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MECHANISM OF DISTURBANCE OF INHIBITORY ELECTROGENESIS IN SPINAL α-MOTONEURONS IN EXPERIMENTAL LOCAL BOTULINUS POISONING

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The character of changes in postsynaptic inhibition in spinal α-motoneurons of cats was studied in the course of experimental local botulinus poisoning. At the beginning of development of the local paralytic syndrome a marked decrease in the amplitude of the reciprocal, and a smaller decrease in amplitude of the polysynaptic IPSPs was observed. On the appearance of total paralysis of the muscles from botulinus poisoning the reciprocal and polysynaptic IPSPs were inhibited even more, but they never disappeared completely and were never converted into depolarization potentials. During the development of the IPSP the synaptic permeability of the motneurons as a rule was reduced.

KEY WORDS: botulinus poisoning; spinal motoneurons; inhibitory postsynaptic potential.

Some workers regard botulinus toxin (BT) as a purely peripheral blocking agent [4, 5]. However, loss of the spinal reflexes and mono- and polysynaptic ventral root potentials of the spinal cord and a decrease in the excitability of the somatic membrane of α-motoneurons always precede the development of the transmission block in the myoneural synapses. This is evidence that the primary disturbance of activity of the centers is connected with the development of the paralytic syndrome [1, 2]. It is still uncertain to what extent the depression of excitability of the nerve cells at the various stages of botulinus poisoning is connected with a change in

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TABLE 1. Characteristics of Reciprocal (I) and Polysynaptic (II) IPSPs in Motoneurons of Cat with Botulism

Experimental conditions	Statistical index	Latent period, msec		Amplitude, mV		Duration, msec		Rise time, msec	
		I	II	I	II	I	II	I	II
Control (healthy animals)	$M \pm m$ n	3,02±0,21 24	4,69±0,09 50	5,3±0,12 24	6,9±0,18 50	64,3±2,12 24	102,7±2,57 50	5,7±0,19 24	8,2±0,26 50
Botulism: stage of paresis (48-72 h)	$M \pm m$ n	3,10±0,11 30	4,80±0,10 60	4,2±0,14* 30	5,8±0,19* 60	47,5±2,71* 30	101,3±1,82 60	7,2±0,24 30	10,1±0,41* 60
stage of flaccid paralysis (≥94 h)	$M \pm m$ n	3,06±0,10 30	4,93±0,14 60	3,6±0,12* 30	4,2±0,16* 60	44,3±2,21* 30	78,94±2,24* 60	8,0±0,27* 30	11,4±0,44* 60

* Here and in Table 2, $P < 0.05$ compared with control.

TABLE 2. Some Membrane Constants of Motoneurons of Cat with Experimental Botulinus Poisoning

Experimental conditions	Statistical index	TPD	R_{in}, mΩ	I_t, nA	Decrease in resistance (ΔG_{IPSP}), %
Control	$M \pm m$ n	65±2,5 70	1,58±0,18 50	4,7±0,57 50	20—40 (33) 23
Botulism: stage of paresis	$M \pm m$ n	55,0±2,3* 85	1,10±0,02 60	7,3±0,93* 60	15—40 (28) 36
stage of paralysis	$M \pm m$ n	51,0±2,8* 70	0,81±0,07* 60	7,85±1,12* 60	10—20* (16) 38

the processes of inhibitory electrogenesis. There are only isolated references in the literature which state indirectly that inhibitory control over mono- and polysynaptic reflexes may be disturbed [11, 12].

It was accordingly decided to study the processes of postsynaptic inhibition in α-motoneurons damaged by BT.

EXPERIMENTAL METHOD

Experiments were carried out on cats weighing 1.5-3.5 kg with a local lesion of one hind limb produced by intramuscular injection of a sublethal dose (0.5 mg/kg) of BT, type A (1 MLD for mice = 0.0001 mg). Acute experiments were carried out at the stage of paresis (second to third day after poisoning) and in the presence of complete paralysis (fourth to sixth day). The preoperative preparation, methods of recording inhibitory postsynaptic potentials (IPSPs), and the methods of determining the membrane constants of the neuron (input resistance – R_{in}, threshold current – I_t) were those generally adopted [6, 7]. Specific synaptic permeability during development of the IPSP (ΔG_{IPSP}) was measured by Larson's method [10]. The transmembrane potential difference (TPD) was recorded on the N-340 automatic ink writer. The results were subjected to statistical analysis by Student's method.

EXPERIMENTAL RESULTS

Because of the unity of excitation and inhibition processes in nerve cells [8, 9] it was decided to study the character of changes in reciprocal and polysynaptic IPSPs of spinal motoneurons in botulinus poisoning at the same times as in the earlier investigation [2].

The results showed that at the stage of paresis the amplitude and duration of IPSPs in response to stimulation of 1a afferents was appreciably reduced in 35% of recorded motoneurons. During stimulation of the same afferents of the flexor reflex the amplitude of the polysynaptic IPSPs was reduced in 20% of nerve cells. For that reason, during the statistical analysis (Table 1) it transpired that at the stage of paresis a decrease in the indices was observed only in the group of reciprocal IPSPs and the polysynaptic IPSPs showed only a tendency to decrease. In botulism, at the beginning of development of the paralytic syndrome, the disturbance of inhibitory electrogenesis, like that of excitatory [2], is thus not total in character but extends only to a proportion of the functioning motoneurons.

Later, during the development of complete paralysis of the muscles of the affected limb, a decrease in the amplitude and duration of the reciprocal IPSP was observed in 80%, and of the polysynaptic IPSP in 74%, of recorded cells, and statistical analysis showed that the decrease in the parameters of the different types of IPSP in the α-motoneurons compared with the control was highly significant. However, the IPSPs did not disappear completely in any of the experiments and they were not converted into depolarization responses. Consequently, these results show that the degree of severity of the paralysis of the skeletal muscles is directly dependent on the number of damaged spinal motoneurons; the disturbance of inhibitory electrogenesis at the various times evidently follows a parallel course to the inhibition of excitatory electrogenesis [2]. Since the generation of IPSP and of excitatory postsynaptic potentials is due to certain types of ion transport [9], in the next series of experiments changes in the specific synaptic permability of the motoneuron membrane were studied during the development of the IPSP. It will be clear from Table 2 that at the stage of paresis of the muscles in botulinus poisoning, when disturbance of the membrane constants was detected only in some of the motoneurons, the ion permeability still possessed the normal wide scatter of values, and statistical analysis showed no significant difference from the control. In the later stage of the paralytic syndrome, however, when inhibitory electrogenesis was substantially disturbed in the overwhelming majority of recorded α-motoneurons, profound disturbances of the constants of the neuron membrane appeared, the indices of ion transport fell, and the scatter of the data was smaller. Statistical analysis showed that disturbance of IPSP generation was accompanied by a significant decrease in specific synaptic permeability. It can be concluded that BT evidently inhibits excitatory and inhibitory processes simultaneously in the α-motoneurons of the anterior horns of the spinal cord. In this respect it differs fundamentally from tetanus toxin, which blocks the liberation of inhibitory mediator in the synapses of the CNS [7]. The fact that in botulism, especially at the stage of development of total paralysis, the indices of the functional state of the membrane are substantially disturbed, suggests that depression of excitatory and inhibitory electrogenesis is connected with damage to the mechanisms of ion transport through the α-motoneuron membrane. An important role in the disturbances of central transmission is perhaps played by deficient liberation of mediator from the axon endings of the damaged neurons, but this is a matter for further research.

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STATE OF NEUROMUSCULAR TRANSMISSION IN RATS WITH EXPERIMENTAL HYPOPARATHYROIDISM

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A disturbance of neuromuscular transmission, characterized by a decrease in the threshold strength of indirect stimulation, a decrease in the amplitude of the combined action potential of the muscle, a shortening of the latent period and of the absolute and relative refractory phases, and changes in the character of the response of the muscle to indirect repetitive stimulation was found in experiments on albino rats with experimental hypoparathyroidism. After intravenous injection of neostigmine into the experimental animals the various indices showed a tendency to return to their values in the control experiments. It is concluded that the disturbance of neuromuscular transmission is connected with a presynaptic defect and that it may be of definite importance in the development of the motor disturbances observable in hypoparathyroidism.

KEY WORDS: hypoparathyroidism; neuromuscular synapse; calcium; acetylcholine.

A leading place in the clinical picture of hypoparathyroidism is occupied by the syndrome of tetany, the pathogenesis of which can, it is reasonable to suppose, be elucidated by investigation of the functional state of the neuromuscular synapse, to which purpose the investigation described below was devoted.

EXPERIMENTAL METHOD

Experimental hypoparathyroidism was produced in albino rats by electrical coagulation of the parathyroid glands. The animals were used in the experiments on the fifth to eighth day after the operation. The development of hypoparathyroidism was judged from the serum calcium concentration, determined photometrically. At the time mentioned above it had fallen from 8.7 ± 0.28 to 4.7 ± 0.52 mg %.

Under pentobarbital anesthesia the tibial nerve was dissected and divided, and the peripheral end was stimulated by single, paired, and repetitive square pulses of supramaximal strength and 0.1 sec in duration. For repetitive stimulation a volley of 15-20 pulses with a frequency of 5 to 400 Hz was used. Electrical responses of the gastrocnemius muscle were recorded by silver electrodes, the active electrode being placed at

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