THE SELECTIVE ACTION OF CERTAIN CHEMICAL STIMULANTS ON REFLEXES FROM CHEMORECEPTORS

COMMUNICATION 7. THE POINT OF ACTION OF STREPTOMYCIN IN THE INTEROCEPTIVE REFLEX ARC

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In previous reports [2, 3, 5, 6, 7, 8] it was shown that streptomycin, injected intramuscularly or intravenously, or into the subarachnoid space, shows a depressing action on unconditioned reflexes from chemoreceptors. This result was obtained in experiments on both narcotized and nonnarcotized animals and from the study of various effectors of reflex arcs.

Different results were obtained from experiments to study the resistance of reflexes arising from stimulation of mechanoreceptors and peripheral nerves to streptomycin, mainly afferent pathways from exteroceptors in the skin. In some experiments these reflexes were quite unchanged, in others they were increased, and in only a small number of experiments were they diminished, and then less so than in parallel experiments performed on the chemoreceptors.

In view of these findings it was necessary to determine the point of action of streptomycin in the interoceptive reflex arc.

Some idea of this might be gathered from certain observations made in the previous reports. In vew of the fact that in the majority of parallel experiments on the effect of streptomycin on reflexes from chemoreceptors and reflexes from mechanoreceptors, the latter were not depressed, it may be thought that the efferent part of the reflex arc was not exposed to the depressing action of streptomycin. For a final solution of this problem special experiments were carried out.

EXPERIMENTAL METHOD AND RESULTS

Usually we judge the effect of streptomycin on the interoceptive reflexes by changes in the magnitude of the vasomotor reactions. These reactions are known to be effected through the sympathetic and parasympathetic division of the autonomic nervous system and also by means of the secretion of adrenalin by the adrenal glands. For this reason, in the first series of experiments on 8 cats we studied the effect of streptomycin on the sympathetic division of the autonomic nervous system.

According to the investigations of G. V. Anrep [1], stimulation of the peripheral section of the celiac nerve by an electric current leads to a biphasic rise in the blood pressure. The first phase proceeds rapidly and is the result of direct contraction of the vessels in the region innervated by the celiac nerve; the second phase, producing a smaller and slower increase in pressure, depends on the secretion of adrenalin from the adrenal glands into the blood stream. Thus on this experimental model it is possible to determine the effect of the test substance on both the nervous and humoral routes of transmission of the stimulus from the sympathetic nerve to the vascular system.

In an acute experiment using urethane narcosis, the peripheral section of the celiac nerve was stimulated with an electric current from an induction coil before and at various times after the intramuscular injection of streptomycin (100,000–300,000 units). As a record of the effect we measured the blood pressure in the common carotid artery, which was registered.

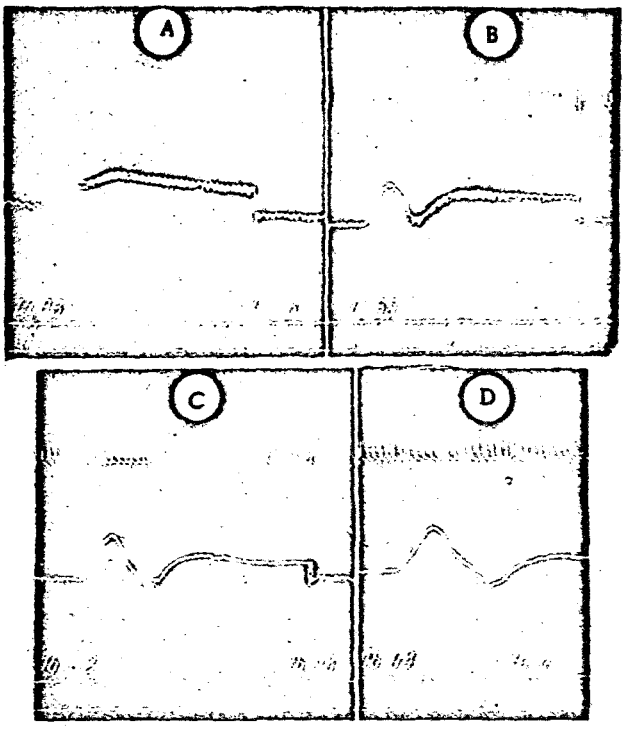

Fig. 1. The Influence of streptomycin on the effect of stimulation of the peripheral section of the celiac nerve.

A) Normal basis; B, C, D) the effect of stimulation of the celiac nerve at different intervals after injection of streptomycin (given in 15 hours 18 minutes in a dose of 250,000 units). Interpretation of the curves (from above downwards): respiration, blood pressure, time record (5 seconds), record of stimulation.
Experiment No. 22 dated September 5, 1953. Cat weighing 3.9 kg.

The reaction developing in response to stimulation of the nerve varied in its character. In some observations, immediately after the beginning of stimulation of the celiac nerve the arterial pressure gradually rose, then fell slightly and remained at a high level for a considerable time (evidently as a result of the reaction of the adrenal glands, secreting adrenalin). In these experiments streptomycin did not change the magnitude of the vasomotor reaction (Fig. 1). In another group of experiments in response to stimulation of the celiac nerve there arose a monophasic increase in the level of the arterial blood pressure, which was much briefer than in the previous experiments. In these cases also injection of streptomycin had practically no effect on the character and magnitude of the blood pressure reaction to stimulation of the celiac nerve.

Thus the results of the experiments showed that streptomycin has no action on the sympathetic division of the nervous system.

In the second series of experiments on 11 cats we studied the action of streptomycin on the parasympathetic division of the autonomic nervous system. The subject of the experiments was the heart.

The experiments were performed under urethane narcosis. Both vagus nerves were divided and the peripheral section of one of them was stimulated by an electric current from an induction coil before and at various intervals

after the intramuscular injection of streptomycin (150,000-250,000 units). The effect was judged by the blood pressure recorded in the common carotid artery. In ordinary conditions in response to a short (5-10 seconds) stimulation of the peripheral end of the vagus nerve there arose a considerable and rapidly developing reduction in the arterial pressure, accompanied by a marked slowing of the tachycardia (vagus pulse).

In 7 experiments the reaction of the heart to stimulation of the vagus nerve under the influence of streptomycin was unchanged or else showed an extremely slight reduction, not more than by 12-18 %, which hardly exceeded the limits of variation of this reaction as observed in control experiments.

In the remaining 4 experiments under the influence of streptomycin a partial blockade could be observed in the transmission of the stimulus from the vagus nerve to the heart. The size of the reaction of the arterial pressure in these experiments was reduced by 32-40 %. It is very probable that this effect is due to the presence of some affinity of the antibiotic to the parasympathetic division of the nervous system, although not often apparent. Analysis of the results of these observations, in comparison with those obtained earlier, suggests that the blocking action of the antibiotic on reflexes from chemoreceptors is concerned least of all with its influence on the efferent part of the reflex arc. We are left with the assumption that it depends on the action of streptomycin on the afferent part of this arc.

Direct action of streptomycin on the receptors is excluded by the conditions of the experiment. (perfusion of the organ). The possibility is also excluded of the influence of streptomycin on the peripheral conductors of the impulses from the tissue receptors to the central nervous system, since in a third, special series of experiments, also performed on cats, it was proved that the antibiotic blocks the conduction of impulses along the nerve only in unusually high concentration (20,000 units/ ml and above), which does not occur in these animals.

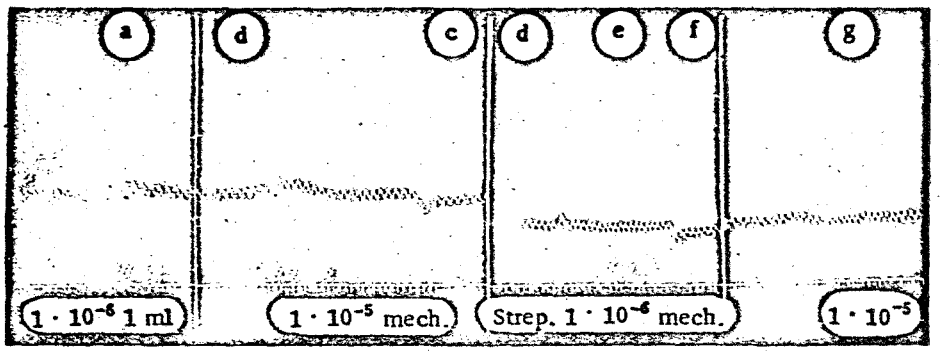

Fig. 2. The influence of streptomycin on reflexes from the chemoreceptors of the pericardium in the decerebrate cat.
a,b, c) Initial reflexes; d) injection of streptomycin (1000 units); e, g) depression of reflexes from chemoreceptors after injection of streptomycin; f) reflex from mechanoreceptors (in contrast to the reflexes from the chemoreceptors this is unchanged). Interpretation of the curves as in Fig. 1. Experiment No. 437 dated September 23, 1955. Cat weighing 3.5 kg.

Consequently, from our observations the selective depressive action on reflexes from chemoreceptors is connected with the action of streptomycin on the central section of the afferent part of the interoceptive reflex arc. In an attempt to localize this section, in the first place we excluded the cortical end of the internal analysor since the majority of the experiments were conducted on animals under narcosis.

Previously published experiments [2] showed that section of the brain at the level of the corpora quadragemina does not affect this described depressive action of streptomycin. This suggests that the point of action of streptomycin is situated either in the pons and medulla or in the spinal cord. The results of the fourth series of experiments made it possible to define precisely the section of the central nervous system.

Experiments were performed on cats, whose brains were sectioned under ether narcosis at a level between the anterior and posterior corpora quadragemina. Using the method described earlier reflexes were produced from the pericardium of these animals, from the chemoreceptors (to nicotine) and from the mechanoreceptors (to the rapid introduction of warm physiological saline into the pericardial cavity). To judge the effect we recorded the blood

pressure and respiration (of 19 animals undergoing this form of operation, 6 survived). Streptomycin was injected intravenously in a dose of 90,000-100,000 units.

In 4 experiments the influence of streptomycin was studied on the reflex produced by nicotine in a dilution of $1 \cdot 10^{-6}$. In three of these, under the action of the antibiotic the reflex completely disappeared, while in one experiment it was diminished by 75 %. The reflex to nicotine in a dilution of $1 \cdot 10^{-5}$ was completely suppressed in two out of 4 experiments, in the third it was reduced by 85 % and in the fourth, by 63 %.

In contrast to the experiments on intact animals, in this series of experiments the reflexes from the mechanoreceptors were diminished in 5 out of 6 experiments under the influence of streptomycin, in two by 20 %, in two more by 30-33 % and in one by 50 %; in only one experiment were these reflexes unchanged. However in experiments on decerebrated animals also it was clearly shown that the resistance of the reflexes from the chemoreceptors of the pericardium to the action of streptomycin was incomparably smaller than the resistance of the reflexes from the mechanoreceptors of the pericardium (Fig. 2).

The experiments described above exclude the possible action of the antibiotic on the region of the spinal cord since the afferent conducting pathways from the pericardium for the most part pass through the spinal cord directly into the medulla [4, 9, 10, 11].

The following observations, made previously [5, 6, 7, 8] lead us to the same conclusion: the antibiotic (in experiments on narcotized animals) suppresses equally the reflexes from the chemoreceptors of the kidneys, spleen, intestine and hind limbs, the afferent pathways from which lead through the spinal cord, and the reflexes from the chemoreceptors of the pericardium, the lesser ciruclation and the carotid sinus, the afferent pathways from which for the most part pass directly to the medulla, passing through the spinal cord.

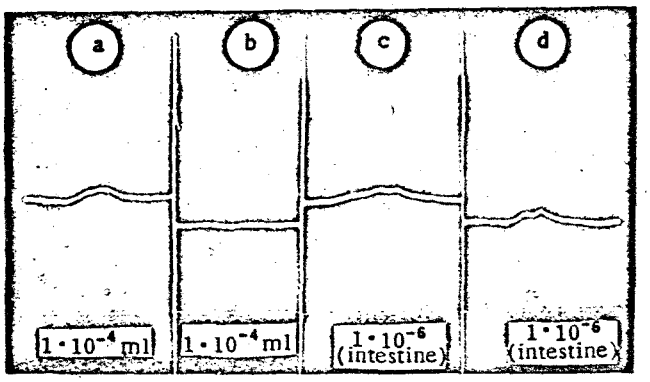

Fig. 3. The influence of exclusion by streptomycin of the chemoreceptors of the spleen on the excitability of the chemoreceptors of the small intestine.
a) Initial reflex from the chemoreceptors of the spleen; b) total suppression of excitability of the chemoreceptors of the spleen resulting from perfusion with a solution containing streptomycin (1000 units/ min); c) initial reflex from the chemoreceptors of the small intestine; d) reflex from the chemoreceptors of the intestine at the moment of suppression of the chemoreceptors of the spleen (not diminished in size). Interpretation of the curves as in Fig. 1 and 2. Experiment No. 241 dated November 25th, 1954. Cat weighing 2.9 kg.

It therefore follows from our experiments that streptomycin, injected parenterally, depresses reflexes from chemoreceptors by means of a blockading action in the bulbar intermediate centers of the conducting part of the internal chemical analysor. More accurate determination of the point of action of streptomycin in the interoceptive reflex arc was found to be impossible by experimental methods available to us.

In connection with the conclusions which we reached, the question arose of the nature of the influence shown by streptomycin on the above mentioned section of the interoceptive reflex arc. This could be a side effect, brought

about by the depressive action of the drug on the tissue receptors with which the antibiotic came into contact during parenteral injection into the animal (earlier the possibility of streptomycin lowering the excitability of the chemoreceptors by direct contact with the drug was shown — 3, 5, 6). However, against this view was first of all the fact that in experiments to study the influence of streptomycin (by parenteral injection) on reflexes from chemoreceptors of the same or other "test organs" conditions could not possibly arise for an essential lowering of the excitability of all the chemoreceptors of the internal environment of the animal (with the doses of streptomycin used the maximum concentration of antibiotic in the blood did not exceed 50-150 units/ml, and for depression of chemoreceptors by direct action of the drug on them a concentration of 400-1666 units/ml is required).

In order to check this possible side action of streptomycin we performed a fifth series of experiments on 19 cats in which we simultaneously perfused (by the usual method) two reflexogenic zones (the intestine and spleen). All forms of receptor in one of these zones were excluded (by novocain) or else only the chemoreceptors (by direct action of streptomycin on them), and we watched to see whether this resulted in any inhibition of reflexes from the chemoreceptors of the other reflexogenic zone, not subjected to the action of streptomycin. If exclusion of the receptors of one of the perfused organs did in fact cause reflex inhibition of the central elements of the internal chemical analysor, then the blood pressure and respiration reactions in response to stimulation of the second reflexogenic zone would be considerably reduced, but this did not occur in the majority of our experiments (Fig. 3). Nor was the threshold of excitation of the chemoreceptors of the second organ altered, not subjected to the action of the antibiotic; only in a very small number of experiments (less than one third) was there any reduction in the magnitude of the reflexes from the chemoreceptors of the second reflexogenic zone.

Finally, experiments in which minimal doses of the antibiotic were injected suboccipitally, published earlier by us [8], excluding the factor which we have discussed, enabled us finally to discount the idea of a side action of streptomycin on reflexes from chemoreceptors.

Consequently, an experimental analysis of the mechanism of depression by streptomycin of the reflexes from the chemoreceptors had enabled us to prove that on parenteral injection, the drug shows a direct blockading effect on the bulbar intermediate center of the conducting section of the internal chemical analysor.

SUMMARY

It was established in acute experiments on cats that streptomycin has practically no sympatholytic adrenolytic or parasympatholytic effect in doses which depress the reflexes from chemoceptors. It was, likewise demonstrated that streptomycin disturbs the transmission of the impulse by the nerve only in high concentration. If chemoceptors of one zone are excluded by streptomycin (in its direct contact with receptors of this zone), excitability of chemoceptors of the other zone, as a rule, remain normal. Finally, it was shown that in parenteral administration streptomycin depresses the reflexes from the chemoceptors of the pericardium in brain section at the level of corpora quadrigemina. These observations, together with the data which were published in previous reports and evidence obtained from literature on the paths of transmission from the receptors of various reflexogenic zones of internal organs permit the following conclusion — the places of application of depressing effect of streptomycin in chemoceptor reflex arc are the bulbar intermediate centers of the transmissive portion of the interoceptive chemical analysor.

LITERATURE CITED

[1] G. V. Anrep, Proceedings of the Society of Russian Doctors in St. Petersburg, 1913, vol. 80, pp. 54-71.

[2] I. E. Gaber, Study of the Role of the Nervous System in the Pathogenesis and Treatment of Tuberculosis,* Leningrad, 1954, pp. 320-329.

[3] I. E. Gaber and G. S. Kan, Biull. Eksptl. Biol. i Med. No. 9, 48-53 (1953).

[4] A. M. Grinshtein, Pathways and Centers of the Nervous System,* Moscow, 1946.

[5] G. S. Kan, Proceedings of the 2nd All-Union Conference of Pathophysiologists,* Kiev, 1956, pp. 154-156.

[6] G. S. Kan, Antibiotics,* Moscow, 1956, pp. 76-80.

[7] G. S. Kan, Biull. Eksptl. Biol. i Med. No. 5, 40-43, (1956).*

[8] G. S. Kan, Biull. Eksptl. Biol. i Med. No. 6, (1957).**

* In Russian.

** See C. B. Translation.

[9] A. A. Nikitin, Dystrophic Changes in the Organs and Tissues After Trauma to the Spinal Ganglia,* Candidate's Dissertation, Leningrad, 1947.

[10] V. N. Chernigovskii, Trudy Voenno-morsk. Med. Akad. vol. 17, 395, Leningrad (1949).

[11] J. T. Irving, B. A. McSwiney and S. F. Suffolk, J. of Physiol. 1937, v. 89, p. 407-419.

* In Russian.