MECHANISM OF THE DIURETIC ACTION OF MORPHINE IN RATS

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Injection of morphine into rats after an ordinary diuretic stimulates both water and sodium excretion. In adrenalectomized or hypophysectomized animals, morphine has no such action. Morphine reduces the ascorbic acid concentration in the adrenals. Injection of ACTH into intact rats also promotes the excretion of water and salts.

KEY WORDS: morphine, diuresis, salt excretion, pituitary–adrenal system.

Morphine inhibits water diuresis in animals, evidently by increasing the secretion of ADH [4, 9, 10]. Against the background of spontaneous excretion of urine, morphine induces polyurina and an increased salt excretion [2, 13, 14], the mechanism of which has not been explained.

Since morphine stimulates the pituitary–adrenal system [12], it was decided to study whether this effect is connected with the diuretic and salt-excretory action of the drug.

EXPERIMENTAL METHOD

Experiments were carried out on 65 albino rats weighing 160-200 g, kept in metabolism cages on a constant food and water intake. The daily water consumption, diuresis, and excretion of sodium, potassium (flame photometry), and creatinine (Folin's method) under the influence of morphine (1.5 mg/100 g body weight) was determined in intact animals and in rats 3 days after adrenalectomy or 6 days after hypophysectomy. The adrenalectomized animals received DOCA in a dose of 0.5 mg/100 g body weight. Hypophysectomy was performed by the paratracheal method [1]. The effect of ACTH (4 units/100 g body weight) on the excretion of urine and the effect of morphine on the ascorbic acid concentration in the adrenals [7] also were investigated 1, 2, 6, and 12 h after injection of the drug.

EXPERIMENTAL RESULTS

Injection of morphine was followed by a diuretic effect accompanied by increased sodium excretion;

TABLE 1. Effect of Morphine on 24-Hourly Diuresis in Intact and Adrenalectomized Rats (M ± m)

Experimental conditions	Number of experiments	Water intake (in ml)	Diuresis (in ml)	Sodium (in μeq)	Potassium (in μeq)	Creatinine (in mg)
Intact rats						
control	20	19±1,12	6,3±0,56	12,1±2,98	558±48	2,1±0,23
morphine (1.5 mg/100 g)	20	16±1,24	10,4±0,90	31,0±5,64	777±47	2,1±0,29
After adrenalectomy						
control	21	22±0,89	10,4±0,49	10,5±1,41	581±21	1,3±0,27
morphine (1.5 mg/100 g)	21	17±1,05	9,3±0,55	11,1±1,66	594±38	1,0±0,12

Note. Here and in Tables 2 and 3 the values of P are not given when they exceed 0.05

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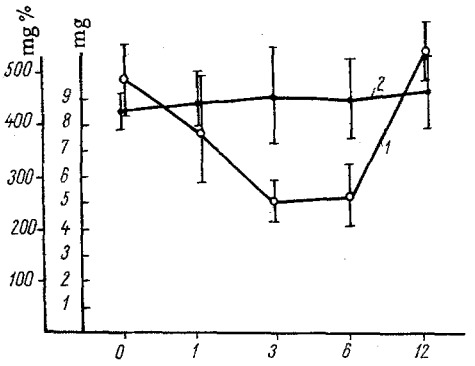

Fig. 1. Effect of morphine on ascorbic acid concentration in rat adrenals: 1) ascorbic acid concentration; 2) weight of adrenals. Limits of variations of both parameters shown. Abscissa, time after injection of morphine (1.5 mg/100 g body weight); ordinate: left – ascorbic acid concentration, right – weight of adrenal.

TABLE 2. Effect of Morphine on 24-Hourly Diuresis in Intact and Hypophysectomized Rats (M ± m)

Experimental conditions	Number of experiments	Water intake (in ml)	Diuresis (in ml)	Sodium (in μeq)	Potassium (in μeq)	Creatinine (in mg)
Intact rats						
control	16	19,4± 1,0	5,7± 0,46	13,8± 1,66	685± 76	2,9± 0,20
morphine (1,5 mg/100 g)	16	18,4± 1,0	11,0± 0,71 $P<0,001$	49,7± 6,8 $P<0,001$	727± 57	3,1± 0,25
After adrenalectomy						
control	24	16,8± 0,94	7,8± 0,68	18,0± 2,6	654± 44	2,3± 0,22
morphine (1,5 mg/100 g)	23	14,4± 0,98	8,3± 0,62	17,6± 1,5	574± 60	2,3± 0,22

TABLE 3. Effect of ACTH on 24-Hourly Diuresis in Rats (M ± m)

Experimental conditions	Number of experiments	Water intake (in ml)	Diuresis (in ml)	Sodium (in μeq)	Potassium (in μeq)	Creatinine (in mg)
Control	10	20,7± 1,13	6,2± 0,66	10,2± 0,77	675± 0,77	1,1± 0,11
ACTH (4 units/100 g)	10	19,5± 1,33	10,2± 1,02 $P<0,01$	15,5± 0,89 $P<0,01$	1019± 96 $P<0,02$	1,2± 0,15

this effect depended on a decrease in tubular reabsorption, because the 24-hourly excretion of creatinine, a measure of filtration, was unchanged (Table 1). Considering that glucocorticoids promote diuresis and increase salt excretion [5, 6, 8], the effect of adrenalectomy on the response to morphine was tested. Experiments showed that no response to morphine appeared under these conditions (Table 1); this indicates that adrenocortical hormones participate in the diurétic and sodium-excretory effects of morphine. In fact, as Fig. 1 shows, morphine activates the function of the adrenal cortex, judging from the decrease in the ascorbic acid concentration in it. These observations are in agreement with results obtained by other workers [12].

Other workers [11, 15] have shown that in the absence of the pituitary morphine can no longer increase the corticosterone concentration in the adrenals and peripheral blood. It was natural to suggest that the diuretic effect of morphine is connected with its activating action on the adenohypophysis, which stimulates corticosteroid production.

Experiments on hypophysectomized animals confirmed this view (Table 2). Moreover, after injection of ACTH into intact rats the 24-hourly excretion of urine and salts increased (Table 3). These results are in agreement with previous observations on dogs [3].

It can accordingly be concluded that morphine activates ACTH secretion by the adenohypophysis, and

this, by causing an increase in the synthesis and secretion of glucocorticoids by the adrenal cortex, is responsible for the increase in the diuresis and salt excretion produced by morphine through inhibition of the reabsorption of water and electrolytes.

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