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SOME BIOCHEMICAL AND BEHAVIORAL EFFECTS OF MORPHINE IN BENACTYZINE-TREATED RATS

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Considerable importance in the regulation of spontaneous motor activity is attached to the nigrostriatal complex and, in particular, to interaction between antagonistic cholinergic and dopaminergic mediator systems in this brain structure. The state of equilibrium and balance between them is essential for normal functioning of the striatum and for the performance of physiological locomotor activity [15]. Central cholinolytics, by shifting the balance toward dopaminergic mechanisms, also induce behavioral disorders in the form of motor excitation, whereas drugs depressing dopaminergic activity may have a sedative or even a cataleptogenic action depending on their dose. Besides other pharmacological agents, the narcotic analgesics also give a hypokinetic effect and are able to modify dopamine (DA) metabolism in intact animals [9], but if the balance between the mediator systems is disturbed the character of their influence on dopaminergic transmission is still unexplained.

To study this influence the action of morphine was studied on behavior and on some indices of DA metabolism in the striatum of rats after preliminary injection of the central cholinolytic benactyzine.

EXPERIMENTAL METHOD

The behavioral effects of benactyzine were assessed by the spontaneous motor activity test, which is usually used to study the behavior of animals under the influence of drugs, including correlation between their action on cholinergic mediation processes and behavior [1, 7]. The biochemical studies included determination of the DA and homovanillic acid (HVA) concentrations in the caudate nucleus by modified methods in [10, 14]. Experiments were carried out on noninbred male rats weighing 180-250 g. The animals' motor activity was recorded throughout the experiments by the "Animex" apparatus (model DSE, sensitivity and tuning 40 μA), and the recording began 10 min after the animal was placed in the chamber. During the first hour motor activity of intact animals was recorded in all the experimental groups (background); activity of rats of group 1 (the control) was then recorded, physiological saline was injected, activity of the rats of group 2 was recorded, and they were given benactyzine in a dose of 40 mg/kg. The animals of groups 3 and 4 received injections of morphine 30 min after benactyzine in doses of 2 and 10 mg/kg, respectively. Rats of groups 5 and 6 received only morphine in doses of 2 and 10 mg/kg, respectively. Motor activity was recorded for 1 h after injection of morphine. The mean number of movements for the group was expressed as a percentage of the background value and compared with the control for similar time inter-

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vals; the significance of differences was determined by Student's t-test. For the biochemical investigation the rats were decapitated 1 h after the injection of morphine and 90 min after the injection of benactyzine. All injections were intraperitoneal, in a volume of 1 ml/kg body weight.

EXPERIMENTAL RESULTS

Data on motor activity of the animals obtained during the experiments are shown in Table 1.

Clearly benactyzine induced marked motor hyperactivity in the animals which lasted not less than 90 min, and morphine, if injected 30 min after benactyzine, had the opposite effect. A more detailed interpretation of this effect of morphine can usefully be made after analysis of the results of the biochemical tests (Table 2).

As Table 2 shows, the DA concentration in the corpus striatum under the influence of these drugs remained unchanged compared with the control under all experimental conditions, whereas the HVA level underwent significant changes. Benactyzine caused a marked decrease in the HVA concentration in the animals, whereas morphine, injected 30 min after benactyzine, had the opposite action.

These results show that definite correlation exists between changes in the motor activity of the animals after injection of morphine preceded by benactyzine and the effect of morphine on the HVA concentration in the rat striatum. For instance, when injected in a dose of 2 mg/kg, morphine did not affect the HVA level compared with the control and did not change the number of movements made by the rats during 1 h after the injection. After preliminary administration of benactyzine, morphine in the same dose increased the HVA concentration, when lowered by the cholinolytic, to the control level and significantly reduced the motor hyperactivity of the animals (compare the numbers of movements made by rats of group 2 and 3 in Table 1). An increase in the dose of morphine to 10 mg/kg against the background of benactyzine led to an even greater increase in the HVA level in the striatum and completely abolished the hyperactivity induced by benactyzine. In intact animals morphine in a dose of 10 mg/kg evoked an even greater increase in the HVA concentration compared with the control than if preceded by benactyzine (compare the HVA levels in rats of groups 4 and 6 in Table 2) and led to marked hypodynamia throughout the first hour after injection. This effect of morphine could be seen to increase with an increase in its dose.

It can be concluded from an examination of these results that injection of the central cholinolytic benactyzine under these experimental conditions had an indirect effect on processes of dopaminergic transmission, evidently by disturbing equilibrium between the cholinergic and dopaminergic mediator systems in the striatum. Under these circumstances the fall in the level of HVA, the principal extraneuronal metabolite of DA, while the concentration of mediator remained unchanged, is evidence of a decrease in the rate of DA turnover. These changes in DA metabolism in the striatum were accompanied by behavioral disturbances in the form of motor excitation. Under these conditions, against the background of disturbance of the balance between the mediator systems, as the present investigation shows, the narcotic analgesic morphine has a correcting action, raising the HVA level but leaving the DA concentration unchanged, and consequently accelerating the DA turnover. Under these circumstances the motor excitation — a form of behavior characteristic of activation of the nigrostriatal dopaminergic system, was abolished.

There is evidence in the literature that narcotic analgesics are involved in processes of dopaminergic transmission. We know, for example, that the hypokinesia and catalepsy induced by morphine are potentiated by preliminary injection of α-methyl-p-tyrosine, an inhibitor of DA synthesis; apomorphine, a specific DA agonist, prevents the rise in the HVA level induced by the narcotic analgesic methadone; dopamine receptor blockade reduces ED_{50} of morphine [4, 5, 16]. The results of the present investigation point to a connection between the behavioral effects of morphine and an increase in the rate of DA turnover in the striatum, not only after isolated injection of the narcotic analgesic into intact animals, but also when it acted against the background of the central cholinolytic benactyzine, and they do not contradict existing notions in the literature of the role of dopaminergic transmission in the mechanism of the hypokinetic action of narcotic analgesics. At the same time, the results of this investigation suggest that the mechanism of action of narcotic analgesics, if given after preliminary administration of central cholinolytics, remains the same as if they are given alone.

TABLE 1. Motor Activity of Rats after Intraperitoneal Injection of Benactyzine in a Dose of 40 mg/kg and Morphine (M ± m)

Experimental conditions, dose, mg/kg	Number of animals	Number of movements (% of background)			
		60 min (bkgd)	90 min	120 min	150 min
Control	10	100±21	81±12	42±9*	36±13*
Benactyzine	10	100±36	699±49**	—	303±64**
Benactyzine + morphine (2)	10	100±18	593±41**	—	139±29**
Benactyzine + morphine (10)	10	100±25	546±83**	—	70±18
Morphine (2)	6	100±8	—	39±9*	—
Morphine (10)	6	100±13	—	7±3**	—

Legend. $P < 0.05$ compared with background (one asterisk), compared with control (two asterisks).

TABLE 2. DA and HVA Concentrations in Caudate Nucleus of Rats after Intraperitoneal Injection of Benactyzine in a Dose of 40 mg/kg and of Morphine (M ± m)

Experimental conditions, dose, mg/kg	No. of expts.	DA	HVA
		μg/g	
Control	15	9,90±0,54	0,81±0,02
Benactyzine	9	9,88±0,74	0,51±0,06*
Benactyzine + morphine (2)	5	8,70±0,43	0,82±0,01
Benactyzine + morphine (10)	5	10,38±0,67	1,27±0,04*
Morphine (2)	6	9,20±0,42	1,09±0,15
Morphine (10)	6	9,05±0,50	1,57±0,12*

Legend. Asterisk — $P < 0.05$ compared with control. For HVA determination five rats used in each experiment.

The facts given above, together with others of a similar kind in the literature [11, 12], apparently suggest that narcotic analgesics, like neuroleptics, which give sedative or cataleptogenic effects, are able to block postsynaptic dopamine receptors, i.e., they have a similar mechanism of action to that of neuroleptics. However, some observations suggest that the biochemical mechanisms which lie at the basis of these observed similar effects of narcotic analgesics and neuroleptics may differ. For instance, unlike neuroleptics, morphine and other narcotic analgesics in doses increasing the rate of DA turnover do not affect the cyclic AMP content in the striatum [3] and do not inhibit DA-induced stimulation of DA-sensitive adenylate cyclase [8]. It has been suggested that narcotic analgesics affect DA metabolism through their action on dopaminergic presynaptic autoreceptors [2, 13]. The elucidation of the mechanism of action of narcotic analgesics on nigrostriatal dopaminergic structures requires further investigations, but the recently expressed view [6, 13] that the influence of narcotic analgesics on processes of dopaminergic transmission is mediated through specific sensory opiate receptors, which are widely represented in the striatum, is currently the favorite.

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