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.

LITERATURE CITED

1. S. V. Anichkov and I. S. Zavodskaya, The Pharmacotherapy of Peptic Ulcer [in Russian], Leningrad (1965).
2. É. Sh. Matlina, in: Research into New Apparatus and Methods at the First Moscow Medical Institute [in Russian], No. 5, Moscow (1967), p. 136.
3. G. A. Merkulov, A Course in Histopathological Techniques [in Russian], 5th edn., Leningrad (1969), p. 241.
4. I. I. Triiger, in: Some Current Problems Concerning Peptic Ulcer [in Russian], Chita (1976), p. 42.
5. J. Kopin, in: Catecholamines and Stress, Oxford (1976), p. 1.
6. R. Kvetnansky and Z. Mikylay, Endocrinology, 84, 738 (1970).
7. É. Sh. Matlina, in: Catecholamines and Stress, Oxford (1976), p. 353.
8. J. P. Tranzer, H. Thoenen, R. L. Snipes, et al., Prog. Brain Res., 31, 33 (1969).
9. H. Selye, Essays on the Adaptation Syndrome [Russian translation], Moscow (1960).

EFFECT OF STROPHANTHIN AND CELANIDE ON THE CEREBRAL CIRCULATION AND METABOLISM

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KEY WORDS: cerebral blood flow; brain oxygen and glucose demand; cardiac glycosides.

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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TABLE 1. Effect of Strophanthin (0.05 mg/kg, intravenously) on the Cerebral Blood Flow and Some Parameters of Brain Metabolism

Parameter tested	Initial level	After injection of strophanthin, % of initial level				
		1–3 min	10 min	30 min	60 min	90 min
Volume velocity of cerebral blood flow	75,8±2,4 ml / 100g/min	+8,9±1,7	—4,4±2,9	—16,3±2,7	—17,0±3,1	—18,8±3,5
P		<0,001	>0,1	<0,001	<0,001	<0,001
BP	102,2±3,0 mm Hg	+20,4±1,4	+8,0±2,7	—6,8±2,7	—10,4±3,0	—12,4±3,8
P		<0,001	<0,01	<0,05	<0,005	<0,005
Difference: for oxygen	22,4±1,4%		+38,1±5,7	+52,4±4,2	+64,3±5,3	+67,1±3,8
P			<0,001	<0,001	<0,001	<0,001
for glucose	12,5±2,0 mg%		+29,0±19,4	+58,0±25,3	+73,5±14,0	+82,9±22,5
P			>0,05	<0,05	<0,001	<0,005

TABLE 2. Effect of Celanide (0.1 mg/kg, intravenously) on the Cerebral Blood Flow and Some Parameters of Brain Metabolism

Parameter tested	Initial level	After injection of celanide, % of initial level				
		1–3 min	10 min	30 min	60 min	90 min
Volume velocity of cerebral blood flow	76,3±2,7 ml/ 100 g/min	+12,5±3,8	—6,9±4,9	—15,6±4,1	—16,4±3,8	—17,3±3,8
P		<0,01	>0,1	<0,005	<0,001	<0,001
BP	105,0±3,3 mm Hg	+20,8±3,6	+5,4±4,7	—8,8±3,7	—17,8±4,6	—18,4±4,7
P		<0,001	>0,1	<0,05	<0,005	0,001
Difference: for oxygen	23,8±1,7%		+40,3±4,7	+61,9±5,8	+67,8±9,4	+66,7±8,2
P			<0,001	<0,001	<0,001	<0,001
for glucose	11,7±1,6 mg%		+24,3±19,0	+54,0±18,3	+69,0±11,7	+86,6±11,5
P			>0.1	<0.05	<0,001	<0,001

of the cerebral vessels was achieved by ligation of the extracranial branches of the carotid and vertebral arteries [2]. The systemic BP was recorded in the carotid artery by a mercury manometer. The pressure in the venous system of the brain was measured with a water manometer. Blood clotting was prevented by intravenous injection of heparin; pO_2 and pH of the blood were determined by the AZIV-2 instrument. Arterial blood for testing was taken from the carotid artery, venous blood from the outflow from the venous sinus. The oxygen saturation of the blood, in percent, was determined by a nomogram from the values of pH and pO_2 of the blood. The oxygen demand of the brain was determined from the arteriovenous oxygen difference and the value of the cerebral blood flow, allowing for the oxygen capacity of the blood. The blood glucose concentration was determined with orthotoluidine reagent [4]. The glucose demand of the brain was estimated from the arteriovenous glucose difference. The glucosides tested, namely strophanthin (0.05 mg/kg) and celanide (0.1 mg/kg), were injected intravenously.

EXPERIMENTAL RESULTS

The results are given in Tables 1 and 2. Strophanthin (18 experiments) caused a significant increase in the cerebral blood flow on average by 8% during the 5-7 min after its injection, followed by a gradual fall, so that after 90 min it averaged 18% of the initial values. In most experiments BP showed biphasic changes: initially it rose, especially after 3 min (on average by 20%), after which it fell gradually compared with the initial level. In some experiments (3 of 13) BP remained above the initial level until the end of observation (60-90 min). The pressure in the venous system of the brain fell gradually after injection of strophanthin, and 90 min after injection it was 22.9 ± 2.7% below the initial level ($P < 0.001$). The resistance of the cerebral vessels increased for 20 min after injection of the drug (after 20 min its mean level was 14% higher than initially). Later the cerebrovascular resistance fell gradually.

The oxygen saturation of the arterial blood after injection of strophanthin was the same as initially. In the venous blood there was a significant decrease in the oxygen concentration, which was on average 20% below the initial level 60-90 min after injection of the drug. Some decrease was observed in pH of the arterial and venous blood. For instance, the mean initial values of pH for arterial and venous blood were 7.4 ± 0.01 and 7.3 ± 0.01 respectively. The pH of the arterial and venous blood fell 90 min after injection of strophanthin by 0.47 ± 0.08 and 0.92 ± 0.09% respectively ($P < 0.001$). The glucose concentration in the arterial blood showed

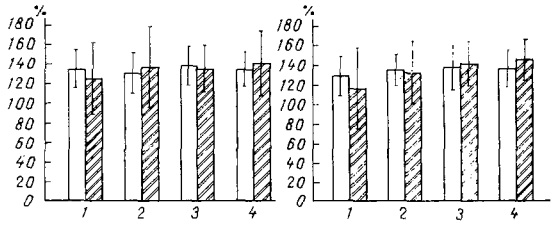

Fig. 1. Effect of strophanthin (0.05 mg/kg, intravenously) on oxygen (unshaded columns) and glucose (shaded columns) consumption by the brain. Initial values taken as 100%; 1-4) values 10, 30, 60, and 90 min respectively after injection of glycoside.

Fig. 2. Effect of celanide (0.1 mg/kg, intravenously) on oxygen and glucose consumption by the brain. Legend as to Fig. 1.

a tendency to fall after injection of strophanthin (it was reduced after 90 min by 5.7 ± 2.4%, $P < 0.05$). The glucose level in the venous blood was lowered by a greater degree, and 90 min after injection of strophanthin it was 14.9 ± 3.9% below the initial level ($P < 0.01$). As reflected in the values of their arteriovenous difference, oxygen and glucose consumption by the brain tissues increased (Fig. 1).

Celanide* (14 experiments), like strophanthin, induced biphasic changes in the volume velocity of the cerebral blood flow and systemic BP. Initially there was a significant increase of the cerebral blood flow on average by 12% lasting 3-10 min, accompanied by a mean rise of BP by 20%. Later the blood flow and BP fell gradually, and 60-90 min after injection of the drug they were on average 20% below their initial values ($P < 0.001$). The pressure in the cerebral veins fell toward the end of the experiments (90 min) on average by 23% ($P < 0.001$). The cerebrovascular resistance rose during the 20 min after injection of celanide (after 20 min its mean value was 14% higher than initially). Later the cerebrovascular resistance fell gradually, and after 90 min in most experiments (6 of 10) it was below the initial level.

No significant changes were produced in the oxygen concentration in arterial blood by celanide, whereas in the cerebral venous blood the partial pressure of oxygen fell gradually, to 23% below its initial value after 60-90 min. The pH of the arterial blood was significantly reduced by 0.61 ± 0.09% 90 min after injection of celanide and that of the venous blood was reduced by 1.04 ± 0.15% (initial values 7.39 ± 0.01 and 7.30 ± 0.01 respectively). The glucose level fell gradually in the arterial and venous blood after injection of celanide and 90 min after the injection it was 13.0 ± 2.7% ($P < 0.001$) and 23.4 ± 3.4% ($P < 0.001$) respectively lower than initially. Data on changes in the oxygen and glucose demand by the brain tissues under the influence of celanide are given in Fig. 2.

The results of this investigation thus showed that strophanthin and celanide frequently induced biphasic changes in the cerebral hemodynamics. Initially the cerebral blood flow increased regularly, despite some increase in the cerebrovascular resistance; this can be explained by the parallel rise in BP. Later the cerebral blood flow decreased gradually as a result of a fall in BP. The cerebrovascular resistance began to fall gradually during this period (in some cases it fell below its initial value). The regular fall of venous pressure facilitated drainage of blood from the venous system of the brain. The fall in the oxygen and glucose concentration in the cerebral venous blood, evidence of their more active utilization by the brain, is particularly interesting.

The favorable therapeutic effect of cardiac glycosides in patients with cerebrovascular disturbances, observed by clinicians [9-14], is evidently due not only to their effect on the cardiovascular system, but also to their ability to improve the blood flow and metabolism in brain tissue.

LITERATURE CITED

1. M. D. Gaevyi, Fiziol. Zh. (Ukr.), 13, No. 3, 417 (1967).
2. M. D. Gaevyi and S. P. Trofimenko, Fiziol. Zh. SSSR, No. 10, 1457 (1970).
3. M. D. Gaevyi, Pharmacology of the Cerebral Circulation [in Russian], Moscow (1980), pp. 112-113.

*Lanatoside.

4. V. V. Men'shikov, Technical Instructions on the Use of Unified Clinical Laboratory Methods of Investigation [in Russian], Moscow (1973), pp. 59-61.
5. G. I. Mchedlishvili, N. P. Kometiani, and L. G. Ormotsadze, Byull. Éksp. Biol. Med., No. 9, 19 (1972).
6. P. P. Onitsev, Cardiac Glycosides [in Russian], Moscow (1960).
7. A. S. Saratikov and L. P. Alekseeva, Farmakol. Toksikol., No. 5, 584 (1963).
8. Chan Çanh Thac and M. D. Gaevyi, Byull. Éksp. Biol. Med., No. 11, 562 (1981).
9. G. I. Éninya and É. S. Smeltere, Action of Drugs on Parameters of the Cerebral Circulation in Chronic Cerebrovascular Insufficiency [in Russian], Riga (1980), pp. 39-42.
10. M. Ardenne, J. Quandt, and P. Reitnauer, Wien. Med. Wschr., 127, 34 (1977).
11. W. Birkmayer, F. Hawliczek, V. Samec, et al., Arch. Psychiat. Nervenkr., 202, 346 (1961).
12. W. D. Heiss and I. Podreka, Eur. Neurol., 17, Suppl. 1, 135 (1978).
13. W. Kieb and G. Schmidt-Modrow, Med. Welt (Stuttgart), 28, 1730 (1977).
14. F. Solti, A. Peter, G. Simonyi, et al., Acta Med. Acad. Sci. Hung., 18, 163 (1962).

ACTION OF THE DIETHYLAMINO ANALOG OF ETHMOZINE ON FAST SODIUM CURRENT PARAMETERS IN NORMAL AND DEPOLARIZED MYOCARDIAL FIBERS

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The diethylamino analog of ethmozine* (DAAE) is a new antiarrhythmic compound of the phenothiazine series synthesized at the Institute of Pharmocology, Academy of Medical Sciences of the USSR. The high antiarrhythmic activity of this compound [6] is due to its ability to induce effective and prolonged inhibition of the fast sodium current of myocardial fibers [2, 4, 5]. Nevertheless, the question of the effect of DAAE on kinetic parameters of the fast sodium current remains unexplained. Investigation of the action of this compound on parameters of the sodium current in depolarized heart tissue also is interesting, for we know that many antiarrhythmic agents, especially lidocaine, selectively inhibit the fast sodium current in ischemized and depolarized myocardial fibers [8, 11, 14-16].

The aim of the present investigation was to study the action of DAAE on the fast inward sodium current and of its kinetic parameters in normal and depolarized myocardial fibers.

EXPERIMENTAL METHOD

The fast inward sodium current was recorded under membrane voltage clamp conditions, using a double sucrose gap by a method similar to that described previously [3, 7, 12]. Isolated trabeculae, obtained from the atria of Rana catesbiana, were used as test objects; the length of the trabeculae was 3-4 mm and their diameter 80-120 μ. A trabecula was perfused in a testing compartment 250 μ wide with Ringer's solution of the following composition (in mM): NaCl 114, KCl 2.7, $CaCl_2$ 1.8, glucose 5, Tris-HCl 10, pH 7.5. Only those trabeculae on which a resting potential of 75-80 mV was recorded after immersion in the perfusion chamber were used in the experiments. The myocardial fibers were depolarized by two methods: by passing a direct current through the fiber under membrane voltage clamp conditions and by increasing the potassium ion concentration in the perfusion fluid to 8-9 mM. The membrane potential in the depolarized fibers was maintained 15 mV

*Ethmozine is 2-carbethoxyamino-10-(3-morpholylpropionyl)-phenothiazine hydrochloride.

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