THE EFFECT OF CHLORTETRACYCLINE ON INTEROCEPTIVE REFLEXES FROM THE INTESTINE

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From a number of clinical observations it appears that chloretetracyline (biomycin), when given internally, sometimes causes undesirable side effects in the form of hyperemia of the mucous membrane of the mouth, nausea, vomiting, diarrhea and other manifestations of irritation of the gastrointestinal tract. The intravenous injection of chlortetracycline is accompanied from time to time by increased intestinal peristalsis, which may be prevented by preliminary injection of ecmolin with novocain [2].

It may be supposed that the irritation phenomena in the gastrointestinal tract after administration of chlortetracycline were associated primarily with stimulation of the interoceptors with which the alimentary tract is abundantly supplied.

N. V. Kaverina, V. M. Khayutin and L. A. Baraz [3] showed that chlortetracycline and certain other antibiotics of the tetracycline group produce well-marked interoceptive reflexes on the arterial blood pressure and respiration when they are introduced into the perfusion fluid of an isolated segment of intestine. These authors, however, studied the transient action of chlortetracycline on interoceptors, by injecting 1-2 ml of a solution of the drug into the perfusion fluid, and under these circumstances they observed a transient rise in the arterial pressure and an increase in the rate of respiration.

Nevertheless, when chlortetracycline is used clinically, it is present in the intestine and blood stream for a longer period of time, and it probably does not merely bring about reflexes affecting the gastrointestinal tract but, like any other chemotherapeutic preparation, it may alter the functional condition of the nervous elements of the intestine.

G. S. Kan [4, 5, 6], and I. É. Gaber and G. S. Kan [1], for instance, showed that large doses of streptomycin, acting for a long time on tissue isolated from the general blood stream, as a rule produced depression of the excitation of the tissue chemoreceptors; the same thing was observed in response to the intramuscular, intravenous and subarachnoid injection of streptomycin.

In the present investigation we studied the changes in the interoceptive reflexes under the influence of the prolonged action of chloretetracycline on the chemoreceptors of the intestine.

EXPERIMENTAL METHOD

Experiments were performed on cats under urethane anesthesia. Using V. N. Chernigovskii's method [7] a segment of the small intestine, 10-20 cm in length, was isolated from the general circulation, while keeping its nervous connections intact. The isolated segment of intestine was perfused through the intestinal artery with Ringer-Locke solution (pH = 7.3-7.5).

In order to determine the state of excitation of the chemoreceptors, 1-2 ml of an acetylcholine solution in dilutions of $1:10^{-4}$, $1:10^{-5}$ and $1:10^{-6}$ was injected into the perfusate, and determinations made of the threshold doses eliciting an obvious reflex in the form of a transient rise in the arterial pressure (from 8 to 20 mm Hg) and of a strengthening and quickening of the respiration (from 13 to 20 per minute). Next, by means of a syringe or from a vessel connected to the perfusion tube, solutions of chlortetracycline in solvents with different salt contents (see below) were injected into the perfusion fluid, the time and volume of the preparation injected being varied.

After the arterial pressure had returned to its original level, acetylcholine in threshold doses was again injected into the perfusion fluid.

The change in the excitation was tested during the 20-60 minutes after the conclusion of the action of the chloretetracycline by means of injection of acetylcholine every 5-10 minutes.

In other experiments the excitation of the chemoreceptors directly to chlortetracycline in threshold doses was determined after the prolonged action of this same antibiotic on the interoceptors in subthreshold and threshold doses.

EXPERIMENTAL RESULTS

In preliminary experiments 1-2 ml of a solution of chloretetracycline hydrochloride in distilled water or Ringer-Locke solution, in a concentration of 1.0-2.5 mg/ml, was injected into the perfusion fluid in order to ascertain the character of the reflexes caused by this irritant and to determine its threshold doses. These solutions had a pH of 5.75-6.0.

In the first place it was found that the injection of 1-2 ml of distilled water or of Ringer-Locke fluid, acidified to pH = 5.75-6.0, did not result in any essential change in the arterial pressure or respiration.

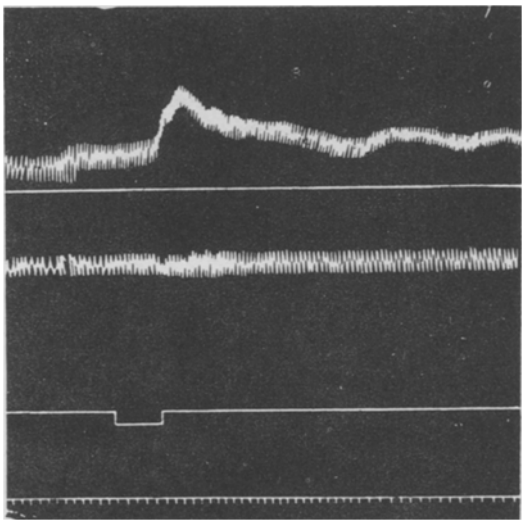

Fig. 1. Reflex in response to the injection of 5 mg chlortetracycline into the vessels of a perfused segment of intestine. Significance of the curves (from above down): arterial pressure in the carotid artery; initial level of the arterial pressure; respiration; stimulus marker; time marker (5 seconds).

In response to the injection of 1-2 ml of chlortetracycline solution in a concentration of 1.0 to 2.5 mg/ml, a reflex increase in the arterial pressure of 5-15 mm Hg was usually observed, and sometimes an increase in the respiration rate of 5-10 oscillations per minute. Such changes in the arterial pressure corresponded, approximately, to the reflex obtained after injection of 1-2 ml of acetylcholine in dilutions of $1:10^{-5}$ and $1:10^{-6}$ (Fig. 1).

The intensity of the reflex to chloretetracycline, just as to acetylcholine, varied in accordance with the individual properties of the animal and its functional condition (depth of anesthesia and so on), but in the same experiment it was almost identical on the repeated injection of these stimuli.

These results confirmed the reports in the literature [2] and showed that the interoceptive reflex produced by chloretetracycline did not depend, in the conditions of our experiment, on the acid reaction of the solution, but were caused by the drug itself.

In the next series of experiments the same solutions of chlortetracycline (1-2 ml in a concentration of 1.0-2.5 mg per ml) were injected several times (from 5 to 20) into the perfusion fluid at intervals of 5-10 minutes, during which time the changed arterial pressure and respiration returned to their initial values.

In 5 of the 6 experiments the reflexes to acetylcholine were decreased to 25% after frequent repetition of the action of chloretetracycline, but the weakening of the reflexes was not lasting. In 3 experiments the reflexes in response to the injection of threshold doses of chlortetracycline were reduced insignificantly.

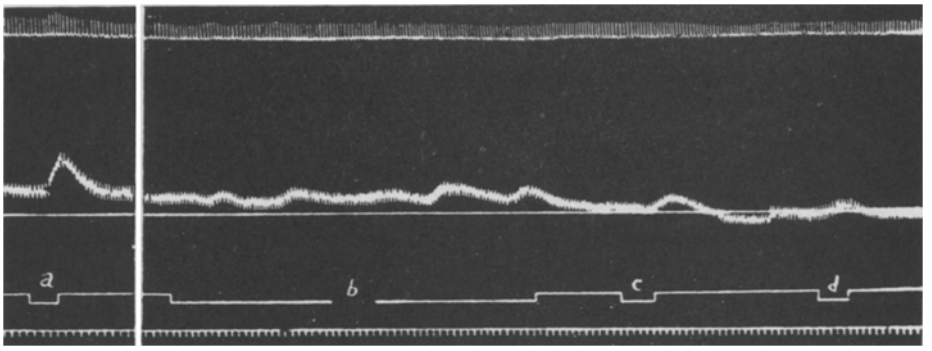

Fig. 2. Weakening of the reflex to acetylcholine after prolonged irrigation with a solution of chlortetracycline. a, c, d) Reflex to injection of 20γ of acetylcholine; b) perfusion with 15 ml of chloretetracycline in a concentration of 9 mg/ml through the vessels of an isolated loop of small intestine for four minutes. Significance of the curves (from above down): respiration, arterial pressure in the carotid artery; initial level of the arterial pressure; stimulus marker; time marker (5 seconds).

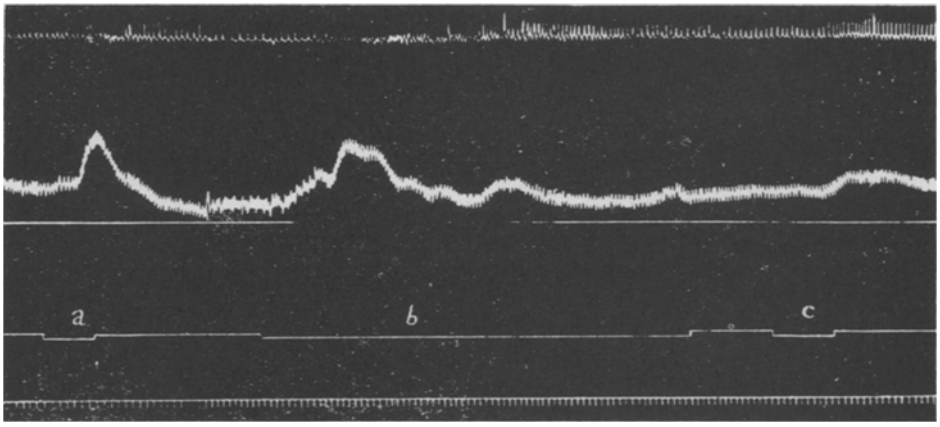

Fig. 3. Weakening of the interoceptive reflex to chlortetracycline in the course of exposure to the drug and after the exposure had ceased. a) Reflex in response to injection of 2 ml of chlortetracycline in a concentration of 9 mg/ml; b) prolonged injection of chlortetracycline in a concentration of 9 mg/ml for a period of 4 minutes 10 seconds; c) reflex to the injection of 2 ml of chlortetracycline in a concentration of 9 mg/ml after the prolonged administration of chlortetracycline. Significance of the curves (from above down): respiration; arterial pressure, initial level of the arterial pressure; stimulus marker; time marker (5 seconds).

Repeated but brief exposures to the action of chlortetracycline were thus capable, to some degree, of depressing the reflexes.

In a third series of experiments the interoceptive reflexes to acetylcholine were investigated after the more prolonged and continuous action of chlortetracyline in the same threshold concentrations.

In this series a preliminary test was made of the interoceptive reflexes to acetylcholine after the prolonged injection of acidified Ringer-Locke solution into the perfusion fluid, since when 3.5-5.0 mg/ml of chlortetracycline was dissolved in it, the pH of the solution became 5.75-6.0, and on attempting to alkalize the solution to the pH of Ringer-Locke solution the chlortetracycline was precipitated.

Other physiological buffer solutions were therefore selected and tested. The most suitable solution in this respect was one which differed from Ringer-Locke solution in that the calcium chloride (capable of precipitating chlortetracycline in a feebly alkaline medium) and the sodium bicarbonate were withdrawn from the latter solution; these two compounds were replaced by the equivalent amount of disodium hydrogen phosphate. Subsequently the potassium chloride was also withdrawn and replaced by the equivalent amount of sodium chloride. On perfusion with this solution for 3-4 minutes, no changes were observed in the reflexes or if there were changes they were insignificant.

In the third series, 16 experiments were carried out using this solution, to study the interoceptive reflexes to acetylcholine before and after the prolonged action of chlortetracycline on the chemoreceptors of the intestine.

Investigation of the reflexes to acetylcholine showed that in 12 of the 16 experiments, after the action of chlortetracycline the reflexes were diminished (Fig. 2). In one experiment the decrease amounted to only 20%, in 10 experiments it was from 33 to 83% and in one experiment the reactions disappeared altogether. In 9 experiments of the same series the action of chlortetracycline was applied 2-3 times in the course of the experiment, and it was found that even in cases where the first application had no effect on the magnitude of the reflexes, the second diminished them by 25-60%. In 3 experiments the second perfusion led to an even greater reduction in the reflexes by comparison with the first perfusion; only in 2 experiments were the reflexes slightly increased after the second perfusion.

In the fourth series of experiments we investigated the changes in the interoceptive reflexes elicited by chlortetracycline, after the drug had been injected over a long period of time into the perfusion system in threshold and slightly higher doses. The experiments were conducted along the same lines as the previous series.

It was found that after injection of chlortetracycline solutions in a concentration of 5-6 mg/ml into the perfusion fluid, in 7 to 10 experiments a diminution in the vascular reflex caused by this drug could first of all be observed, while the drug was still being given. An apparent adaptation to its stimulating action took place while the action was still proceeding (see Fig. 2). This was shown in even greater relief after injection of chlortetracycline in concentrations of about 9 mg/ml. In these experiments it was found also that depression of the excitation of the chemoreceptors by chlortetracycline took place not only in the period of its action but also for a certain interval of time after its administration had ceased and pure Ringer-Locke solution was being perfused (Fig. 3).

Chlortetracycline thus possesses an undoubted stimulating action on the chemoreceptors of the intestine, as a result of which it evokes interoceptive reflexes on the arterial blood pressure and respiration.

Exposure to this antibiotic for short periods of time brings about no changes in the excitation of the chemoreceptors, but after its repeated administration a slight depression of the excitation to acetylcholine is observed, although only to a very feeble degree. In response to the more prolonged, continuous action of the antibiotic, a marked and lasting depression of the interoceptive reflexes caused by acetylcholine takes place, as well as of those caused by chlortetracycline itself (less prolonged in the latter case). Depression of the interoceptive reflex to chlortetracycline appears while the drug is still being given.

Chlortetracycline thus not only causes interoceptive reflexes but also changes the state of excitation of the component parts of the arc of these reflexes and especially, it seems, the chemoreceptors. This is evidently of importance when interpreting the clinical phenomena observed during the administration of chlortetracycline, such as, for example, manifestations of irritation of the gastrointestinal tract and of gradual habituation to the drug.

SUMMARY

Interoceptive reflex action on arterial blood pressure and respiration is caused by chlortetracycline administered for a short time into the perfusion flow of the isolated intestinal section. Its prolonged administration produces a temporary depression of the interoceptive response to acetylcholine and chlortetracycline in the threshold doses.

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