EFFECT OF NEUROLEPTICS AND TRANQUILIZERS ON CONTENT OF FREE AND BOUND FRACTIONS OF NORADRENALIN IN THE RAT BRAIN STEM DURING AGGRESSION

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Aggression evoked by prolonged isolation of animals is accompanied by an increase in the free and a decrease in the bound noradrenalin fractions. Haloperidol, in a dose of 2 mg/kg, not only has a sedative effect but also reduces the content of the free and bound noradrenalin fractions in the brain stem of control animals. In animals with experimental aggressiveness, haloperidol lowers the free noradrenalin level but has virtually no effect on the contents of its bound fraction. Seduzen, in the same dose, lowers the content of free noradrenalin in intact and isolated rats.

Neuroleptic drugs are widely used at the present time in clinical practice for the treatment of diseases accompanied by emotional disturbances. One of the writers has shown previously that an important role in the mechanism of action of neuroleptics is played by a change in catecholamine metabolism and, in particular, by exhaustion of the functionally active noradrenalin fraction. The role of catecholamines in the manifestations of various emotional reactions is also mentioned in the literature [1, 2, 5, 7].

In the investigation described below the effect of experimental aggression on the content of free and bound heparin in the brain stem of rats and the effect of neuroleptics (haloperidol) and tranquilizers (seduxen) on the content of free and bound noradrenalin fractions in the brain stem of rats during aggression were studied.

EXPERIMENTAL METHOD

Experiments were carried out on male rats weighing 180-280 g. Haloperidol was injected intraperitoneally in a dose of 2 mg/kg. The animals took part in the experiment 1 h after receiving the drug at the height of its sedative effect, as judged from the appearance of signs of catalepsy. An aggressive state was induced by the method of Gen et al. [4], based on prolonged isolation of the animals.

The supernatant and granular fraction were separated in the usual way [10] by centrifugation of a brain tissue homogenate at 1000 g for 30 min in 0.25 M sucrose solution. Noradrenalin was determined by the method of Euler and Lishaiko [3].

In addition, incorporation of tritiated DOPA into the supernatant and granular fractions of the brain stem from normal rats and rats with aggression was studied. The intensity of incorporation of DOPA-H^3 was determined from the change in radioactivity in these fractions recorded on a scintillation counter (Nuclear Chicago).

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TABLE 1. Incorporation of DOPA-H^3 into Supernatant and Granular Fraction of the Brain of Intact and Aggressive Rats

Group of animals	Incorporation of DOPA-H^3 (pulses/min/g tissue)
Control:	
Supernatant fraction	4200 (3600-4800)
Granular fraction	1670 (1450-1890)
Experimental:	
Supernatant fraction	10800 (9600-12000)
Granular fraction	1870 (1540-2200)

EXPERIMENTAL RESULTS

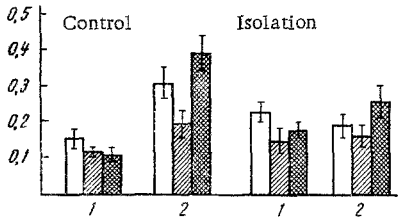

Fig. 1. Effect of heloperidol and seduxen on noradrenalin content in supernatant and granular fractions of brain stem of intact and isolated rats. Unshaded columns: no drugs given; shaded columns – haloperidol; cross-hatched columns – seduxen. Abscissa: 1) supernatant fraction; 2) granular fraction; ordinate, noradrenalin content (in μg/g tissue).

The total noradrenalin content in the brain stem of the control rats averaged 0.43 (0.38-0.48) μg/g tissue, and in rats during aggression 0.39 (0.34-0.44) μg/g; i.e., it was virtually unchanged. Since the free fraction of noradrenalin is functionally active, in the next series of experiments the effect of prolonged isolation on the level of free and bound noradrenalin, located in the supernatant and granular fractions respectively of the brain, was studied.

The noradrenalin content in the supernatant fraction of the brain stem of intact animals averaged 0.15 μg/g fresh tissue; most of the noradrenalin (0.30 μg/g) was present in the bound form. A similar ratio between the free and bound fractions of noradrenalin of the brain has been obtained by other workers [9, 10]. In rats with experimental aggression an increase in the free noradrenalin fraction, on the average by 30%, was observed, whereas the noradrenalin level in the granular fraction of the brain was reduced by 37%. These results were also confirmed by the results of experiments to study incorporation of DOPA-H^3 into the supernatant and granular fractions of the brain (Table 1).

It is clear from Table 1 that the intensity of incorporation of the label into the supernatant fraction was increased in the aggressive animals.

Guarino et al. [5] found no significant changes in the total noradrenalin content in whole brain homogenate of isolated animals. However, the noradrenalin content measured separately in the supernatant and granular fractions of the brain of aggressive animals was not investigated by these workers. The results of the present experiments show a redistribution of noradrenalin between these fractions. The fact that in aggressive animals an increase in the noradrenalin level in the supernatant fraction is accompanied by a simultaneous decrease in its content in the granular fraction suggests that during prolonged isolation the binding of noradrenalin in the granules is probably disturbed, and the accumulation of the free, functionally active fraction of noradrenalin is one of the possible causes of the aggressive state of isolated animals.

The object of the next section of the investigation was to compare the effect of neuroleptics (haloperidol) and of tranquilizers (seduxen) on the noradrenalin content in the supernatant and granular fractions of the brain stem of intact and isolated rats.

As the results given in Fig. 1 show, haloperidol caused a marked decrease in noradrenalin in the granular (by 43%) and supernatant (by 30%) fractions of the brain stem of the control animals. In animals with experimental aggression, haloperidol reduced the free noradrenalin concentration (by 30%) but had virtually no effect on the noradrenalin level in the granular fraction of the brain stem. Seduxen in the same dose (unlike haloperidol) reduced the content of free noradrenalin only, both in the control and in the experimental animals. The increase in the noradrenalin content in the granular fraction of the brain produced by seduxen is not statistically significant.

The results of the experiments to study the effect of haloperidol on the noradrenalin content of the brain suggest that this neuroleptic is concerned in noradrenalin metabolism. This hypothesis is confirmed

by the investigations of Sharman [8], who showed that administration of haloperidol leads to an increase in the content of homovanillic acid, a hydrolysis product of noradrenalin, in the brain. So far as the concrete causes of the decrease in the noradrenalin level by haloperidol are concerned, the results described suggest that haloperidol disturbs the binding of noradrenalin by the granules. However, the possibility likewise is not ruled out that the haloperidol effect is due to increased liberation of noradrenalin from the granules. The decrease in noradrenalin in the supernatant fraction of the brain may be indirect evidence of activation of the enzymes concerned with its conversions, monoamine oxidase and carboxy-O-methyltransferase. The mechanism of action of haloperidol in all probability is similar to the mechanism of action of reserpine, which also lowers the level of free and bound noradrenalin, thereby exhausting the noradrenalin depots [6, 10].

So far as the effect of seduxen is concerned, its sedative effect can be regarded as due to a decrease in the content of the free, functionally active fraction of noradrenalin in the brain stem of the control and isolated animals.

On the basis of these results it can be concluded that the positive therapeutic effect of haloperidol and seduxen in the treatment of patients with emotional disturbances is connected with the participation of these preparations in noradrenalin metabolism, in fact, with the restoration of the normal ratio between the adrenalin fractions in the free and bound states.

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