ANTAGONISM BETWEEN L-DOPA AND APOMORPHINE IN THEIR EFFECTS ON RAT BEHAVIOR

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The effect of apomorphine and L-dopa on the apomorphine behavioral stereotype, on aggressiveness, and on the thresholds of emotional reactivity and aggressiveness induced by painful electrical stimulation, and on orienting motor activity was studied in male albino rats. Whereas the action of these substances given separately was similar in direction, definite antagonism was observed between apomorphine and L-dopa when given together with respect to all behavioral tests. Apomorphine (5 mg/kg), given after L-dopa, increased the dopamine concentration even higher in the forebrain and diencephalon without affecting the noradrenalin level. It is suggested that an increased concentration of functionally active mediator inhibits the activity of postsynaptic receptors sensitive to it.

KEY WORDS: *apomorphine; L-dopa; dopamine; stereotyped behavior; aggressiveness.*

Besides the dopamine precursor L-dopa, which has been used for some considerable time in the treatment of parkinsonism, the therapeutic effect of another dopaminergic substance has recently been reported, namely apomorphine [6, 11], a direct stimulator of dopamine receptors [3, 12]. After combined administration of L-dopa and apomorphine their therapeutic effect was potentiated to some degree, whereas many side effects (nausea, vomiting, dyskinetic phenomena) were mutually reduced [6, 11]. The mechanism of this paradoxical effect is uncertain. Meanwhile, analysis of the changes in the behavioral effects of L-dopa and apomorphine when given together to experimental animals proved interesting. Apomorphine and L-dopa are known to inhibit orienting motor activity, to induce stereotyped behavior and spontaneous aggressiveness, or to potentiate aggressive responses induced by provocation in rats and mice, mainly through activation of the dopaminergic system in the CNS [2-4, 12].

To analyze the effects of their combined administration, these behavioral tests were accordingly chosen. Their effects on the dopamine (DA) and noradrenalin (NA) content in the rat brain also were studied in parallel experiments.

EXPERIMENTAL METHOD

Eighty male albino rats weighing 220-300 g were divided into groups each containing 8-10 animals. Apomorphine hydrochloride was injected subcutaneously in a dose of 1-20 mg/kg and L-dopa intraperitoneally in doses of 50-200 mg/kg. Control animals received distilled water in the same volume. The intensity (in points) and duration (in min) of apomorphine stereotyped behavior were assessed by the method of Costall and Naylor [5]. Aggressive responses arising in rats after injection of apomorphine [9] were assessed by the number of fights and the total duration of the aggressive posture during observation for 5 min, 30, 60, and 90 min after injection of apomorphine. The degree of emotional reactivity was judged from the thresholds (in volts of alternating current) of squeaking (emotional reactivity) and aggressiveness in a pair of rats induced by painful electrical stimulation of the paws through the metal wire mesh floor of the chamber. In parallel tests orienting motor activity was determined as the number of pulses in the course of 2 min in an actometer. After

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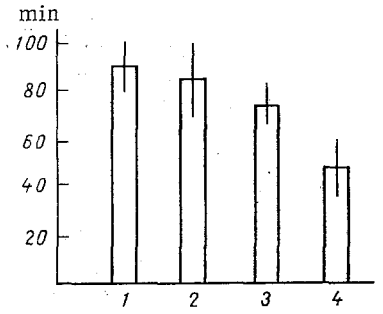

Fig. 1. Effect of L-dopa on duration of apomorphine stereotype (in min). 1) Apomorphine (5 mg/kg); 2) apomorphine + L-dopa (50 mg/kg); 3) apomorphine + L-dopa (100 mg/kg); 4) apomorphine + L-dopa (150 mg/kg).

the behavioral tests the animals were killed and their brains immediately cooled and divided into forebrain (cerebral cortex, hippocampus, striatum) and diencephalon (thalamus, hypothalamus, septum, preoptic region, corpora quadrigemina). The NA and DA content was determined by a fluorescence method [13].

EXPERIMENTAL RESULTS

Apomorphine in doses of 1-20 mg/kg induced stereotyped behavior in the rats and, starting with doses of 5 mg/kg, aggressiveness 5-90 min after the injection. L-Dopa in doses of 50-150 mg/kg caused no significant change in the intensity of stereotyped behavior, but considerably shortened its duration, especially in a dose of 150 mg/kg (Fig. 1). L-Dopa also moderated apomorphine aggressiveness, reducing the number of fights 60 min after injection, although L-dopa itself is known to be capable of inducing aggressive responses and of potentiating provoked aggressiveness in experimental animals [1, 2, 7].

When given separately L-dopa and apomorphine (1-10 mg/kg) inhibited orienting motor activity and potentiated emotional reactivity and aggressiveness 30 min after injection; however, after their combined administration a completely opposite picture was observed: Orienting motor activity was increased and emotional responses depressed (Fig. 2).

Apomorphine (5-20 mg/kg) did not change the DA and NA content in the two parts of the brain 30-60 min after injection. Injection of L-dopa (50 mg/kg) was accompanied by accumulation of DA, but the NA level was substantially unchanged. Apomorphine (5 mg/kg) given after L-dopa considerably increased the DA content in both parts of the brain compared with the effect of L-dopa given separately (50 mg/kg; Table 1).

L-Dopa and apomorphine thus act similarly on orienting motor activity and emotional responses, but their combined administration reveals distinct antagonism in relation to these behavioral tests. L-Dopa also reduces aggressiveness and the behavioral stereotype induced by apomorphine. Similar antagonism has also been observed among other dopaminomimetics and, in particular, between amphetamine and amantadine [10]. The mechanism of this phenomenon is uncertain. It is difficult to accept the explanation that the polycyclic molecule of apomorphine includes in its composition a molecule of thioridazine, a substance with sedative action [6]. This could explain the antagonism of apomorphine against L-dopa, but not vice versa. In the present experiments apomorphine, given after L-dopa, increased the DA content in the rat brain, evidently through inhibition of deamination of the mediator [6]. Recent investigations have shown a close correlation between receptor activity and content of mediator [4, 6, 8]. For instance, it has been shown [4] that the potentiation of receptor activity causes a decrease in DA synthesis by a feedback mechanism. After administration of L-dopa together with apomorphine it can be tentatively suggested that the opposite mechanism operates,

TABLE 1. Effect of Apormorphine (5 mg/kg), L-Dopa (50 mg/kg) and a Combination of Both 30 min after Injection on DA and NA Content in Rat Brain (in μg/g tissue; M ± 2.5m)

Substance	Number of animals	Forebrain		Diencephalon	
		DA	NA	DA	NA
Control	12	2,27±0,12	0,34±0,02	1,60±0,12	0,44±0,09
Apomorphine	8	2,31±0,14	0,31±0,04	1,86±0,18	0,50±0,20
L-Dopa	8	4,49±0,50	0,37±0,04	2,56±0,20	0,57±0,12
L-Dopa + apomorphine	6	9,92±0,84	0,45±0,03	5,57±0,32	0,54±0,10

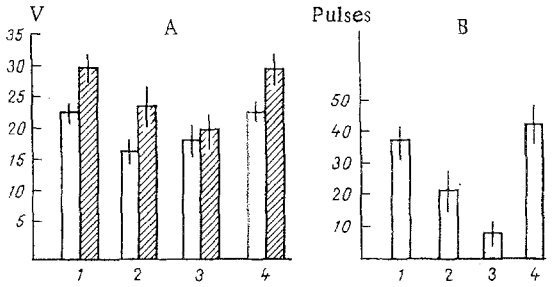

Fig. 2. Effect of L-dopa (150 mg/kg) and apomorphine (5 mg/kg) 30 min after injection on thresholds of emotional responses and orienting motor activity. Ordinate: number of pulses. A) Unshaded columns show threshold of emotional reactivity, shaded columns threshold of aggressiveness (in V); B) ordinate, number of pulses; 1) control; 2) apomorphine (5 mg/kg); 3) L-dopa (50 mg/kg); 4) apomorphine + L-dopa.

when an increased level of functionally active mediator depresses the activity of postsynaptic receptors sensitive to it, as a result of which the effects both of dopamine and of the stimulator of dopamine receptors (apomorphine) are reduced.

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METABOLISM OF NITRAZEPAM IN THE INTESTINE OF ALBINO RATS

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In the rat intestine nitrazepam is transformed to an amine and acetamide. In the duodenum and small intestine the reduction of nitrazepam and its subsequent acetylation are catalyzed by enzymes in the mucosa. In the cecum and large intestine these processes are due to the action of the microflora and tissue enzymes, and in the rectum to the action of the microflora alone.

KEY WORDS: *metabolism of nitrazepam; intestine; antibiotics.*

The pathways of metabolism of nitrazepam have been studied in the liver [6] but not in the intestine, where this substance may have its pharmacological properties modified by the

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