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Pituitary-Adrenal Axis and Oral Morphine Consumption in Rats

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VAN REE, JAN M. AND RAYMOND J. M. NIESINK. *Pituitary-adrenal axis and oral morphine consumption in rats.* PHARMAC. BIOCHEM. BEHAV. 9(4) 493–498, 1978.—Removal of the pituitary gland in rats leads to suppression of oral morphine and quinine intake behavior. Experiments measuring oral intake of solutions containing graded concentrations of morphine or quinine, revealed that the detection acuity for bitter taste is changed in hypophysectomized (hypox) animals. Treatment of these rats with ACTH $_{1-24}$ restored oral morphine intake towards that of intact rats. Morphine consumption in hypox rats was not affected by administration of ACTH$_{1-10}$ or ACTH$_{11-24}$, but was normalized by treatment with corticosterone. Adrenalectomy also diminished oral morphine intake. It is concluded that hypophysectomized animals refuse a morphine solution because their threshold for bitter taste quality is altered, presumably due to a diminished release of corticosteroids.

Morphine Quinine Pituitary-adrenal axis ACTH Corticosterone

OPIATE self-administration in rats has been studied using the intravenous [16,17] and the oral route of drug administration [4, 10, 11, 14]. Application of the simple oral method is limited primarily because morphine is a bitter substance. This limiting factor has been circumvented by passive premedication with morphine [11]. Morphine preference has also been observed in non-premedicated rats for which hydration was contingent upon drinking morphine solution [14] or by presenting morphine in a sucrose solution [10].

Based on the hypothesis that drug self-administration is comparable with consummatory behavior, the involvement of the hypothalamus in morphine ingestion was investigated [1,9]. Lesions in the lateral hypothalamus in rats induce rejection of morphine solutions [1] and, subsequently, evidence has been presented that a similar blockade of oral morphine intake can be obtained by removal of the pituitary gland [19].

The present experiments were designed to investigate the effect of hypophysectomy on oral morphine consumption in more detail and to establish the factors which are responsible for the altered morphine intake behavior of hypophysectomized rats.

METHOD

Animals

Male rats of a Wistar strain, weighing between 160–200 g were used. The animals were maintained in a temperature-controlled environment (25 ± 1°C) with a regular day-night cycle. Standard rat food was available ad lib. During experimentation the rats were housed individually. The animals were given free access to 1 or to 2 bottles with liquid. The position of the bottles (right or left) was alternated daily to allow for possible positional preferences.

Surgical Procedures

The pituitary gland was removed by the transauricular approach under light ether anesthesia. Bilateral adrenalectomy was performed under light ether anesthesia. For sham operations, rats were submitted to the same surgical procedure, except for removal of the gland. After the operation, adrenalectomized animals were allowed to drink physiological saline instead of tap water in order to keep them in a satisfactory condition. At the end of the experiments, the animals were killed by decapitation. The adrenals were removed, dissected free of fat on ice and weighed. The sella turcica was inspected macroscopically to verify successful hypophysectomy.

Solutions and Injections

Tap water was used to prepare solutions with the various drugs for drinking. Concentrations of the drugs are expressed as percentage by weight of solute in volume of solvent. Except for tap water, the various solutions contained 5% sucrose to make them more acceptable to the animals. For adrenalectomized animals physiological saline was used instead of tap water. Fresh solutions were prepared daily.

ACTH-like peptides were administered subcutaneously (0.5 ml/injection) as long acting Zn-phosphate preparations every other day (20 or 40 μg/injection). Corticosterone was dissolved in ethanol and diluted with saline. It was injected subcutaneously every day (3 or 10 mg/kg b.w.). Placebo animals received 0.5 ml of the vehicle solution. The injections were started the day following operation.

General Test Procedure

Four days after operation the animals were placed in ex-

perimental cages where they remained for the duration of the experiment. They were allowed to adapt to the experimental environment for 3 days. Thereafter, fluid intake was determined using a one-bottle forced-choice procedure or a two-bottle choice procedure, in which the animals could select 1 of the 2 test solutions. Fluid consumption was measured daily for 4 days by weighing the drinking bottles. Body weight (b.w.) of the animals was recorded every other day.

Experimental Procedures

Experiment 1. This experiment was performed to establish a morphine solution which would be equiaversive to a quinine solution in both intact and hypophysectomized (hypox) rats. Five groups of 7 intact animals were given the opportunity to drink a morphine solution (0.2%) or a quinine solution (0.00625; 0.01; 0.0125; 0.025 or 0.05%) using the two-bottle test procedure. Two groups of 5 hypox rats were allowed to choose between 0.0025% quinine solution—higher concentrations were rejected (see results)—and 0.005% or 0.01% morphine solution.

Experiment 2. To test the ability of hypox rats to drink morphine or quinine solutions, groups of hypox rats and sham-operated controls were allowed to consume various concentrations of morphine or quinine solutions using the one-bottle forced-choice procedure. The concentrations of morphine were twice (equiaversive to) that of quinine. The actual concentrations of morphine were 0.005% (8 hypox and 9 controls), 0.01% (8 hypox and 9 controls) and 0.02% (28 hypox and 9 controls); those of quinine were 0.0025% (9 hypox and 10 controls), 0.005% (11 hypox and 9 controls) and 0.01% (14 hypox and 10 controls). Using the same test procedure oral morphine and quinine intake was measured in groups of 8 animals 3 months after hypophysectomy. The different groups were allowed to consume tap water, morphine solution (0.02%) or quinine solution (0.01%).

Experiment 3. This experiment is dealing with the influence of peptides related to ACTH and corticosterone on oral morphine intake in both hypox rats and controls. Various groups of hypox animals and sham-operated controls were allowed to consume tap water, morphine (0.02%) or quinine (0.01%) solution using the one-bottle forced-choice procedure. Animals offered tap water were treated with placebo (10 hypox and 6 controls); those offered morphine solution were treated with either placebo (42 hypox and 24 controls), $ACTH_{1-24}$ (15 hypox and 8 controls), $ACTH_{4-10}$ (17 hypox and 9 controls), $ACTH_{11-24}$ (16 hypox and 12 controls), corticosterone 3 mg/kg (14 hypox and 5 controls), or corticosterone 10 mg/kg (21 hypox and 6 controls); those offered quinine solutions were treated with either placebo (14 hypox and 10 controls) or $ACTH_{1-24}$ (7 hypox and 8 controls).

Subsequently, 2 groups of 10 adrenalectomized animals were given morphine solution (0.02%) or vehicle solution as their only liquid available.

Experiment 4. To test whether $ACTH_{1-24}$ would influence daily water and food intake, 20 animals were placed in standard metabolic cages. Half of the rats were treated with $ACTH_{1-24}$, the others with placebo. The experimental procedure and injection schedule was similar to the previous experiments. Water and food intake and urine production was measured daily.

Experiment 5. This experiment was performed to establish the influence of hypophysectomy in animals that had already experience with oral morphine consumption before the operation. Three groups of 6 sham-operated animals treated with either placebo, $ACTH_{1-24}$ or $ACTH_{1-10}$ were hypophysectomized after 4 days of oral morphine intake using the same procedure as outlined in Experiment 3. Following operation, the rats were placed back in their experimental cages and were allowed to consume tap water for 3 days. Thereafter, the animals were given access to a morphine (0.02%) solution again for 4 days. Treatment of the animals was continued following the normal schedule.

Experiment 6. These experiments were designed to test whether $ACTH_{1-24}$ treatment was able to change preference performance of hypox animals. First, 4 groups of 5 naive rats were tested for their preference for morphine-sucrose (MS) solution versus sucrose (S). The various concentrations of morphine were 0.0006%, 0.002%, 0.006% and 0.02%. Second, groups of hypox animals treated with placebo or $ACTH_{1-24}$ were allowed to choose between sucrose (S) solution and tap water (T) (number of animals (n): 10 resp. 9) or morphine-sucrose(MS) solution and S solution (n: 7 resp. 9) or MS solution and T (n: 8 resp. 9). The concentration of morphine was always 0.02%.

Analysis of the Data

The mean of the daily fluid intake during the 4 test days was calculated per animal and used for further analysis. Group means and standard errors were determined. Statistical comparisons are based on two-tailed Student's *t*-tests.

Drugs

The following drugs were used: morphine (morphine hydrochloride; O.P.G. Holland), corticosterone, $ACTH_{1-24}$, $ACTH_{4-10}$ and $ACTH_{11-24}$ (Organon International B.V. Holland).

RESULTS

Preference for Morphine Versus Quinine (Experiment 1)

Intact and hypophysectomized (hypox) rats were tested for their preference for morphine versus quinine solutions. It appeared (Fig. 1) that a 0.01% quinine solution was approximately equiaversive to the 0.02% morphine solution. In hypox animals 40% of the rats on the lower dose of morphine consumed more than 60% of their daily fluid intake as morphine solution, while 30% of these animals took more than 60% as quinine solution (20 observations). For hypox animals on the high dose of morphine, these percentages were 18% as morphine solution and 72% as quinine solution (28 observations). Thus, like in intact animals, a morphine concentration that was twice that of quinine appeared to be equiaversive in hypox rats.

Oral Intake Following Hypophysectomy (Experiment 2)

The oral morphine intake in hypox animals was markedly diminished as compared to sham-operated controls when morphine solution was offered as the only liquid available (Fig. 2). The decrease was more pronounced when the concentration of the drug was higher. A similar pattern was observed with animals which were given access to various quinine solutions. No consistent differences with respect to fluid intake were present between animals that could consume morphine and an equiaversive quinine solution. Calculating the amount of fluid intake per 100 g b.w. (Table 1), it appeared that hypophysectomy stimulated tap water intake and markedly decreased morphine and quinine intake.

In animals tested 3 months after hypophysectomy, the mean daily tap water intake was 13.0 ± 0.9 ml/100g b.w. A

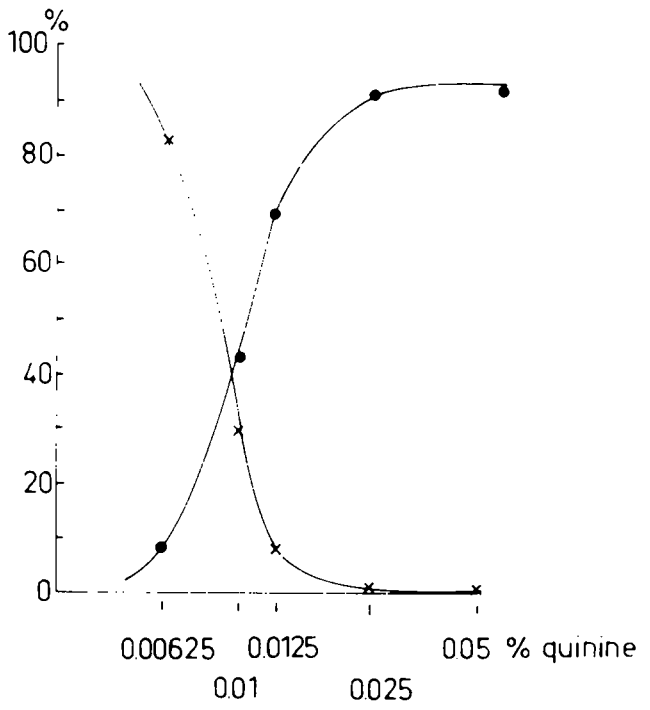

FIG. 1. Determination of a quinine solution that is equiaversive to a solution of 0.02% morphine in naive animals. Groups of animals (n=10–14) were allowed to choose between the morphine solution and quinine solution. The concentration of quinine is plotted versus the percentage of animals (%) that consume more than 60% of their daily fluid intake as morphine solution (●–●) or as quinine solution (x–x).

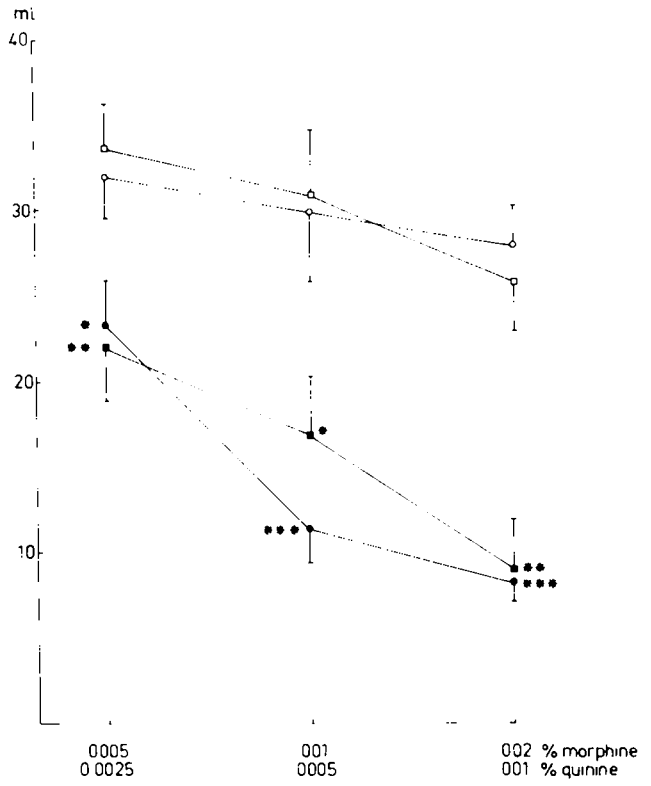

FIG. 2. Daily fluid intake of hypophysectomized (filled symbols) and sham-operated rats (open symbols) which were allowed to consume different concentrations of morphine (○) or quinine (□) solutions in the one-bottle forced-choice procedure. The mean fluid intake (ml) of at least 9 animals per group is plotted versus the concentration of the drugs. Vertical bars indicate SEM. *Different from sham-operated rats. (*$p<0.05$; **$p<0.01$; ***$p<0.001$)

TABLE 1

MEAN (± SEM) DAILY FLUID INTAKE, EXPRESSED AS ML/100 G B.W., OF SHAM-OPERATED AND HYPOPHYSECTOMIZED RATS. GROUPS OF ANIMALS, TREATED WITH PLACEBO, ACTH-LIKE PEPTIDES OR CORTICOSTERONE (CS), WERE ALLOWED TO CONSUME TAP WATER, MORPHINE (0.02%) OR QUININE (0.01%) SOLUTIONS USING THE ONE-BOTTLE FORCED-CHOICE PROCEDURE. THE NUMBER OF ANIMAL PER GROUP IS INDICATED IN BRACKETS. DIFFERENCES BETWEEN SHAM-OPERATED AND HYPOPHYSECTOMIZED RATS ARE EXPRESSED AS THE CALCULATED LEVEL OF STATISTICAL SIGNIFICANCE (p). PEPTIDES WERE ADMINISTERED SUBCUTANEOUSLY EVERY SECOND DAY ($ACTH_{1-21}$ AND $ACTH_{11-21}$: 20 μg/INJECTION, $ACTH_{4-10}$: 40 μg/INJECTION) AND CS WAS INJECTED SUBCUTANEOUSLY EVERY DAY

Treatment	Sham-operated		Hypophysectomized		p
tap water					
placebo	12.1 ± 0.5	(6)	19.2 ± 1.5	(10)	<0.01
morphine-solution					
placebo	13.9 ± 0.9	(24)	5.4 ± 0.6	(42)	<0.001
$ACTH_{1-21}$	16.1 ± 2.4	(8)	23.6 ± 1.6	(15)	<0.02
$ACTH_{4-10}$	17.5 ± 2.8	(9)	6.2 ± 1.2	(17)	<0.001
$ACTH_{11-21}$	11.6 ± 1.1	(12)	5.8 ± 0.8	(16)	<0.001
CS (3 mg/kg)	10.6 ± 1.9	(5)	12.6 ± 1.7	(14)	>0.05
CS (10 mg/kg)	13.2 ± 1.6	(6)	16.0 ± 2.1	(21)	>0.05
quinine solution					
placebo	13.0 ± 1.1	(10)	6.7 ± 1.6	(14)	<0.01
$ACTH_{1-21}$	12.4 ± 1.2	(8)	18.3 ± 2.2	(7)	<0.05

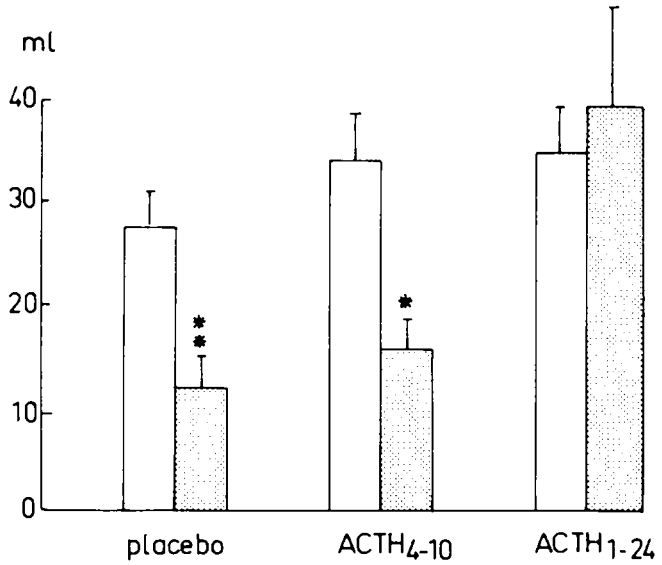

FIG. 3. Mean daily fluid intake (ml) of animals treated with placebo, $ACTH_{1-10}$ or $ACTH_{1-24}$ (6 animals per group) before (open column) and after (shaded column) removal of the pituitary. *Different from before hypophysectomy (*$p<0.05$; **$p<0.005$).

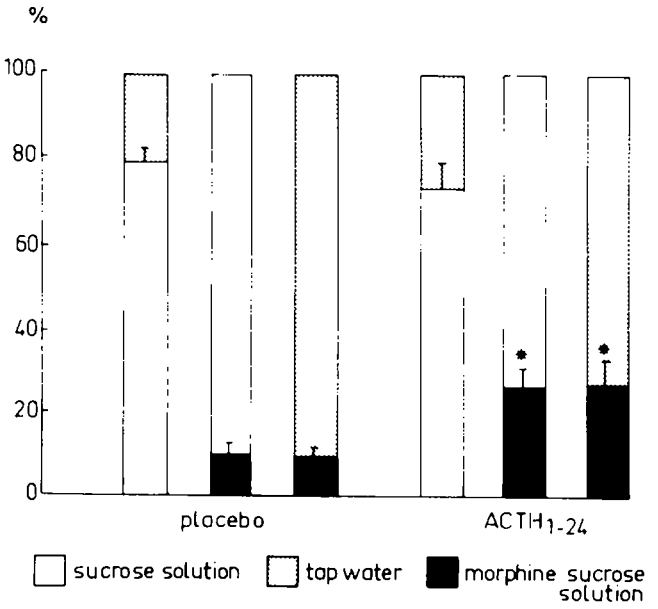

FIG. 4. The effect of treatment with $ACTH_{1-24}$ on preference performance of hypophysectomized animals. Different groups of animals (n 7–10) were allowed to choose between sucrose solution and tap water or between sucrose solution and morphine-sucrose solution or between tap water and morphine-sucrose solution. The amount consumed as the indicated solution is expressed as the percentage and SEM (vertical bars) of total daily liquid intake. *Different from placebo treated animals ($p<0.05$).

similar amount of fluid intake was observed in animals which were given morphine or quinine in their drinking water. The actual intake in these animals was resp. 11.3 + 1.4 ml/100 g b.w. and 15.6 + 2.3 ml/100g b.w.

Treatment of Hypox Rats and Effect of Adrenalectomy (Experiment 3)

$ACTH_{1-24}$ (20 μg/injection) completely abolished the reduction of oral morphine and quinine consumption in hypox rats (Table 1). Treatment with $ACTH_{1-10}$ or $ACTH_{11-24}$ (resp. 40 μg and 20 μg injection) was not effective in this respect. Daily injection with corticosterone (3 mg/kg or 10 mg/kg) also restored oral morphine consumption in hypox rats. Thus, the effect of $ACTH_{1-24}$ might be mediated by stimulation of the adrenal cortex. Therefore, adrenalectomized rats were given a morphine solution as their only liquid available. The mean fluid intake of these animals was 17.0 ± 1.8 ml/100 g b.w. which is significantly lower than that of adrenalectomized animals that were offered vehicle solution (23.9 + 0.4 ml/100 g b.w., $p<0.002$).

$ACTH_{1-24}$ and Tap Water Intake (Experiment 4)

Daily fluid intake of animals treated with $ACTH_{1-24}$ and given morphine solution was somewhat augmented as compared to that of animals on tap water in both controls and hypox animals. To test whether $ACTH_{1-24}$ would influence daily water and food intake, naive animals were placed in standard metabolic cages and treated with either $ACTH_{1-24}$ or placebo. Daily water intake was not affected by peptide treatment (13.6 ± 0.5 ml/100 g b.w. vs. 13.2 ± 0.4 observed for controls), neither was daily food intake (15.2 ± 0.6 g vs. 14.7 ± 0.7 g) and urine production (8.6 + 0.6 ml vs. 8.0 + 0.2 ml). Thus, $ACTH_{1-24}$ did not affect food and water consumption in normal animals.

Effect of Prior Experience (Experiment 5)

Hypophysectomized animals that had already experience with oral morphine consumption before the operation exhibited similar effects as observed in morphine naive rats. Mean daily fluid intake of placebo treated animals was markedly decreased as compared to that prior to hypophysectomy (Fig. 3). Similar results were obtained with rats treated with $ACTH_{1-10}$. However, rats receiving $ACTH_{1-24}$ continued to consume morphine solution at the same level as that found before hypophysectomy.

Preference Performance Following Hypophysectomy (Experiment 6)

Naive rats were tested for their preference for morphine-sucrose (MS) solution versus sucrose (S) solution. The intake of MS solution expressed as percentage of total daily fluid consumption appeared to be 50%, 38%, 29% and 23% when respectively a 0.0006%; 0.002%; 0.006% and 0.02% morphine solution was offered. Hypox animals, allowed to choose between S solution and tap water (T), showed a clear preference for S solution (Fig. 4). This preference was not changed by treatment with $ACTH_{1-24}$. The morphine intake of placebo treated hypox rats was low when the animals could choose between MS and S or MS and T. However, the morphine intake was significantly increased in hypox rats treated with $ACTH_{1-24}$ and exposed to the same experimental procedure.

Adrenal Weight

The adrenal weight (per pair of adrenals) of intact and sham-operated animals was respectively 31 ± 2 mg and 30 ± 2 mg, while that of hypox animals was 10 ± 1 mg. Treatment with $ACTH_{1-10}$, $ACTH_{11-24}$ or corticosterone did not affect adrenal weight. Adrenal weight of hypox rats

treated with $ACTH_{1-24}$, did not differ from that of sham-operated controls. The same amount of $ACTH_{1-24}$ in intact rats did not significantly affect adrenal weight. The adrenals of animals which were hypophysectomized 3 months before weighed 7.5 ± 0.6 mg.

DISCUSSION

The present results show that solutions of morphine and quinine are equiaversive when the concentration of morphine is twice that of quinine. This finding agrees well with data reported by other authors [13,14]. Similar results were obtained in hypox animals, suggesting that the removal of the pituitary does not induce differences between morphine and quinine with respect to their bitter taste qualities. However, oral morphine and quinine intake was markedly suppressed in hypox rats. This might suggest that removal of pituitary hormones alters taste detection and recognition, since both morphine and quinine intake in equiaversive concentrations were reduced to the same extent (Fig. 2). Hypox animals may be more sensitive to the bitter taste of the drugs which may strengthen the aversive components. Recovery occurs from the effect of hypophysectomy on morphine and quinine intake, because in rats, in which the pituitary was removed 3 months prior to testing, morphine and quinine intake were not different from that of controls. Ziskind and Amit [19] also have found a decreased oral morphine consumption in hypox rats, but, at variance with the present findings, they reported that in their animals morphine intake was more reduced than quinine intake. This difference is difficult to interpret since these authors did not present data concerning quinine intake of sham-operated controls and preference for quinine versus morphine solution in their hypox animals.

$ACTH_{1-24}$ was able to reverse the blockade of morphine and quinine intake in hypox rats. Treatment was effective when morphine or quinine solution was the only fluid available, but also when the rats could choose between morphine and control solutions. Although interactions between ACTH-like peptides and morphine have been demonstrated in vitro and in vivo [5, 12, 15, 18], these presumably cannot account for the effect of $ACTH_{1-24}$, since both morphine and quinine intake were restored by $ACTH_{1-24}$ treatment of hypox rats.

The effectiveness of $ACTH_{1-24}$ might be at least partly mediated by stimulation of the adrenal cortex yielding corticosteroid-release. Like $ACTH_{1-24}$, corticosterone treatment also normalized oral morphine intake of hypox rats, and removal of the adrenals led to a similar diminished morphine intake as hypophysectomy. Thus, the rejection of morphine and quinine solutions by hypox animals may be caused by the absence of corticosteroids. It has been argued that oral morphine intake in hypox rats is diminished as a result of alterations in taste detection. Indeed, corticosteroids play a profound role in the detection and recognition of taste [3,6]. The data obtained with both the one-bottle forced-choice and the two-bottle choice procedure revealed that threshold for bitter taste recognition is increased in hypox rats. Thus, it might be postulated that in the absence of corticosteroids this threshold is increased. This is supported by studies concerning the role of adrenal corticosteroids in sensory processes (for review see [3,6]). Experiments in humans and animals have shown that removal of adrenal cortical hormone activity leads to a significant increase in detection acuity for the sensory modalities of taste and of other sensory signals. Treatment with steroid hormones resulted in a return to normal thresholds. On the other hand, patients with Cushing's syndrome, in which corticosteroid secretion is supranormal, have a decreased ability to detect the sensory modality of taste and other qualities. Removal of the adrenal glands in these patients restores abnormal sensory acuity. It is not clear, whether the corticosteroids exhibit their effect on sensory mechanisms in peripheral nervous systems or in higher integrative centres of the nervous system or in both. Changes in reactivity to taste properties of sucrose and quinine solutions have been reported in animals with septal or amygdaloid lesions [2,8]. These changes might be more related to adaptive effects than to alterations in the threshold for taste qualities [7]. However, it is unlikely, that an altered adaptation to the introduction of morphine solution markedly contributes to the observed disturbance in hypox rats, since removal of the pituitary in rats which had already experience with oral morphine consumption, also led to a decrease intake behavior.

The present findings indicate that the pituitary-adrenal axis markedly influences oral morphine consumption, presumably by altering the sensory modality of bitter taste.

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