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MECHANISMS OF INHIBITION OF SYNAPTIC TRANSMISSION IN THE SYMPATHETIC GANGLIA OF RATS WITH ALLOXAN DIABETES

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In experiments on isolated cranial sympathetic ganglia of rats with alloxan diabetes the preganglionic nerve was stimulated and combined presynaptic action potentials (APs) and EPSPs of neurons of the ganglion were recorded. In rats with moderately severe alloxan diabetes progressive depression of rhythmic APs of the ganglion correlated completely with inhibition of the excitatory power of the presynaptic endings, i.e., with a decrease in the liberation of mediator and exhaustion of its operative fraction. In rats with the severe form of diabetes postsynaptic inhibition of neurons of the ganglion also was observed. The dynamic characteristics of conversions of the mediator, assessed on the basis of examination of posttetanic potentiation patterns, showed a very small change in the output of mediator but a substantial (by 38%) depression of replenishment of the mediator reserves per second compared with the control.

KEY WORDS: synaptic ganglion; synaptic transmission; alloxan diabetes.

Diabetes mellitus causes severe disturbances of the activity of the central and peripheral nervous system [2-4, 7, 8, 12, 13], including the autonomic division. In this disease degenerative changes are found in the lateral horns of the spinal cord and in the autonomic ganglia [2, 8, 12], and these must inevitably cause changes in the functional properties of these formations. However, no detailed investigation of the function of such important centers as the sympathetic ganglia has yet been carried out in diabetes.

This paper gives the results of an investigation of the function of the synaptic structures of the cranial cervical sympathetic ganglion (CCSG) of rats with alloxan diabetes.

EXPERIMENTAL METHOD

Experiments were carried out on 31 Wistar rats weighing 150-250 g. To obtain diabetes the rats were given a subcutaneous injection of alloxan in a dose of 17-50 mg/100 g body weight [9]. The blood sugar con-

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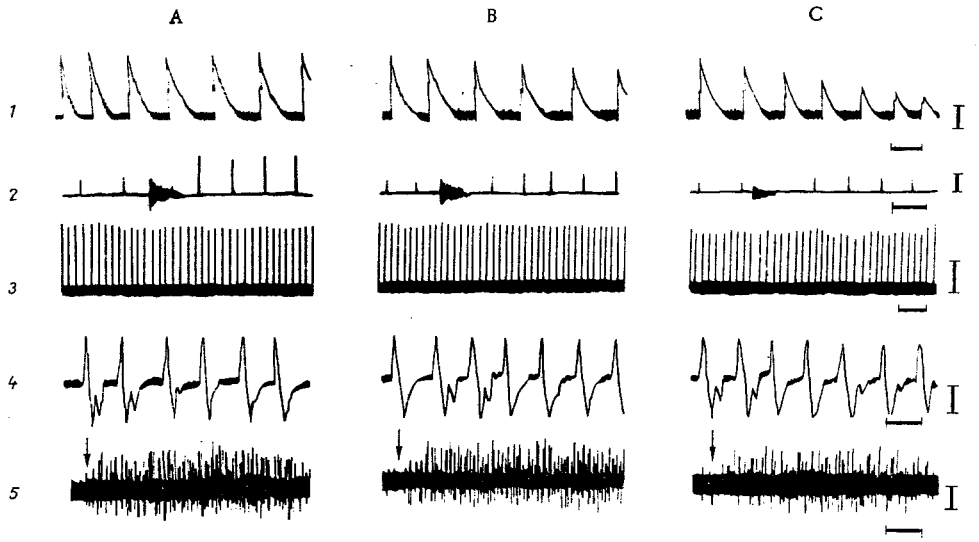

Fig. 1. Spike discharge from CCSG of control rat (A), rat with moderately severe (B; blood sugar 210 mg%), and with severe alloxan diabetes (C; blood sugar 395 mg%). 1) Orthodromic potentials in response to stimulation of preganglionic nerve and frequency of 15 Hz; activity of CCSG during depression of homosynaptic APs. Posttetanic potentiation to testing stimulation of preganglionic nerve at 1 Hz, conditioning stimulation 40 Hz, 10 sec; 3) antidromic potentials during stimulation of postganglionic nerve at 60 Hz; 4) heterosynaptic potentials during stimulation of preganglionic nerve at 10 Hz; 5) response of ganglion to standard dose (50 μg) of acetylcholine. Time of application indicated by arrow. Calibration: amplitude 150 μV (1, 2), 200 μV (3, 4), and 30 μV (5); time 0.06 sec (1), 1 sec (2, 5), and 0.1 sec (3, 4).

centration was determined by the Somogyi–Nelson method. Seven animals not receiving alloxan served as the control. The 15 rats with signs of wasting, glucose urea, and hyperglycemia (blood sugar 150-250 mg%, 1-5 weeks after injection of alloxan) were classed in the group with moderately severe diabetes, and 9 rats were classed in the group with severe diabetes (blood sugar 250-460 mg%, 5-20 weeks after injection of alloxan).

Bilateral extirpation of CCSG was carried out under pentobarbital anesthesia (50 mg/kg, intraperitoneally). The CCSG preparations were placed in a bath containing Krebs' solution at 35-38°C. Suction pipets were used to stimulate the preganglionic nerve and to record the potentials of the ganglion. In response to stimulation of the preganglionic nerve of measured strength and frequency (duration of stimuli 0.1 msec) action potentials (APs) of CCSG were recorded, and after delicate curarization (10^{-4}-10^{-5} M D-tubocurarine) the combined presynaptic AP and EPSP of the CCSG neurons also were recorded [11].

EXPERIMENTAL RESULTS

In a series of experiments the threshold of appearance of the ganglionic AP in the diabetic animal was rather higher than in the control rats. However, the considerable scatter of this characteristic prevented this fact from being statistically significant.

During repetitive activation of the highly excitable B_1 group of fibers, and also during supramaximal stimulation, involving less excitable B_2 and C groups of fibers in the response, depression of the ganglionic responses in the diabetic rats was observed at lower frequencies and developed more rapidly than in healthy animals. A proportional decrease in the amplitude of AP and the combined presynaptic AP and EPSP of the CCSG neuron was observed. By the use of several experimental methods [1, 5, 14] the "bottleneck" responsible for the progressive inhibition of synaptic transmission in CCSG of the diabetic animals was determined.

The record shown in Fig. 1, curve 1 revealed depression of the regular orthodromic responses of CCSG of the healthy rat, an animal with moderately severe diabetes, and an animal with severe and prolonged diabetes. Clearly against the background of marked depression of orthodromic responses in the presence of marked diabetes, APs of CCSG evoked by antidromic and heterosynaptic stimulation (Fig. 1: curves 3, 4) were almost unchanged. The response of the chemo-reactive structure of CCSG to acetylcholine was substan-

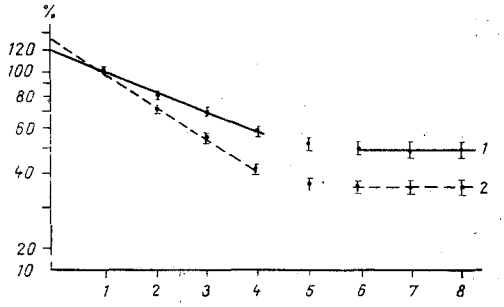

Fig. 2. Curves of depression of posttetanic potentiation of amplitude of APs of CCSG in control rats (1) and animals with moderately severe alloxan diabetes (2). Abscissa, No. of consecutive series of posttetanic potentiation (each series consisted of a period of conditioning stimulation with a frequency of 30 Hz, lasting 110 sec, and a testing period lasting (10 sec), during which stimulation was applied with a frequency of 1 Hz; ordinate, amplitude of APs of CCSG in percent of initial series of posttetanic potentiation (averaged amplitude of 5 last APs of test period, in logarithmic units). Vertical lines represent confidence limits of means.

tially inhibited only in severe diabetes (Fig. 1: curve 5). As regards posttetanic potentiation of the responses – an index of the efficiency of the mechanism of mediator secretion, its intensity was reduced in moderately severe and, in particular, in severe diabetes.

The characteristics of the various stages of synaptic transmission thus obtained suggested that progressive depression of the rhythmic APs of CCSG of animals with moderately severe alloxan diabetes is connected on the whole with a disturbance of the function of the presynaptic formations. In animals with prolonged and severe diabetes this depression was also explained by postsynaptic inhibition, evidently connected with worsening of the state of the ganglionic neurons and a lowering of the reactivity of the cholinergic formations of the neurons to acetylcholine.

Disturbances of the synaptic function of CCSG in animals with moderately severe diabetes during the conduction of regular impulses may be due to a decrease in the output of mediator in response to each presynaptic volley as the result of the ease with which the operative fraction of acetylcholine is exhausted. To assess the dynamic characteristics of mediator output per impulse a, and the replenishment of its reserves per second k, as fractions of available mediator in the population of presynaptic endings, the method described previously [5, 14] was used. The basic assumption was linearity of the relations between input and output of the system, so that the amplitude of the postsynaptic response of CCSG in the course of repetitive stimulation could be used as a measure of mediator secretion. Test responses to preganglionic stimulation with a frequency of 1 Hz were recorded during the 10 sec after repeated series of stimulation of the preganglionic nerve for 110 sec at a frequency of 30-40 Hz.

Curves describing depression of standardized values of responses of CCSG in the course of consecutive series of posttetanic potentiation, close to exponential in character, were steeper in alloxan diabetes and flattened out on a plateau parallel to the abscissa at a lower level than in control experiments (Fig. 2).

The values of a and k obtained by analysis of these curves point to marked depression of mediator production in animals with moderately severe diabetes (on average by 38% compared with the control), which must lead to rapid exhaustion of the mediator. Meanwhile, secretion of the mediator was substantially unchanged. Similar changes in the kinetics of mediator metabolism have been observed during the initial period of deepening insulin hypoglycemia and acute hypoxia [6], and they are comparable with the characteristics of mediator metabolism obtained in CCSG perfusion experiments [10].

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ACTION OF PROSTAGLANDINS E_1 AND E_2 ON THE INTERNAL CAROTID ARTERY

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In experiments on the internal carotid artery of a dog isolated from the rest of the circulation, the following effects of prostaglandins (PG) E_1 and E_2 were discovered. PG E_1 caused either a constrictor or a dilator effect with habituation during repeated exposures, whereas PG E_2 had only a constrictor effect without any habituation. The duration of the effects of PG E_2, especially relaxation, was much longer than that of the effects of serotonin; residual contraction of the vascular smooth muscles was frequently observed; PG E_1 and PG E_2 potentiated the effects of serotonin and often of noradrenalin.

KEY WORDS: angiospasm; prostaglandins; internal carotid artery; serotonin; smooth muscles of blood vessels.

In the arterial system of the brain the most typical sites for the onset of spasm are the large arteries and, in particular, the internal carotid arteries [2]; for that reason investigations of the pathophysiological mechanisms of development of angiospasm are best carried out on these vessels. In the last decade the various prostaglandins (PG) have attracted considerable attention of investigators because of their possible role in the development of spasm of the cerebral arteries [9, 12, 13]. PG may have a direct action on the smooth muscles of arteries, by penetrating into their wall from the blood or from the medium surrounding the vessel, or if synthesized within the vessel wall itself.

The object of this investigation was to study the action of PG E_1 and E_2 on the internal carotid artery of the dog, isolated from the rest of the circulation; the work was a further development of the writers' studies of the role of these physiologically active substances in the development of pathological constriction, i.e., of angiospasm, in the brain [5].

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