SELECTIVE DOPAMINERGIC REGULATION OF STEREOTYPED FORMS OF AGGRESSIVE AND DEFENSIVE BEHAVIOR

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L-Dopa and apomorphine, which act on dopaminergic synapses, selectively induce and control the trigger mechanisms of stereotyped forms of behavior in rabbits (striking with the paws, licking, and chewing). These forms of behavior can act as highly specific and sensitive test responses for quantitative studies of neuropsychotropic drugs acting on central dopaminergic synapses.

KEY WORDS: *stereotyped behavior; dopaminergic mechanisms; L-dopa, apomorphine, and amphetamine; neuropsychotropic drugs.*

Neuropsychotropic drugs, which selectively act on central dopaminergic (DA) mechanisms, evoke stereotyped behavioral reactions (sniffing, licking, biting, turning, and so on) in animals. In recent years stereotyped responses of animals have been extensively used as specific and sensitive indicators of activity of DA agonists and antagonists [4-8]. Stereotyped responses are species-specific components of the behavior of invertebrate and vertebrate animals. The pharmacological control of the many different forms of sterotyped animal behavior has not yet received special investigation.

The object of the present investigation was accordingly to study the role of DA agonists (L-dopa, apomorphine, and amphetamine) in the regulation of stereotyped forms of behavior in rabbits: striking with the hind limbs, licking, and biting.

EXPERIMENTAL METHOD

Experiments were carried out on 76 chinchilla rabbits weighing 3-4 kg. The number of synergic blows struck by the hind limbs every 3 min was recorded for 60-90 min. For this purpose the rabbit was placed in a box with a transducer to record the blows. Experiments were carried out on five rabbits at a time. The number of blows was recorded on the N 3020-5 automatic writer. In addition, the appearance of responses of licking and biting the box by the rabbits was noted. Stereotyped responses (blows with the limbs, licking, biting) were studied in the following series of experiments: series I (control), injection of 0.9% physiological saline or no treatment of any sort; series II, formation of a conditioned active avoidance reflex; series III, after injection of L-dopa; series IV, after injection of apomorphine, to stimulate DA receptors; series V, after injection of L-dopa, followed by one of the following substances: D,L-amphetamine, the serotonin precursor 5-hydroxytryptophan (5-HTP), strychnine nitrate, and caffeine sodium benzoate. The active avoidance reflex to painful electrical stimulation was studied in an apparatus divided into "safe" and "unsafe" compartments.

EXPERIMENTAL RESULTS

In the control experiments the rabbits struck with their limbs only occasionally (Table 1). Painful electrical stimulation of the animal (current of 8.5 mA, duration of stimulation 300 msec) or placing the animal in the safe compartment of the apparatus in

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TABLE 1. Changes in Frequency of Blows with the Limbs in Rabbits after Injection of DA Agonists. Blows Counted Every 3 Min (M ± m)

Drugs, mg/kg	Mode of injection	Frequency of blows, min	
Control		0,03±0,005	(2664/57)
L-dopa, 5	Intravenously	0,36±0,12*	(50/5)
L-dopa, 25	"	2,14±0,11†	(634/25)
L-dopa, 100	"	4,20±0,44‡	(240/10)
L-dopa, 200	"	8,12±1,08**	(112/4)
Apomorphine, 2	Subcutaneously	3,54±0,32‡	(158/5)
Apomorphine, 4	"	5,86±0,40††	(149/4)
D,L-Amphetamine, 1-5	Intraperitoneally	0,08±0,26	(375/18)
D,L-Amphetamine, 5+L-dopa, 25	Intraperitoneally + intravenously, after 60 min	8,70±0,88**	(157/8)

Legend. In parentheses: numerator, number of measurements; denominator, number of animals.
*P < 0.001 compared with control.
†Compared with L-dopa (5 mg/kg).
‡Compared with L-dopa (25 mg/kg).
**Compared with L-dopa (100 mg/kg).
††Compared with apomorphine (2 mg/kg).
†—†† Differences significant when P < 0.05. Statistical significance determined by Student's t test.

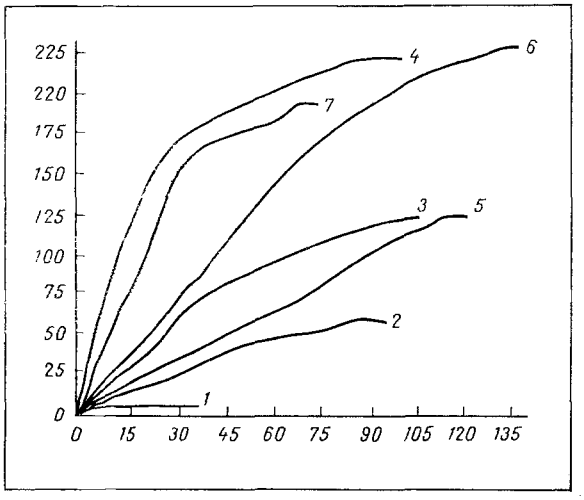

Fig. 1. Changes in mean number of blows with the limbs after injection of DA agonists. Abscissa, time (in min); ordinate, number of blows with limbs, total for each successive period of 3 min. 1) L-dopa 5 mg/kg; 2) L-dopa 25 mg/kg; 3) L-dopa 100 mg/kg; 4) L-dopa 200 mg/kg; 5) apomorphine 2 mg/kg; 6) apomorphine 4 mg/kg; 7) D,L-amphetamine 5 mg/kg + L-dopa 25 mg/kg. Number of animals in each group and methods of injection of drugs as in Table 1.

which the rabbit had previously received nociceptive stimulation, evoked characteristic behavior: The rabbit ran into the unsafe compartment, turned its head toward the safe compartment, and struck with its hind limbs. Consequently, pain and fear were the causes of this behavior, and the behavior itself possibly was a demonstration of threatening.

Injection of small doses of L-dopa (5-10 mg/kg, intravenously) and apomorphine (1-2 mg/kg, subcutaneously) caused the rabbits to strike with their hind limbs. The

total number of blows and their frequency, and also the duration of this behavior, depend on the dose of L-dopa and apomorphine (Table 1, Fig. 1). In 56% of experiments, blows with the limbs after injection of L-dopa occurred after a latent period of 1 min or less. Amphetamine (1-5 mg/kg, intraperitoneally), strychnine (0.1 mg/kg, subcutaneously), caffeine sodium benzoate (15-20 mg/kg, subcutaneously), and 5-HTP (25 mg/kg, intravenously) did not cause blows with the limbs. Amphetamine (5 mg/kg), given 60 min before L-dopa (25 mg/kg), potentiated the behavioral effect of L-dopa three- to fourfold (Fig. 1). Caffeine (15 mg/kg), given 30-60 min before L-dopa, also had a potentiating effect. Strychnine (0.1 mg/kg) had no such effect. Observations on blows with the limbs, licking, and biting showed that L-dopa and apomorphine caused different behavioral responses. Injection of L-dopa (5-50 mg/kg) evoked blows with the limbs only. After injection of apomorphine (2-4 mg/kg) the rabbits struck the box with their limbs, licked it, and bit it. Only large doses of L-dopa (200 mg/kg) evoked responses similar to the effects of apomorphine. Ernst [5] also observed that injection of L-dopa in a dose of 150 mg/kg evoked blows with the limbs and biting in rabbits.

The results show that forms of inborn behavior in rabbits such as striking with the hind limbs, licking, and biting can be evoked selectively and regulated in rabbits by means of L-dopa, the direct precursor of dopamine, and apomorphine, which stimulates DA receptors. These responses evidently reflects a state of emotional stress in the animals. This idea of the connection between blows with the limbs and negative emotions was originally expressed by Charles Darwin [1] and confirmed by physiological experiments [2]. Observations showing that blows with the limbs are an essential component of active avoidance behavior in rabbits made in the course of the present experiments show that this motor response is a form of defensive and aggressive behavior. It has recently been found that injection of L-dopa causes fights among mice [8] and that intragastric injection of dopamine increases the frequency of fights in rats [3]. The results of the present experiments, together with the data in the literature, indicate that dopamine plays an important role in the regulation of aggressive and defensive behavior in animals.

Special attention is merited by the fact that blows with the limbs in rabbits proved to be a highly specific and sensitive test reaction for administration of L-dopa. It can be concluded from a comparison with data in the literature [8] that this reaction is now the most specific and sensitive behavioral test reaction for administration of L-dopa. On this basis it is suggested that blows with the limbs evoked by L-dopa be called a dopa stereotype. These results indicate that stereotyped behavior in rabbits (blows with the limbs, licking,and biting) can be recommended as new test reactions for the investigation of neuropsychotropic drugs acting on central DA synapses. These test reactions can be regarded as models of pathological involuntary movements. It can be concluded from the results of this investigation and of others reported in the literature [4-8] that the development of comparative studies of pharmacological regulation of stereotyped forms of behavior in animals of different species will be of great help to the elucidation of the principal neurochemical factors controlling animal behavior and will also contribute to the creation of new and improved methods of testing neuropsychotropic drugs.

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