EFFECT OF STROPHANTHIN AND CELANIDE ON THE COURSE OF DEVELOPMENT OF POSTISCHEMIC CEREBROVASCULAR PHENOMENA

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Cardiac glycosides are widely used in the treatment of acute and chronic cardiac failure, when disturbances of the cerebral circulation of ischemic character frequently arise. The action of cardiac glycosides on the cerebral circulation has been very inadequately studied, and the results have sometimes proved contradictory [3, 6]. We know that in the postischemic period phasic changes in the cerebral blood flow frequently arise, and in the literature [5, 8, 9, 12] they are described as phenomena (syndromes) of reactive hyperemia (hyperperfusion) and nonrecovery of the blood flow (hypoperfusion). In view of the absence of information on the effect of cardiac glycosides on the dynamics of development of these phenomena it was decided to undertake the present investigation.

EXPERIMENTAL METHOD

Experiments were carried out on 40 anesthetized (pentobarbital sodium, 0.05-0.07 g/kg) cats of both sexes weighing 2.0-4.2 kg, under artificial respiration. The total cerebrovascular resistance was recorded by means of a resistograph connected to the common carotid arteries. Isolated perfusion of the brain was secured by ligation of certain vessels of the head and neck [2]. The perfusion pressure and the general arterial pressure in the carotid artery (PP and BP, respectively) were recorded by mercury manometers. Blood clotting was prevented by intravenous injection of heparin. Cerebral ischemia for 15 min was induced by stopping the perfusion pump with the valves closed. The general BP fell during the period of ischemia to 30-20 mm Hg on account of hemorrhage followed by retansfusion of the blood after ischemia (at the time of starting up the perfusion pump). According to data in the literature [5], this reduction of BP during occlusion of the carotid arteries leads to cerebral ischemia and preservation of the function of the bulbar centers. In the present experiments occlusion of the vertebral arteries was stopped at the moment of ischemia.

The experiments were divided into four series of which two were controls. In series I (control) the dynamics of changes in PP and BP in the postischemic period was studied. In series II changes in the same parameters were investigated against the background of the action of cardiac glycosides. In series III the response of the cerebral vessels and of BP of strophanthin was studied in the postischemic period. Experiments in which the action of strophanthin on PP and BP in intact animals were studied (series IV) served as the control for series III. The glycosides for testing (0.05 mg/kg of strophanthin and 0.1 mg/kg of celanide*) were injected intravenously in all experiments.

EXPERIMENTAL RESULTS

Phasic changes in PP in the cerebral vessels were observed in the control experiments (series I, six experiments). For 20-30 min after ischemia, PP thus was lower than initially; at the 10th minute the degree of its fall amounted to 29.5 $\pm$ 4.1% ($P < 0.001$). By 30-40 min PP was restored to its initial value, and thereafter it continued to rise, to exceed the initial level by 52.8 $\pm$ 4.9% 90 min after ischemia ($P < 0.001$). This high level of PP was preserved until the end of the experiments (observations for a period of 120 min). Consequently, under the conditions of resistography, postischemic cerebrovascular phenomena are clearly manifested: The phase of lowering of PP corresponds to the phenomenon of reactive hyperperfusion and the phase of elevation of PP to the phenomenon of hypoperfusion (delayed nonrecovery of the blood flow). The causes of these phenomena have not yet been adequately studied, although there are several communications on this problem in the literature [1, 4, 5, 7].

In the experiments of series II similar cerebral ischemia was induced 40-90 min after intravenous injection of strophanthin (seven experiments) and celanide (eight experiments). After preliminary injection of strophanthin the phase of

*Lanatoside.

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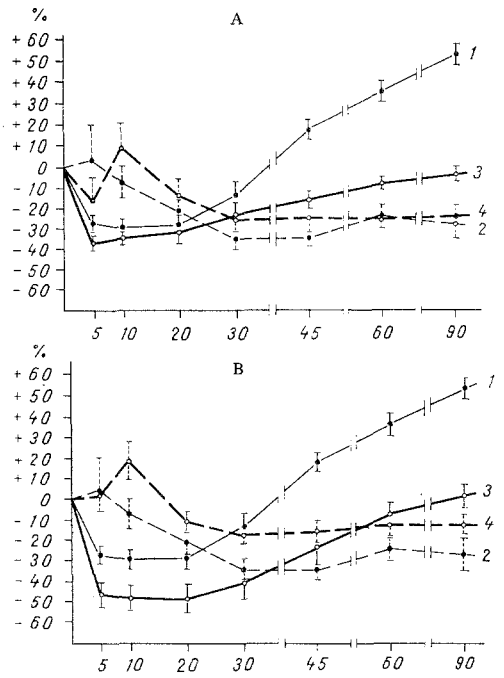

Fig. 1. Effect of strophanthin (A) and celanide (B) on PP changes in brain vessels and systemic arterial pressure (BP) in postischemic period. 1, 2) PP and BP in control experiments, respectively; 3, 4) PP and BP, respectively, after administration of glycosides. Abscissa, time (in min); ordinate, changes in parameters (in % of initial).

postischemic lowering of PP continued in most cases (in five of seven) to the end of the period of observation. Only in one experiment was PP restored to its initial level after 90 min, and in another experiment PP rose to 8% above the initial level. A similar character of postischemic changes in PP was observed in experiments with preliminary administration of celanide. Consequently, nonrecovery of the blood flow for 90-120 min after ischemia was practically never seen after administration of glycosides, whereas the hyperperfusion phenomenon not only lasted longer, but also was more marked (especially in the case of celanide) than in the control. For instance, after strophanthin and celanide PP in the brain vessels 10 min after ischemia was 33.8 $\pm$ 4.1 and 47.7 $\pm$ 6.2%, respectively, below the initial value, whereas in the control experiments at this time PP was 29.5 $\pm$ 4.1% below the initial level. However, the postischemic lowering of BP against the background of glycosides was less marked than in the control experiments. The dynamics of development of the postischemic cerebrovascular phenomena is illustrated in Fig. 1.

In the six experiments of series III strophanthin was given 90-120 min after ischemia. To begin with a moderate (by 9% on average) and short (10-20 min) rise in PP was observed, followed by a small fall; BP was raised on average by 30%. These experiments showed that injection of strophanthin during the period of a developed hypoperfusion phenomenon caused no significant changes in the cerebrovascular resistance to the blood flow. In intact animals (series IV, 12 experiments without ischemia), incidentally, strophanthin caused a longer and greater rise of PP (on average by 25%) than in the ischemized animals, and in some cases the phasic (constrictor-dilator) response of the cerebral vessels to strophanthin was clearly exhibited. The rise in BP was greater in the ischemized animals. Consequently, the response of the vessels of the ischemized brain to strophanthin was depressed.

Preliminary injection of cardiac glycosides thus substantially modifies the dynamics of development of postischemic cerebrovascular phenomena. The ability of glycosides to inhibit the development of postischemic hypoperfusion, during which the postischemic damage to the brain tissue is aggravated, may be particularly interesting. Some clinicians have noted the beneficial effect of strophanthin in cerebrovascular disturbances [10] resulting from a homogeneous increase in the blood flow in both intact and ischemic regions of the brain [12], in agreement with the results of the present investigation.

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ATYPICAL ANTIDEPRESSANTS: EFFECT OF SYNAPTOSOMAL UPTAKE OF SEROTONIN AND GABA

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Ability to inhibit uptake of monoamines by the neuron membrane is a characteristic property of the tricyclic antidepressants [2-4, 7], which also inhibit the uptake of gamma-aminobutyric acid (GABA), although less strongly than serotonin and catecholamines [2, 4]. Besides tricyclic compounds of the imipramine type, another group of preparations has been discovered which, in their chemical structure and spectrum of pharmacological activity, including their effect on neuromediator uptake, differ from the other known antidepressants, but give rise to a definite therapeutic effect in various depressive states [5]. The bicyclic antidepressant trazodone, for instance, like imipramine, selectively inhibits serotonin uptake [11], whereas the original Soviet tetracyclic antidepressant pyrazidol inhibits noradrenalin and GABA uptake only a very little [4].

Since the mechanism of action of the atypical antidepressants has not been adequately studied, it appeared important to compare a number of structurally different antidepressants with respect to their effect on synaptosomal uptake of labeled serotonin and GABA.

EXPERIMENTAL METHOD

The coarse synaptosomal fraction was obtained by centrifugation of a 10% rat brain homogenate in 0.32 M sucrose at 1000g for 10 min. The supernatant was again centrifuged for 20 min at 11,000g. The residues thus obtained, containing synaptosomes, mitochondria, and myelin, were resuspended in 0.7 ml and 0.32 M sucrose per gram weight of original brain. To obtain material for the experiment 50 μl of the resulting suspension of coarse synaptosomal fraction (average 1 mg protein) was added to 1 ml of an incubation medium containing 100 mM NaCl, 6 mM KCl, 2 mM $CaCl_2$, 1.14 mM $MgCl_2$, 5 mM Na_2HPO_4, 10 mM glucose, 100 mM sucrose, 0.125 mM pargidine, and 30 mM Tris-HCl buffer, pH 7.4; the labeled mediator and drugs were added in appropriate concentrations. The concentration of ^{3}H-serotonin in these experiments was 83 nM (specific radioactivity 12 Ci/mmole; from the Radiochemical Centre, Amersham, England), and that of ^{3}H-GABA was 10 μM (specific radioactivity 10 Ci/mmole, from New England Nuclear, USA). Incubation was carried out at 37°C for 20 min with continuous agitation. Binding of mediators was stopped by cooling to 0-5°C. Synaptosomes were isolated from the incubation medium and the quantity of bound mediator determined by our modification [6] of the method of Snyder and Coyle [12]. Radioactivity was measured by means of an SL 4000 (Intertechnique) liquid scintillation counter, and the mean number of counts per minute was calculated. Protein was determined by Lowry's method [9]. The results were subjected to statistical analysis and mean values and confidence limits at the P = 0.05 level calculated.

EXPERIMENTAL RESULTS

In the experiments of series I serotonin and GABA uptake by the coarse synaptosomal fraction depending on substrate

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