EFFECT OF AZAPERONE ON THE TIME COURSE OF THE STRESS REACTION AND CATECHOLAMINE CONTENT IN THE ADRENALS OF RATS WITH IMMOBILIZATION STRESS

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KEY WORDS: catecholamines; adrenals; immobilization; stress-protective effect.

Since the sympathicoadrenal system plays an essential role in the development of stress [5], action directed toward this stage may be one way of pharmacological regulation of the stress reaction of an animal.

The aim of the present investigation was to study the effect of azaperone, a neuroleptic of the butyrophenone series on the development of the stress reaction in animals in order to examine its stress-protective effect. The time course of development of the general adaptation syndrome, with identification of its stages [9], was studied in immobilized rats. To analyze changes in the sympathicoadrenal system under the specified conditions the concentration of catecholamines (CA) was determined in the adrenals of the rats and their ultrastructural distribution in the storage vesicles established.

EXPERIMENTAL METHOD

Experiments were carried out on male rats weighing 180 ± 30 g. Stress was produced by immobilizing the animals in special frames for 30 min and 1, 2, 3, 4, 16, 24, 48, and 72 h. After this procedure the weight of the lymphoid organs (thymus and spleen) and of the adrenals was determined and the presence of pathological changes (hemorrhages, erosions, ulcers) in the gastric mucosa was looked for. Lipids were demonstrated histochemically [3] in the adrenal cortex and the thickness of the lipid layer was measured. The concentrations of adrenalin (A) and noradrenalin (NA) and the total CA content were determined [2] in the adrenals. For electron-microscopic study the adrenal medulla was fixed by Tranzer's method [8] to enable differentiation between cells containing A and NA; the material was embedded in Araldite and sections were examined in the JEM-100B microscope.

Azaperone, obtained from the Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, was injected intramuscularly in a dose of 3 mg/kg 30 min before exposure to stress and the injections were repeated every 4 h throughout the period of immobilization.

EXPERIMENTAL RESULTS

Data on the change in weight of the adrenals and lymphoid organs and in the lipid concentration in the adrenal cortex, and also the results of estimation of the state of the gastric mucosa after immobilization for different periods are given in Table 1.

After short-term immobilization (30 min, 1 h) the weight of the adrenals, thymus, and spleen of the animals and the lipid content in the adrenal cortex were reduced. In the gastric mucosa there were no visible changes. These data are evidence of development of a stage of anxiety by the animals [9].

During the next 4 h the adaptive stage of the stress reaction was manifested: the weight of the adrenals and of the lymphoid organs and also the lipid content in the adrenal cortex were fully restored. During the next 20 h the weight of the thymus and the thickness of the lipid layer were unchanged, moderate hypertrophy of the adrenals was observed, with a very small decrease in weight of the spleen, edema, hyperemia, and hemorrhages in the gastric mucosa.

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TABLE 1. Changes in Weight of Adrenals and Lymphoid Organs, in Lipid Concentration in Adrenal Cortex, and State of Gastric Mucosa after Immobilization for Different Periods

Duration of immobolization	Weight, % of weight in intact animals			Thickness of lipid layer, conventional units	State of of gastric mucosa
	of thymus	of spleen	of adrenals		
Intact animals	100±16,6* 137,6±22,8 mg†	100±17,5 (199,8±34,9 mg)	100±8,5 (4,7±0,4 mg)	6,3±1,4	No change
Control					
30 min	64,3±16,1	75,6±13,9	87,2±12,1	3,7±1,2	No change
1 h	78,6±13,4	61,3±13,6	91,5±22,1	2,8±0,9	The same
2 h	75,1±14,0	77,4±15,6	91,5±19,3	3,7±1,1	The same
3 h	98,9±27,1	76,2±12,8	89,4±16,5	4,3±1,4	Hyperemia, single hemorrhages
4 h	100,1±16,5	102,0±13,0	95,7±8.8	6,4±1,7	The same
16 h	103,6±19,0	71,6±13,2	144,7±15,1	6,0±1,8	Edema, hyperemia, multiple hemorrhages
24 h	92,5±10,0	65,5±12,5	155,3±13,7	6,2±1,5	The same
48 h	56,5±17,2	49,3±10.3	223,4±27,6	1,9±0,6	Ulcers (1-3, area 2 ± 0.5 mm^2)
72 h	37,4±6,2	36,5±8,0	242,6±29,1	1,0±0,5	Ulcers (2-4, area 2.5 ± 0.6 mm^2)
Azaperone (3 mg/kg)					
3 h	117,1±18,3	71,2±9,4	74,5±13.7	3,9±1,0	Single hemorrhages
24 h	95,8±16,4	69,3±8,1	128,6±11,7	4,6±1,2	Ulcers (1-3, area 1 ± 0.3 mm^2)
48 h	76,0±14,6	45,6±8,2	125,5±14,8	4,8±1,2	Slight hyperemia

Legend. *) Confidence limits of the mean at P = 0.05 level; †) data calculated per 50 g body weight.

TABLE 2. Concentrations of A and NA and Total (in % of values for intact animals) in Adrenals of Rats after Different Periods of Immobilization Stress

Duration of immobolization	Adrenalin	Nor-adrenalin	Total catecholamines
Intact animals	100±15* (837± ±130 μg/g)	100±18 (643± ±117μg/g)	100±12 (217± ±27 conventional units)
Control			
30 min	76±19	103±21	88±15
1 h	68±11	94±16	74±12
2 h	72±12	94±17	73±12
3 h	61±10	72±12	57±8
4 h	40±7	77±12	52±8
24 h	18±3	27±4	19±3
48h	7±2	11±2	9±2
Azaperone (3 mg/kg)			
3 h	55±8	52±9	53±8
24 h	7±2	17±4	9±2
48 h	14±3	33±6	19±4

Legend. *) Confidence limits of mean at P = 0.05.

After immobilization for 48 h a marked decrease in weight of the lymphoid organs and in the lipid concentration in the adrenal cortex as well as marked hypertrophy of the adrenals were observed. In the gastric mucosa between one and three clearly distinguishable ulcers varying in area from 1.5 to 2.5 mm^2 were found. After longer periods of stress (72 h) these changes were more marked still. Analysis of the results suggests that if immobilization lasted longer than 24 h, the animals' stress reaction changed into a stage of exhaustion.

Data on changes in the concentrations of A and NA and the total CA content in the adrenals of the rats after different periods of immobilization are given in Table 2. The CA content decreased proportionally to the duration of stress. The decrease in the A concentration was greater (especially during the first 4 h of immobilization) than that of the NA concentration. Similar changes in concentrations of A and NA in the adrenals of rats during immobilization have been observed by other workers also [6, 7].

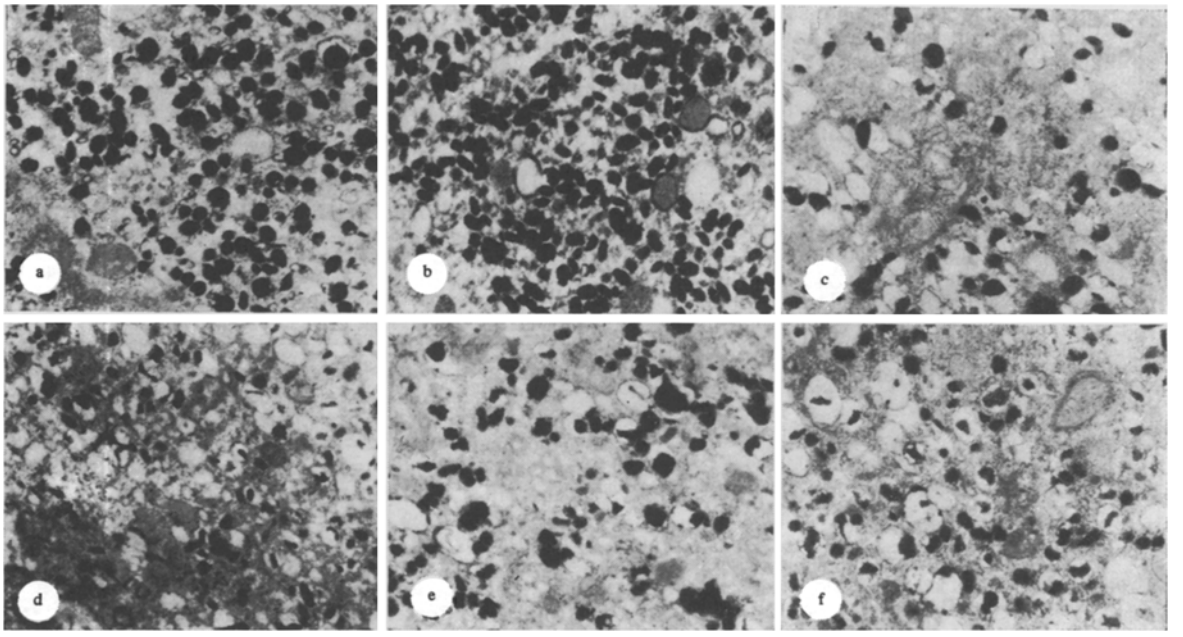

Fig. 1. Electron-microscopic detection of cells of rat adrenal medulla containing A and NA: noradrenocytes (a) and adrenocytes (b) of intact rat; noradrenocytes (c) and adrenocytes (d) of rat immobilized for 48 h; noradrenocytes (e) and adrenocytes (f) of rat immobilized for 48 h and receiving azaperone. 18,000×.

The results of electron-microscopic investigation confirmed the biochemical data on the fall in the CA level after exposure to stress. For instance, after 48 h of immobilization marked depletion of the A and NA reserves could be detected in the storage granules (Fig. 1a-d).

The effect of azaperone on the time course of the stress reaction was evaluated during each of the stages distinguished above: after 3 h (stage of anxiety), 24 h (stage of resistance), and 48 h (stage of exhaustion). In the anxiety stage it was found (Table 1) that the weight of the adrenals, thymus, and spleen and the lipid concentration in the adrenal cortex were unchanged compared with the control.

In animals receiving azaperone adrenal hypertrophy after immobilization for 24 h was less marked and the lipid content in the cortex showed a tendency to fall compared with its level in the control animals. Very small ulcers were observed in the gastric mucosa.

After 48 h of stress in animals receiving azaperone adrenal hypertrophy was even less marked, the thickness of the lipid layer was increased, and no lesions were present in the gastric mucosa such as were observed in the control animals. The study of the A and NA concentrations and the total CA content after administration of azaperone showed (Table 2) no significant difference after immobilization for 3 h in their levels compared with those in the control animals.

In the stage of resistance (24 h) a more marked fall in the A and NA levels in the adrenals was observed after administration of azaperone compared with the control, evidence of increased release of CA from the medula.

However, azaperone prevented the development of the exhaustion stage and the decrease in A and NA content caused by exposure to stress for 48 h, so that there was a higher CA concentration in the medulla after administration of the drug (Table 2). This conclusion also was confirmed by the data of ultrastructural cytochemistry (Fig. 1e, f). The CA content in this case corresponded to that observed in the control animals in the resistance stage. The gastric mucosa showed no pathological ulcers after immobilization for 48 h and administration of azaperone, and this also corresponded to its state in the control animals in the resistance stage.

Analysis of the facts described above suggests that the appearance of ulcers in the gastric mucosa was linked with a fall in the CA concentration. This hypothesis is in agreement with results obtained by other workers [1, 4]. The data show that after a fall in the CA concentration in the adrenals to about 10% (after 48 h of stress) ulcers appeared in the gastric mucosa; if the CA level was higher (about 20% in animals receiving azaperone) ulcers were absent. A similar relationship also could be observed after immobilization for 24 h:

ulcers were not found when the total CA level was about 20% (stress without administration of azaperone); however, after administration of azaperone and a fall in the CA concentration to about 10%, ulcers were found in the gastric mucosa (Table 1).

It can be concluded from these findings that azaperone has a stress-protective action. The intensity of this effect differs in different stages of the stress reaction. Administration of azaperone caused only very slight changes in the time course of development of the stage of anxiety and resistance. However, the stage of exhaustion was much less well marked, which suggests that the phase of resistance is prolonged as a result of the influence of azaperone.

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EFFECT OF STROPHANTHIN AND CELANIDE ON THE CEREBRAL CIRCULATION AND METABOLISM

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The action of cardiac glycosides (CG) on the cerebral blood flow and vascular tone has been inadequately studied and the results are often contradictory [5-7, 9-14]. The writers showed previously [3, 8] that strophanthin and celanide increase cerebral vascular tone and raise the general arterial pressure (BP) or induce a biphasic response (both constriction and dilatation).

The aim of the present investigation was to study the action of CG on the time course of changes in the cerebral blood flow, BP, and venous pressure, and the oxygen and glucose concentrations and pH of venous and arterial blood in the brain.

EXPERIMENTAL METHOD

Acute experiments were carried out on 32 cats of both sexes weighing 2.4-4.3 kg. The animal was fixed to a frame and the blood vessels ligated and cannulated under ether anesthesia. Later, to avoid lasting changes in brain metabolism associated with general anesthesia, the experiments were continued under local procaine anesthesia of the operation wound. Stable ventilation of the lungs was maintained by an artificial respiration apparatus with monitoring of pO_2 and pH of the blood. To create optimal conditions of control respiration, succinyl choline was injected intravenously as a muscle relaxant. The volume velocity of the cerebral blood flow was recorded by an appropriate instrument [1] connected to the common carotid artery. Isolated perfusion

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