EFFECT OF SENSITIZATION ON MUSCLE ELECTRICAL ACTIVITY IN THE LOWER RESPIRATORY TRACT OF RATS

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Certain pathological states (bronchial asthma, chronic bronchitis, air droplet infections) cause changes in the lumen of the respiratory passages [3, 10, 11]. Bronchospasm can be largely abolished by vagotomy or atropine, i.e., it is connected with a change in nervous regulation of the respiratory tract. Pathological disturbances may take place in smooth-muscle tissue, in intramural ganglia, or in other formations in the walls of the respiratory tract. Data in the literature [4-6, 10, 11] indicate that allergic bronchospasm in animals is an excellent model with which to study the pathogenesis of bronchial asthma in man.

EXPERIMENTAL METHOD

The effect of sensitization on electrical activity of the rat respiratory passage was studied. Experiments were carried out on noninbred albino rats weighing 160-200 g. To produce an allergic reaction, the rats received an intraperitoneal injection of 0.1 mg/kg of ovalbumin with 0.8 ml of Almagel on the first day. On the 3rd day these same substances were injected in doses of 1.0 mg/kg and 0.8 ml respectively. The reacting dose of ovalbumin was injected intravenously on the 14th-21st day (of the experiment) in a dose of 10 mg/kg. Intact rats were used as the control. Altogether 14 sensitized and 9 normal rats were used. The animals were anesthetized with thiopental. The cervical part of the trachea was opened and a tracheotomy tube inserted. The respiratory movements were recorded by the thermistor (based on measuring the temperature of the inspired and expired air), inserted into the trachea, or by a pressure transducer, recording movements of the thoracic cage. Electrical activity was derived from the muscles of the dorsal wall of the trachea by means of bipolar tungsten electrodes 10 μ in diameter. A transparent plastic plate, rigidly fixed to a frame, was applied beneath the trachea at the site where electrical activity was recorded, thus preventing mechanical influences from other tissues. The tracheotomy tube also was rigidly fixed to the frame, thereby eliminating mechanical displacements at the site of recording electrical activity during respiratory movements. Drugs (acetylcholine chloride in a concentration of 10-4 g/ml, methylfurmethide 10-7 g/ml, nicotine bitartrate 10-5 g/ml, atropine sulfate 10-6 g/ml, benzohexonium 10-6 g/ml) were injected intravenously in a volume of 0.2 ml. The peripheral end of the right vagus nerve was stimulated electrically in the neck by square pulses with a frequency of 3 Hz, duration 0.15 msec, and amplitude 5 V. The experimental data were subjected to statistical analysis by Student's test. Mean values and their mean error were calculated.

EXPERIMENTAL RESULTS

The experiments showed that during respiration the smooth muscle of the dorsal wall of the trachea possesses electrical activity. In most cases action potentials correspond to the phase of inspiration, and the frequency and duration of the discharges are proportional to the depth of inspiration. Recording mechanical movements of the tracheal wall showed that the beginning of development of tension corresponds to the maximum of electrical activity of the phrenic nerve [9]. Stimulation of the peripheral end of the right vagus nerve disturbs respiration, which becomes rapid, superficial, or even may be completely arrested. Electrical activity of the muscle in this case is increased by 1.6 times, and the appearance of action potentials no longer correlates with the inspiratory phase of the respiratory cycle. When mechanical contraction of the tracheal wall is recorded, the beginning of development of tension corresponds to the maximum of electrical activity of the phrenic nerve.

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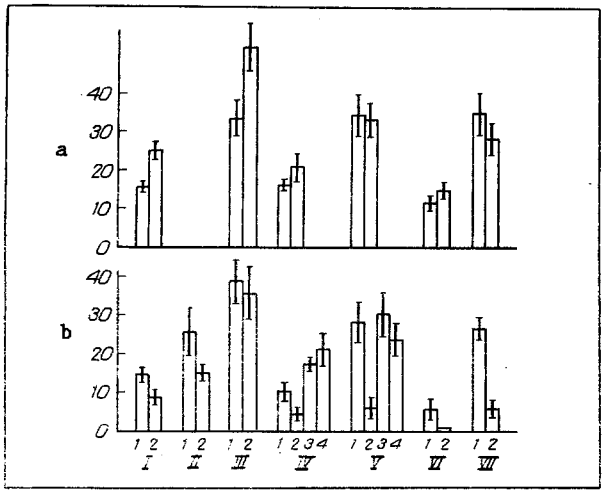

Fig. 1. Effect of drugs on electrical activity of dorsal wall of trachea of normal (a) and sensitized (b) rats. 1) Spontaneous activity, 2) evoked activity before injection of benzohexonium, 3) spontaneous, 4) evoked activity after preliminary injection of benzohexonium. I) Initial activity; after injection of: II) ovalbumin, III) acetylcholine, IV) methylfurmethide, V) nicotine, VI) atropine, VII) benzohexonium. Ordinate, electrical activity of muscles (Hz).

In the sensitized animals (before injection of the reacting dose) the spontaneous electrical activity of the tracheal muscles was virtually indistinguishable from that in normal animals (Fig. 1) but all bursts of electrical activity succeeded one another strictly in the rhythm of respiration. Unlike in normal rats, vagus nerve stimulation in the sensitized animals depressed the evoked responses by 1.6 times, i.e., sensitization disturbs the transmission of nervous impulses from the vagus nerve to the smooth muscle cells of the trachea. On injection of the reacting dose of ovalbumin, spontaneous and evoked activity increased by 1.8 and 1.7 times respectively (Fig. 1), i.e., virtually by the same amount. Ovalbumin probably increases the excitability of a certain stage which is common to both spontaneous and evoked activity.

Bronchoconstriction can be induced also by cholinergic agonists. Intravenous injection of acetylcholine increased spontaneous electrical activity of the tracheal muscles in normal rats twofold, and in sensitized rats by 2.7 times. Against the background of acetylcholine, electrical stimulation of the vagus nerve increased smooth muscle responses of normal animals by 1.6 times, i.e., by the same amount as in the absence of acetylcholine. Although in sensitized animals activity evoked by vagus nerve stimulation was increased, the amplitude of the response was virtually equal to that of spontaneous activity, i.e., the increase of this response was determined only by the effect of exogenous acetylcholine (Fig. 1).

The action of acetylcholine, like that of ovalbumin, may be connected with the neuromuscular junction, neurons of the intramural ganglion, and other structures of the tracheal wall, such as mast cells [8]. In the next series of experiments these effects were analyzed by using nicotinic and muscarinic cholinomimetics and cholinolytics.

Intravenous injection of methyfurmethide did not significantly change either spontaneous or evoked electrical activity of the normal rat trachea. Injection of nicotine into the animal potentiated spontaneous activity of the smooth-muscle wall twofold, i.e., the same as injection of acetylcholine, and the evoked response by 1.24 times. However, the numerical value of evoked activity was equal to that of spontaneous activity. Thus the increase in spontaneous electrical activity of the tracheal muscles induced by acetylcholine is due to intensification of neuronal activity of the tracheal microganglia. Neurons with an excitatory and inhibitory influence may be found in the intramural ganglia of the trachea. The weaker effect of nicotine than of acetylcholine on evoked responses may perhaps be due to the fact that nicotine activates inhibitory pathways by a greater degree than excitatory [7]. Similar results were obtained on an isolated preparation of rat trachea in a study of the neuronal activity of intramural ganglia. It was shown that acetylcholine potentiates neuronal spike discharges by a greater degree than nicotine [1, 2]. In sensitized animals methylfurmethide reduced both spontaneous and evoked electrical activity of the tracheal wall by 1.5 and 2.5 times respectively. Under the influence of nicotine, spontaneous activity was doubled whereas evoked activity was reduced by 1.6 times (Fig. 1).

Atropine weakens electrical activity of muscle in both normal and sensitized animals (Fig. 1). Under the influence of the ganglion-blocker benzohexonium, spontaneous activity of the muscle in normal and sensitized rats was increased by 2.1 and 1.8 times respectively. The amplitude of the evoked responses was not significantly changed by the ganglion blocker in either group of animals. In sensitized animals, however, evoked responses were 4.7 times less than during spontaneous activity, whereas in normal animals, values for spontaneous and evoked activity were virtually identical. In all probability, processes connected with the transmission of nervous impulses from excitatory neurons of the tracheal ganglia to the muscle do not change significantly in sensitized animals.

Examination of the effect of cholinergic drugs shows that under the influence of nicotinic and muscarinic cholinomimetics and cholinolytics spontaneous electrical activity of the smooth-muscle wall of the trachea in normal and sensitized animals changes in the same direction, with only quantitative differences. Stimulation of the vagus nerve, however, induces opposite reactions of the dorsal wall in normal and sensitized rats. In the initial state, and also under the influence of acetylcholine, methylfurmethide, and atropine, responses of the muscle in normal rats to vagal stimulation exceeded the changes in spontaneous activity, whereas in sensitized rats, the evoked responses were weaker than spontaneous activity. Under the influence of nicotine and benzohexonium, evoked responses in normal animals did not differ significantly from those of smooth muscle to injection of these substances. This effect may be connected with activation of inhibitory neurons or with a disturbance of synaptic transmission in the intramural ganglion. Evoked responses in sensitized animals were considerably weaker than spontaneous activity, i.e., in response to vagus nerve stimulation inhibitory pathways are activated, and sensitization potentiates this process. In sensitized animals, injection of methylfurmethide after the ganglion blocker causes enhancement of the spontaneous and, in particular, of evoked activity (by 1.8 and 6.0 times respectively). Injection of nicotine after the ganglion blocker caused virtually no change in spontaneous activity but potentiated evoked activity (Fig. 1). Incidentally, the relationship between spontaneous and evoked responses to methylfurmethide and nicotine in this case was similar to that between responses in intact rats, i.e., the ganglion-blocker masked the action of ovalbumin, probably due to disturbance of sympathetic transmission between the neurons, mainly in the chain of inhibitory influences.

The results are thus evidence of an essential contribution of intramural ganglia to the development of bronchoconstriction in animals. Sensitization of animals disturbs interneuronal and, in particular, inhibitory interactions in the intramural ganglia of the respiratory tract.

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