

THE SELECTIVE EFFECT OF SOME CHEMICAL STIMULI ON REFLEXES FROM CHEMORECEPTORS

COMMUNICATION VI. THE EFFECT OF STREPTOMYCIN ON REFLEXES FROM SPLEEN, KIDNEY AND HIND LIMB CHEMORECEPTORS

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In the earlier publications from this laboratory [1, 2, 3, 4] it was shown that streptomycin, given parenterally, had the ability to cause profound depression of reflexes from the small intestine and carotid sinus chemoreceptors. On the other hand, reflexes arising upon stimulation of the urinary bladder mechanoreceptors and those of the central portion of the tibial nerve proved to be very resistant to the inhibitory effect of the antibiotic.

The present communication presents data of further studies on the effect of streptomycin on interoceptive reflexes from the spleen, kidney and the hind limb.

EXPERIMENTAL METHODS

Experiments were performed on cats under urethane anesthesia. Stimulation of the spleen, kidney and hind limb chemoreceptors was achieved in the following way. The organ was subjected to vascular isolation by the V. N. Chernigovskii technique; the organ then derived its nutrition from oxygenated Tyrode solution. The isolated organ preserved its connection with the organism only by means of its nerves. Acetylcholine or carbon dioxide was then added to the perfusion fluid, thus achieving stimulation of the chemoreceptors.

In some of the cases the tibial nerve was simultaneously exposed in the lower third of the shank (in experiments with perfusion of the lower limb the nerve was exposed on the side of vascular isolation) which was then subjected to induction current stimulation.

Streptomycin (the sulfate or calcium chloride complex) was injected intramuscularly or intravenously after the initial background of chemoreceptor excitability had been established. At different intervals after injection of the antibiotic the reflexes from chemoreceptors were again reproduced, and in a number of cases this applied also to reflexes arising from stimulation of the tibial nerve.

EXPERIMENTAL RESULTS

Effect of streptomycin on reflexes from spleen chemoreceptors. In 7 control experiments it was established that the excitability of chemoreceptors in perfused spleen with respect to the stimuli used was sufficiently high and that it was maintained without appreciable changes for as long as 1½-3 hours during which observations were made.

The effect of streptomycin on reflexes from the spleen chemoreceptors was studied in 17 experiments. The antibiotic was given intramuscularly: in 3 experiments in doses of 250,000 units, in 9 experiments in doses of 350,000 units and in two experiments in doses of 500,000 units. In 3 experiments streptomycin was injected into the femoral vein in doses of 36,000, 60,000 and 100,000 units.

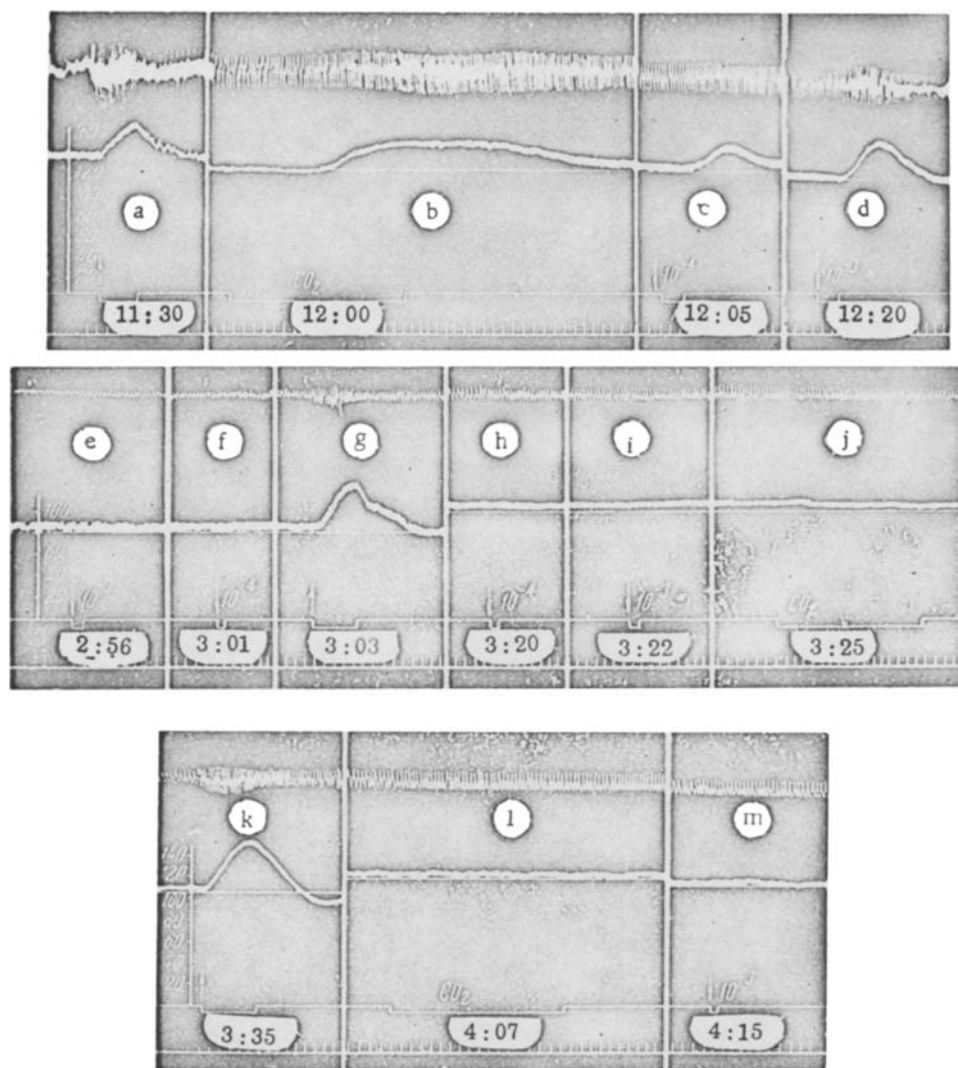


Fig. 1. Effect of streptomycin on reflexes from chemoreceptors in perfused spleen and tibial nerve.

a), b), c), d), e) Initial reflexes from the tibial nerve and spleen chemoreceptors (to various stimuli); **f), g), h), j), k), l), m), o), p)** reflexes from the spleen chemoreceptors after administration of streptomycin (injected at 12:25 intramuscularly in the dose of 350,000 units and at 2:45 intravenously in the dose of 100,000 units); **i), n)** reflex from the tibial nerve after administration of streptomycin (increased by 48 and 63%). Records from above down; respiration, blood pressure, base line, stimulus mark, time marker (5 seconds); \uparrow - stimulation of the tibial nerve; \downarrow - acetylcholine injection. Experiment 189, May 20, 1954. Cat weighing 3.2 kg.

In all the experiments the magnitude of the reflex from spleen chemoreceptors to acetylcholine in dilution 1×10^{-4} (1 ml) was diminished under the influence of streptomycin. In most cases (9 out of 13) the reflex to acetylcholine proved to be either completely inhibited or inverted, i.e., depressor instead of pressor; the reflex was reduced by 87% in one case, by 33-44% in three cases.

The excitability of the spleen chemoreceptors with respect to acetylcholine (1×10^{-4}) proved to be reduced in most experiments as soon as 10-40 minutes after administration of the antibiotic; this was observed in 11 out of 13 cases. Maximal inhibition of the reflex to acetylcholine in the majority of experiments (9 out

of 13) occurred within the first hour following intramuscular injection of the antibiotic. Intravenous injection of the antibiotic inhibited the reflexes more rapidly. In these cases the described effect appeared when minimal doses of streptomycin (60,000-100,000 units per cat) were used.

The effect of streptomycin on reflexes elicited by acetylcholine in 1×10^{-3} dilution (1 ml) was studied in 15 experiments. The reflex to acetylcholine was reduced in most cases (13 out of 15) under the influence of streptomycin. In 6 experiments it disappeared completely, in 2 it was reduced by 75-76%, in another 2 by 50-58% and in 3 by 40-45%. Maximal inhibition of the reflex to acetylcholine (1×10^{-3}) following intramuscular administration of the antibiotic occurred in most cases within the first or second hour, and in the course of 2-2½ hours in the remainder.

In 15 other experiments a study was made of the effect of streptomycin on reflexes from the spleen chemoreceptors to carbon dioxide. In 9 cases the reflex disappeared completely or underwent inversion on injection of the antibiotic, decreased considerably in 4 (by 52-75%), decreased by only 13% in one and was unchanged in one case only. Maximal inhibition of the reflex to carbon dioxide following intramuscular injection of the antibiotic was observed during the first or second hour in 9 experiments. Inhibition of the reflex was more rapid when the preparation was injected intravenously.

Finally, in 7 experiments of this series a parallel study was made of the excitability of the spleen chemoreceptors to one or another stimulus and of reflexes elicited by electric current stimulation of the tibial nerve. In 4 experiments the reflex from the tibial nerve was decreased, but only slightly, under the influence of streptomycin. Maximal reduction of the reflex was by 6.14 and 20%, and only in a single case did it reach 60%. In 3 experiments the reflex was, on the contrary, increased (by 19, 42 and 63%).

Parenterally administered streptomycin thus exerts a marked inhibitory effect on reflexes from the chemoreceptors of perfused spleen connected with the organism by nerves only. Unlike the spleen chemoreceptor reflexes, those from the tibial nerve either increased or decreased, although usually to a considerably lesser extent, under the influence of streptomycin (Fig. 1). It follows from these data that the tibial nerve reflex is more resistant to the action of the antibiotic than the reflexes from the spleen chemoreceptors. Detailed analysis of the data obtained revealed that reflexes from chemoreceptors were inhibited to a much greater degree than reflexes from the nerve; this held true for those cases in which the initial magnitude of these reflexes was the same.

Stimulation of the spleen chemoreceptors led, in a number of cases, to changes in respiration. Streptomycin as a rule inhibited not only the vasomotor but also the respiratory component of the reflex from these chemoreceptors.

The effect of streptomycin on reflexes from kidney chemoreceptors. This effect was studied in 9 experiments. The antibiotic was given intramuscularly in 2 cases in doses of 300,000-400,000 units, intravenously in seven in doses of 70,000-200,000 units.

In 2 experiments nicotine in 1×10^{-6} dilution served as stimulus for renal chemoreceptors. Under the influence of streptomycin the reflex diminished by 75% in one case and was completely inhibited in the second.

In 4 experiments nicotine in 1×10^{-5} dilution was used as stimulus for renal chemoreceptors. Under the influence of streptomycin the reflex to nicotine diminished by 50% in one case, by 80% in another and in the remainder it was completely suppressed.

The effect of streptomycin on reflexes from renal chemoreceptors to nicotine in 1×10^{-4} dilution was studied in 2 experiments. In one case the reflex was reduced by 88%, in the other it disappeared completely.

The effect of streptomycin on reflexes elicited by 1×10^{-3} dilution of nicotine was studied in 3 experiments. In 2 cases the reflexes disappeared completely under the influence of the antibiotic and in one case there was 92% reduction.

Maximal inhibition of reflexes from renal chemoreceptors to the stimuli mentioned above appeared within 40 minutes - 1½ hours when streptomycin was given intramuscularly and after 20-40 minutes when it was given intravenously.

In 2 experiments the threshold of the vascular reflex to stimulation of the tibial nerve was determined during the period of inhibition of reflexes from the renal chemoreceptors; the threshold proved to be equal to 16 cm in

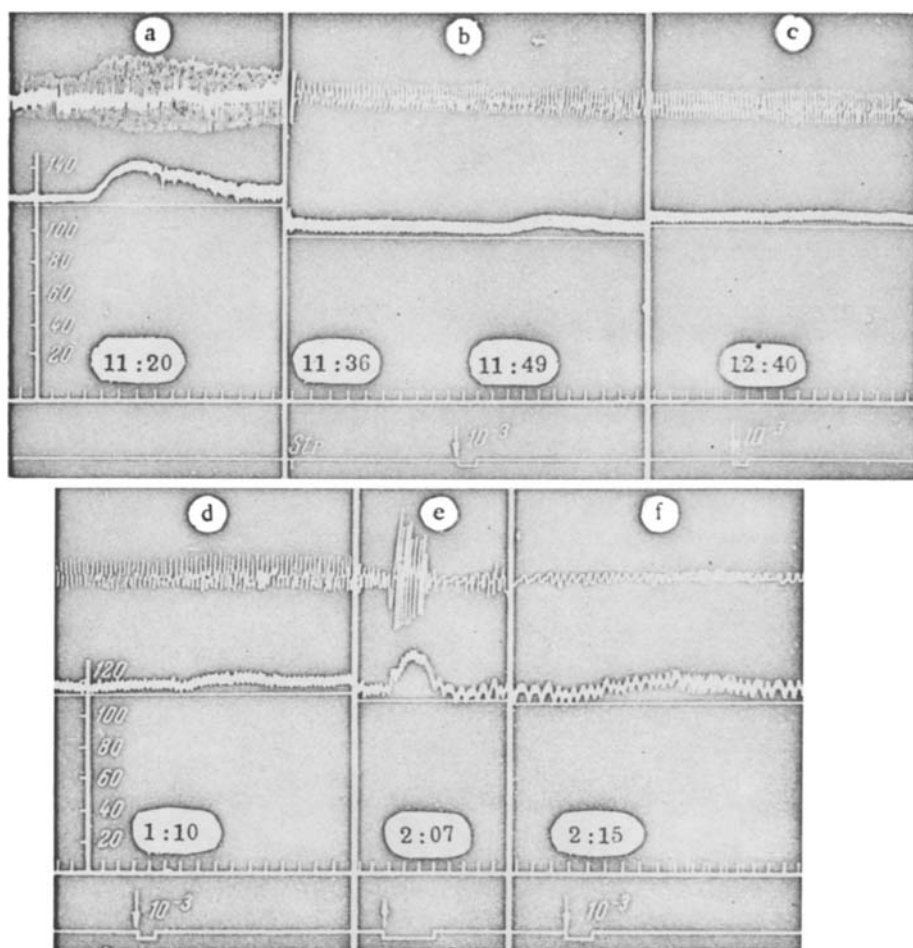


Fig. 2. Effect of streptomycin on reflexes from perfused kidney. a) Initial reflex; b), c), d), f) after administration of streptomycin (intravenous injection at 11:36 in the dose of 100,000 units); g) reflex to stimulation of tibial nerve. Records from above down: respiration, blood pressure, base line, time marker (5 seconds), stimulus mark, \uparrow - stimulation of tibial nerve; \downarrow - acetylcholine injection. Experiment 419, September 2, 1955. Cat weighing 2.8 kg.

one experiment and 15 cm in another (in control experiments the threshold was 14 and 17 cm respectively). These data indicate preservation of high excitability of the vasomotor center against the background of depression of reflexes from renal chemoreceptors (Fig. 2).

The respiratory reflex arising from stimulation of chemoreceptors was depressed to the same extent as the vasomotor reflex under the influence of streptomycin.

Effect of streptomycin on reflexes from tissue chemoreceptors of the hind limb. It was established in 5 preliminary control experiments that the magnitude and character of reflexes from tissue chemoreceptors of the limb remained substantially unaltered throughout 2-4 hours of observation when they were subjected to repeated action of the stimuli used (acetylcholine and tuberculin); the same was true for reflexes from the tibial nerve.

The effect of streptomycin on reflexes from the chemoreceptors of the limb elicited by acetylcholine in 1×10^{-3} and 1×10^{-4} dilution was studied in 13 experiments. In all experiments without exception the effect of the antibiotic was to depress the reflexes to acetylcholine (by an average of 79.5%). In 4 experiments the reflex to acetylcholine disappeared entirely or was inverted; in 5, depression of reflexes by more than 75% was observed, in two, by 50% and over, in two others by 40 and 36%. Depression of reflexes to acetylcholine became

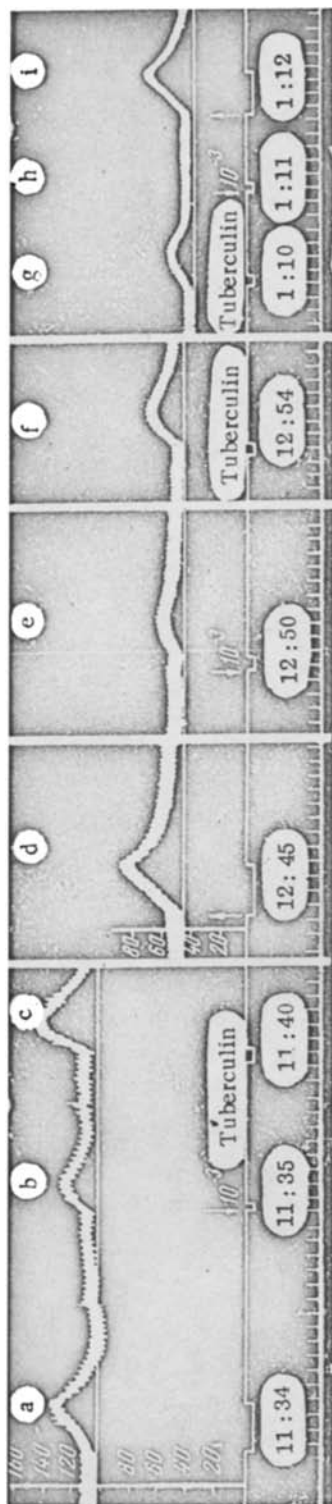


Fig. 3. Effect of streptomycin on reflexes from chemoreceptors and tibial nerve of perfused limb. a), b), c) Initial reflexes; e), f), g), h) reflexes from chemoreceptors after administration of streptomycin (intramuscular injection at 11:43 in the dose of 500,000 units); d), i) tibial nerve reflexes. Records from above down: blood pressure, base line, stimulus mark, time marker (5 seconds). Experiment 116, January 5, 1954. Cat weighing 3.6 kg.

maximally apparent during the first hour in 6 cases and during the second hour following administration of the antibiotic in the remainder.

In all the 13 experiments the effect of streptomycin on the magnitude of reflexes from the tibial nerve of the perfused limb was also studied. In 4 experiments the reflex from the nerve diminished by 20-30%, in 3 by 36-40%, in 5 by 41-76%; in one experiment the reflex increased. Maximal depression of the reflex from the tibial nerve was noted after 20-60 minutes in 4 experiments, in the remainder after 1-2 hours following administration of the antibiotic. It must, however, be pointed out that the reflex from the tibial nerve was not depressed by streptomycin consistently and far from every time the stimulus was applied. The reflex referred to was diminished in 29 out of 44 tests. In seven of these observations the diminution of the reflex was extremely slight (less than 15%). Unlike this, the reflex from the limb chemoreceptors to acetylcholine after administration of streptomycin proved to be diminished in the overwhelming majority of cases (46 out of 49), slight diminution (less than 15%) being noted in only 7 of 46 cases.

It must also be pointed out that in 7 out of 13 experiments with perfusion of the limb, no changes in the reflexes from the tibial nerve were noted during the first phase of the antibiotic's action while in the remainder the reflex even showed an increase of 5-39%, a phenomenon not observed in the study of reflexes elicited by acetylcholine.

Finally, comparison of the effect of streptomycin on reflexes from the tibial nerve and to stimulation of chemoreceptors by acetylcholine applied to each experiment showed that reflexes from chemoreceptors were depressed much more rapidly and to an immensely larger extent (Fig. 3). Analysis of the whole material revealed that in the main only during the late stages of streptomycin's action, especially when large doses of the antibiotic were used, the profound depression of reflexes to acetylcholine was associated with depression of reflexes from the tibial nerve as well, which did not, however, in a single experiment reach the same level as that observed for chemoreceptors.

The data obtained thus showed that parenteral administration of streptomycin in most cases caused marked weakening or complete depression of reflexes from the chemoreceptors of the spleen, kidney and hind limb. This effect occurred more rapidly when the antibiotic was given intravenously than intramuscularly.

The depression of reflexes from chemoreceptors was persistent and remained for $1\frac{1}{2}$ -2 hours when streptomycin was given intramuscularly; the reflexes began to recover gradually after this period of time. The effect was rather more short-lived when the antibiotic was injected intravenously.

Streptomycin depressed both the vasomotor and the respiratory reflexes arising from stimulation of chemoreceptors.

Unlike the chemoreceptor reflexes, reflexes arising from stimulation of a somatic afferent nerve (tibial) tended to increase or remained unchanged under the influence of streptomycin. In some cases these reflexes were diminished. The latter was observed during later periods and the depression of these reflexes was less marked, being relatively transient and appearing when large doses of streptomycin were used. These data indicated that the excitability of the vasomotor and respiratory centers to afferent impulses from a peripheral somatic nerve did not, in most cases, decrease significantly under the influence of the antibiotic. It must also be stressed that under the experimental conditions employed the antibiotic did not come into direct contact with the tissue chemoreceptors of the spleen, kidneys and the limb from which reflexes to chemical stimuli were elicited. Consequently, both the receptors themselves and the efferent part of the reflex arc were not subjected to the action of streptomycin. It follows from this that the depressing effect of the antibiotic on reflexes from chemoreceptors is associated with its blocking influence on that portion of the afferent part of the reflex arc which is situated within the central nervous system.

SUMMARY

Short-term experiments on cats under urethane anesthesia were performed. The effect of streptomycin introduced parenterally was studied on reflexes from chemoreceptors of the spleen, kidney and hind limb. Chemoreceptors were stimulated by acetylcholine, nicotine and carbon dioxide which were introduced into the fluid perfusing these organs, isolated from the general circulation but connected to the organism by the nerves. It was established that streptomycin in a dose of 60,000 to 200,000 units completely eliminates or markedly depresses the reflexes from chemoreceptors when introduced intramuscularly; the maximal effect of the antibiotic is most frequently seen at the end of the first hour or during the second following the intramuscular injection, and during the first hour after intravenous injection. However, the reflexes which appeared in stimulation of the central portion of the large tibial nerve by induction current in the same experimental conditions were different from the reflexes coming from chemoreceptors. They either did not change at all, or showed only slight increase or decrease. Sometimes these reflexes were subjected to pronounced depression. However, this occurred only when large doses of the antibiotic were used at the late stages of its action and to a lesser degree than the reflexes from the chemoreceptors. The authors come to the conclusion that streptomycin has a marked neurotropic effect, which is manifested in depression of the part of the chemoreceptor reflex arc located in the central nervous system.

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