ACTION OF SOME PHARMACOLOGICAL AGENTS ON RECEPTORS OF THE LUNGS

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UDC 612.285.1.014.46

Experiments have shown that veratrine, aconitine, nicotine, and ammonium chloride intensify impulse activity from the stretch receptors of the lungs by sensitizing them to adequate mechanical stimulation. The action of serotonin is evidently due to secondary factors.

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It has long been known that intravenous injection of veratrine alkaloids lowers blood pressure and slows the heart [4]. It has been shown [17] that after division of the cardiac and pulmonary branches of the vagus nerves these reactions do not take place. This suggested that this reflex, whose pathway runs along the afferent fibers of the vagus nerves, commences in the reflexogenic zones of the heart [10, 11] and lungs. However, participation of the heart receptors in these responses was not definitely proved until 1947 [7].

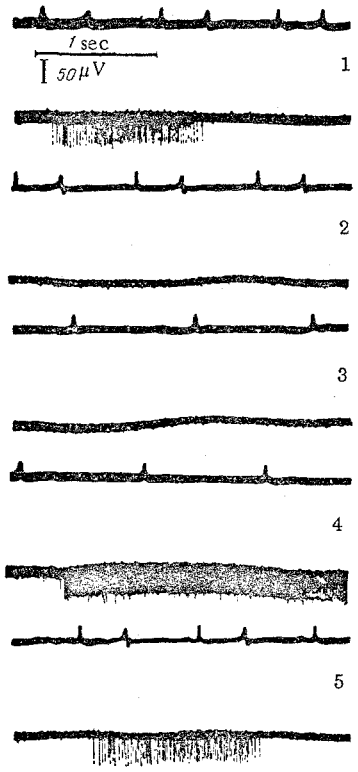

Fig. 1. Effect of veratrine on afferent impulse activity from receptors of the lungs. 1) Background impulse activity; 2) respiration excluded; 3) impulse activity 10 sec after injection of veratrine; 4) respiration resumed; 5) impulse activity 35 min after injection of veratrine.

So far as the lung receptors are concerned, definite experimental proof of their participation in the above-mentioned reflexes on respiration and the blood pressure was obtained by V. V. Zakusov in 1938 [2]. Since a conclusive solution to this problem could be obtained only by the direct action of poisons on the lung vessels, these workers developed a special method of perfusion of a single lobe of the lung with insufflation of oxygen into it. As a result of these investigations it was found that during the action of veratrine, aconitine, and nicotine on the lung receptors, the amplitude of respiration was diminished and its rate increased, and sometimes the complete arrest of respiratory movements was observed. Simultaneously the blood pressure was lowered. If both vagus nerves were divided in the neck before injection of the chemical stimuli, the reflex action of respiration and the circulation from the pulmonary vessels did not develop.

The present investigation is a continuation of these studies using electrophysiological methods. Our object was to discover which receptors of the lungs are sensitive to chemical stimuli and to identify the mechanism of action of pharmacological substances on the receptors of the lungs.

EXPERIMENTAL METHOD

Experiments were carried out on cats weighing from 2.5-4 kg, anesthetized with urethane (600 mg/kg, intravenously) and chloralose (40 mg/kg, intravenously).

The bioelectrical activity of the lung receptors was studied by electrographic recording of impulses in fibers of the vagus nerves. The pulmonary fibers were isolated and identified by Widdicombe's

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method [16], as follows. The skin was divided in the midline of the neck from the larynx downward by an incision 7-9 cm long. The operation field was flooded with physiological saline warmed to 38°. The left vagus nerve was isolated from the neurovascular bundle and freed from its connective-tissue coverings. A bundle of fibers was separated from the nerve trunk and split up into 5 or 6 branches. Bipolar platinum electrodes were placed under each branch in turn. Impulses were recorded by means of an electromyograph (Disa Electronic). If volleys of impulses synchronized with respiration were recorded in a bundle, the branch was divided still further until only one or two functioning fibers with the respiratory rhythm remained. The branch was then divided below the ganglion nodosum. After removal of the physiological saline by suction, the operation field was flooded with liquid mineral oil warmed to 38°. The correct choice of fibers was verified by mechanical stimulation of the surface of the lung with a glass rod and simultaneous recording of electrical activity of the fibers.

One channel of the instrument was used to record the ECG, usually in standard lead 2.

The action of veratrine (25-50 μg/kg), serotonin (50-120 μg/kg), aconitine (10^{-5}), nicotine (10^{-3}), and ammonium chloride (50 mg) was investigated. To avoid tachyphylaxis, the substances were administered at intervals of 30 min. Depending on the experimental conditions, the substances listed above were injected into the femoral vein, the chamber of the right ventricle, or the lobar artery.

EXPERIMENTAL RESULTS

The experimental results showed that veratrine, aconitine, nicotine, and ammonium chloride intensify the high-amplitude impulse activity flowing from the stretch receptors of the lungs. The adequate stimulus for these receptors is distension of the lungs. It will be noted that an increase in activity of these receptors under the influence of chemical stimulation took place only against the background of the action of an adequate stimulus. If these substances were injected when respiration was stopped in the stage of expiration, no high-amplitude impulse activity was recorded in the fibers (Fig. 1). This fact suggests that the chemical stimuli sensitize the stretch receptors of the lungs to adequate mechanical stimulation, in agreement with earlier results obtained in our laboratory [1].

Changes in the activity of the stretch receptors caused by the action of serotonin were somewhat different in character. Our experiments showed that in some cases serotonin intensified the background impulse activity but in others diminished it. This suggests that serotonin had no direct effect on the stretch receptors of the lungs. It is, in fact, difficult to imagine that the same substances, in equal doses, in some cases could cause excitation (or sensitization), and in others inhibition (or desensitization) of the same structures. It would be more logical to suggest that the action of serotonin on the stretch receptors of the lungs is due to secondary factors. Serotonin is known to cause spasm of the smooth muscle of the bronchi [6, 8, 9, 12]. This effect of serotonin can be attributed to changes in the afferent impulse activity flowing from the lungs [16].

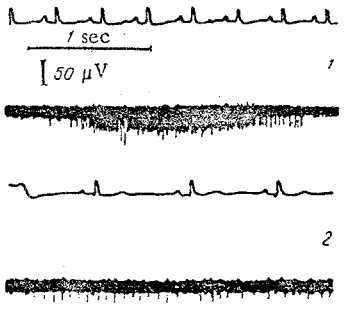

Fig. 2. Effect of serotonin on afferent impulse activity flowing from receptors of the lungs. 1) Background impulse activity; 2) impulse activity 10 sec after injection of serotonin.

The intensity of impulse activity was in fact directly proportional to the degree of stretching of the lungs. The greater the respiratory volume of the lungs, the more intensive the afferent impulse activity during inspiration, because of an increase in the lumen of the bronchi. If, therefore, spasm of the bronchi occurred at the height of inspiration, when the alveoli were fully distended, the impulse activity was increased but if, on the other hand, spasm arose at the end of expiration, the impulse activity was diminished.

This was confirmed by our series of experiments in which changes in activity of the stretch receptors under the influence of serotonin did not take place after preliminary injection of substances lowering the tone of the smooth muscle of the bronchi, such as adrenalin or ephedrine, a result also in agreement with our earlier findings [1]. Other evidence in support of this hypothesis is the fact that tipindole, a selective serotonin antagonist in relation to nervous structures [3], does not abolish this effect of serotonin. In addition, we know from the literature that serotonin does not modify the activity of the pulmonary stretch receptors in animals whose bronchial musculature is insensitive to this substance [5, 15]. It may thus be considered that serotonin

has no direct action on the stretch receptors of the lungs.

We showed in a series of experiments that after injection of veratrine, nicotine and, in particular, serotonin and phenyldiguanidine into the fibers of the lung receptors, low-amplitude, slow impulse activity appeared (Fig. 2). It may be recorded either in the presence or in the absence of an adequate stimulus of the stretch receptors, i. e., of respiration. The nature of this impulse activity is not clear. It may possibly be caused by excitation of special receptors sensitive to chemical stimuli.

The sources of this impulse activity may be receptors excited by collapse of the lungs, if such exist [13, 14]. It may also be considered that the low-amplitude impulse activity is the result of a specific response of the mechanoreceptors to an inadequate stimulus.

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