HEMODYNAMIC ASPECTS OF THE HYPOTENSIVE ACTION OF CAPTOPRIL

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KEY WORDS: captopril; vascular resistance; venous return.

A promising trend in the treatment of essential hypertension is the use of drugs acting on the renin-angiotensin system at the stage of conversion of vasopressor substances in the body [2, 3, 6]. One such drug is captopril, which can prevent the conversion of angiotensin I into angiotensin II, and this is considered to be the basis of its hypotensive action [9, 10]. Meanwhile many hemodynamic aspects of the hypotensive action of captopril have been inadequately studied. There are convincing data that the drug lowers arterial tone [4, 5]. Some workers observe that vasodilatation induced by captopril cannot be explained entirely by its inhibitory action on the angiotensin converting enzyme [7], and that it is probably linked with its action on the system of kinins and prostaglandins [8]. Information on the effect of the drug on the cardiac output is more contradictory [4, 5]: Its action on capacitive vessels, which take part in the regulation of cardiac output through the formation of the venous return, has virtually not been studied.

This paper describes a combined study of the effect of captopril on the resistive and capacitive properties of the systemic vascular bed.

EXPERIMENTAL METHOD

Altogether 14 experiments were carried out on anesthetized (urethane 800 mg/kg, sodium hydroxybutyrate 800 mg/kg), curarized cats which were artificially ventilated. Laparotomy and thoracotomy were performed and a segment of the abdominal aorta below the origin of the renal arteries was isolated. The aorta was excised and polyethylene cannulas, connected to the output of a perfusion pump, were introduced into its central and peripheral ends. To prevent prolonged circulatory arrest in the lower third of the trunk before connection to the perfusion system, the blood flow in the aorta was restored by connecting its ends temporarily through an introduced system of cannulas. From three to six ribs were resected on the left side of the chest, and the auricle of the left atrium was isolated and excised, and a polyethylene cannula, connected to the extracorporeal reservoir, was introduced into it. The reservoir was placed below the level of the heart to create a negative pressure in the chamber of the left atrium, thus ensuring complete return of the blood into the extracorporeal reservoir and preventing blood from entering the left ventricle. Blood was kept in the reservoir at 37°C and supplied by a perfusion pump to the central and peripheral ends of the abdominal aorta. Heparin was injected intravenously beforehand in a dose of 1500 U/kg. In that way the artificial circulation was maintained in the vessels of the systemic circulation and the natural circulation and oxygenation of blood in the pulmonary circulation were maintained [1]. In six experiments, besides an artificial circulation, the venous return from vessels of the systemic circulation was estimated. For this purpose, polyethylene cannulas also were introduced into the cranial and caudal venae cavae, isolated previously. Blood from the venaea cavae was drained into an extracorporeal venous reservoir, from which it was forced by a second perfusion pump into the right atrium through the central end of one of the venae cavae (Fig. 1). The output of the pump was set to be equal to the rate of the blood flow along the venae cavae, so that a stationary blood level was maintained in the venous reservoir when the animal was in its initial state. The perfusion pressure (by an electromanometer) and the volume velocity of the blood flow (by the continuous flow transducer of an electromagnetic flowmeter) at the entrance into the abdominal aorta were recorded in the experiments. The blood level in the extracorporeal

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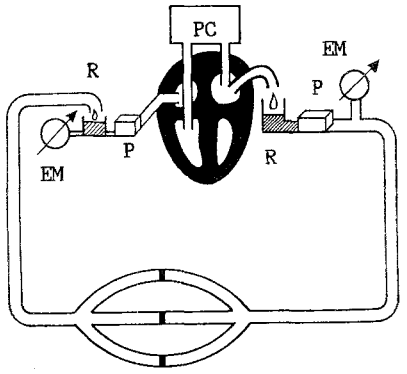

Fig. 1

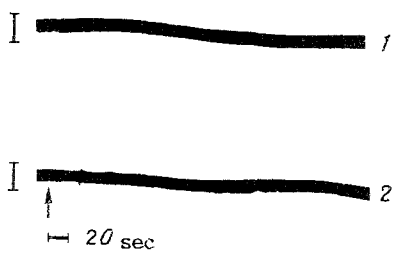

Fig. 2

Fig. 1. Scheme for investigation of resistive and capacitive functions of the systemic vascular bed. EM) Electromanometer, P) perfusion pump, R) extracorporeal reservoir, PC) pulmonary circulation.

Fig. 2. Effect of captopril (1 mg/kg) on perfusion pressure and venous return from vessels of systemic circulation. 1) Perfusion pressure (calibration 15 mm Hg); 2) volume of blood in extracorporeal venous reservoir (calibration 5 ml). Arrow indicates time of injection of drug.

venous reservoir was recorded by means of an electromanometer. Changes in the venous return from the vessels of the systemic circulation were judged from changes in the blood level. The volume velocity of perfusion during the artificial circulation was set so that the pressure in the systemic vessels was between 90 and 100 mm Hg. Captopril was injected intravenously in a dose of 2 mg/kg.

EXPERIMENTAL RESULTS

During the experiments the initial level of pressure in vessels of the systemic circulation was 97 ± 2 mm Hg. This level was achieved when the volume velocity of perfusion was set at 420 ± 50 ml/min.

Captopril caused a definite decrease of the perfusion pressure on average by 13 ± 4 mm Hg ($P < 0.05$), which developed 15-20 sec after injection of the drug, and which continued throughout the period of observation (at least 60 min). This hypotensive action of captopril under artificial circulation conditions was entirely determined by the decrease in the resistance of the systemic vessels to the blood flow.

The effect of captopril on the venous return of blood from vessels of the systemic circulation was not monophasic in two of the six cases. In these experiments 20-30 sec after injection of the drug a transient (for 50-70 sec) increase was observed in the venous return (by 1.5-2 ml according to the blood level in the reservoir), which was followed by a lasting decrease (by 3-5 ml relative to the initial level). In the remaining four experiments injection of captopril caused a decrease in the venous return (Fig. 2). For all the experiments together, the decrease in the outflow of blood from the venae cavae led to a fall in the blood level in the venous reservoir by 3.7 ± 1.2 ml on average ($P < 0.05$). Thus an essential role in the hypotensive action of captopril is played by the decrease in resistance of the vessels of the systemic circulation to the blood flow; captopril increases the capacity of the vascular bed, thereby reducing the venous return of blood to the heart.

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EFFECT OF COMPOUNDS WITH ANXIOLYTIC PROPERTIES ON VOLUNTARY ETHANOL CONSUMPTION BY RATS

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KEY WORDS: ethanol; benzodiazepine tranquilizers; anxiolytic system

Although tranquilizers differing in chemical structure, and mainly of the benzodiazepine series, are actively used in clinical practice for the treatment of characteristic disorders such as anxiety, fear, and emotional stress, it is still not clear whether these drugs affect addiction to ethanol. In view of the latest data on the role of emotionally negative conflict situations in the development of pathological craving for ethanol [1, 8, 11, 13], the possibility that the treatment of alcoholism with tranquilizers may be pathogenetic in character cannot be ruled out [1, 6, 12, 14]. However, there is no direct proof that tranquilizers act on the formation of addiction to ethanol, or on the level of ethanol consumption at times other than during stress.

The aim of this investigation was to study the role of the effects of various chemical compounds with anxiolytic properties on voluntary consumption of 15% ethanol solution by rats at different stages of experimental alcoholism.

EXPERIMENTAL METHOD

The following compounds were used: diazepam, sodium hydroxybutyrate, mebicar,* derivatives of the aminoandrostane series: 17-β-acetylamino-5-androstene-3β,16β-diol (KLI-2), 17-β-amino-5-androstene-3β,16β-diol hydrochloride (KLI-3), 17-β-acetylamino-4-androstene-3,16-dione (KLI-5), and a derivative of the β-carboline series: 1-methyl-6-methoxytetrahydrocarboline (NK-424).

To study the effect of the compounds on alcohol motivation, intact rats weighing 200-220 g were placed in individual cages with free access to water and to 15% ethanol, and the drugs were administered simultaneously for 10 days. To analyze the effect of the compounds on the ethanol consumption of rats with established physical dependence on ethanol, animals which had been in contact with ethanol for 8 months (weighing 450-500 g) were used. Before the experiments the voluntary ethanol consumption of these animals was recorded for 10 days and rats whose daily consumption was not less than 40-50 ml/kg of 15% ethanol solution were used in the experiments [3]. The test compounds were injected intraperitoneally into these animals for 2 weeks in aqueous solution and in the form of a suspension with Tween-80 (aminoandrostanes, β-carbolines, diazepam).

The consumption of water and 15% ethanol solution was recorded daily. The experimental data were subjected to statistical analysis by Student's method.

EXPERIMENTAL RESULTS

Data reflecting the effects of compounds with anxiolytic properties in doses corresponding to ED_{50} of their effect in intact animals on the formation of alcohol motivation and on

*2,4,6,8-tetramethyl-2,4,6,8-tetra-azobicyclo-(3,3,o)-octadione-3.7.

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