3, p > .05$) elevation in the experimental group and suggests it was capable of normal activity in other circumstances.

It might also be questioned whether administration of two doses of drug may have produced a tolerance effect, which may have contributed to a lowering of activity scores across conditions. No absolute answer to this is possible, given the constraints of experimental design. On the other hand it should be emphasized that the design was counterbalanced for both groups. All other things being equal, this would tend to reduce the influence of tolerance. A differential tolerance effect in a given group or across groups remains theoretically possible.

The present findings are consistent with findings from other paradigms (vide supra) and may in fact shed some light upon at least some of them. Hypophysectomy is known to interfere with morphine seeking in the rat. The present findings suggest a loss of activation to opiates after hypophysectomy. It may be speculated that a common mechanism underlies both effects, i.e., that hypophysectomy causes a reduction in drug administration due to reduced behaviorally activating effects. On the other hand, however, sensory alterations (i.e., change in taste perception) may also account for certain findings at least in part (Van Ree & Niesink, 1978). The relative contributions of sensory vs behavioral activating mechanisms remain to be determined empirically.

The present findings are of interest in either case since they provide a novel model for the assessment of pituitary interactions with opiates, and confirm prior studies of various related models.

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