ADAPTATION OF INTEROCEPTIVE REFLEXES FROM INTESTINE TO THE STIMULATING EFFECTS OF TETRACYCLINES

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Adaptation of interoceptive reflexes has been the subject of a number of investigations both in this country and abroad [1-16]. Most authors regard the adaptation of these reflexes as a reaction of adjustment or accomodation.

It was therefore thought of interest to examine adaptation of the reflexes produced by the injection of tetracyclines, as these antibiotics may, when administered clinically, be present in the body for prolonged periods and so may stimulate receptors in various organs, and primarily in the intestines.

It had already been noted [5], in the course of an investigation on the effects of tetracyclines on intestinal interoceptors, that adaptation was seen in the reflexes which developed on prolonged exposure of the interoceptors to these antibiotics, in addition to changes in interoceptor excitability. Experiments in which tetracyclines were injected into the fluid perfusing the vessels of an isolated loop of intestine revealed that adaptation of interoceptive reflexes began while the antibiotics were still acting, and ended in gradual return of the blood pressure, raised by the action of tetracycline, to its original level. This phenomenon has now been studied in greater detail.

METHOD

A segment of small intestine, completely isolated humorally and retaining connection with the body solely by its nerves, was perfused in acute experiments on cats, anesthetized with urethane [1].

Antibiotics of the tetracycline group (chlortetracycline, oxytetracycline, tetracycline) were introduced into the vessels of the isolated intestinal loop over considerable periods in 71 experiments. In some cases it was possible to carry out a second prolonged administration, so that there were 87 examinations in all. The tetracyclines were diluted in slightly modified Ringer-Locke solution [5, 6] in strengths of from 9 to 18 mg/ ml, and injected into the perfusing fluid in volumes of 12-16 ml over periods of 3-5 min, or at a rate of 25-86 mg/ml per min.

The experiments were carried out in the following manner. The initial level of interoceptor excitability was first determined (from the value of the reflex increase of blood pressure) for acetylcholine (10^{-4}–10^{-6}) or one of the tetracyclines (9 mg/ml). The stimuli, in volumes of 1-2 ml, were injected at intervals averaging 5 min. Thereafter the antibiotic was injected continuously for 3-5 min into the perfusing fluid.

RESULTS

After a short interval, the blood pressure usually began to rise to a maximum value, 10-40 mm Hg above the initial pressure. The injection of a tetracycline had a distinct stimulating effect, leading to reflex increase of blood pressure in 64 (75 per cent) of the 87 test injections into the vessels of isolated intestinal loops.

Once the maximum value was reached, the arterial pressure began to fall gradually despite continued injection of antibiotic, to regain, after a variable interval, its original level.

Thus there was adaptation of interoceptive reflexes to the continuously acting stimuli.

The time required for the development of adaptation varied in different experiments and in the course of the same experiment (when the injection was repeated), but it was generally 1.5-3.0 min.

Complete adaptation was observed in 38 and partial adaptation in 18 of 64 experiments. There was little or no evidence of adaptation in 8 experiments.

There were no reflex changes in blood pressure or respiration in the control experiments in which modified Ringer-Locke solution (pH 7.0-8.0) was perfused continuously.

When the injection of tetracycline had ended, the vessels of the intestine were irrigated with ordinary Ringer-Locke solution. During this period the injection of 1-2 ml of the tetracycline or acetylcholine solution produced no reflexes or reflexes which were reduced.

The adaptation which developed while the tetracyclines were being injected thus persisted for some time after the injections ended.

There was a possibility that the return of the arterial pressure to its original level while injection of a tetracycline was still continuing might have been the result of reduced entry of perfusing fluid containing tetracycline into the intestinal vessels as there was usually some reduction in the rate of fluid outflow from the vessels of the perfused loop about this time. This slowing of the flow might have been the result of a vasoconstrictor effect of tetracycline or of mechanical compression of the vessels by intensified peristaltic activity in the intestine, an effect usually observed to follow injection of tetracyclines. Another possibility was that decline of the reflex was due to inactivation of the antibiotics as the solutions passed through the intestinal vessels.

To determine the effect of changes in the lumen of the vessels and the resultant slowing of the inflow of tetracyclines, the rate of the perfusion flow was deliberately reduced in some experiments (reduction of the pressure in the Mariotte vessel) to simulate the rate observed in various phases of adaptation associated with the injection of tetracyclines. Such slowing was found to have no effect on reactions to injection of tetracyclines or acetylcholine.

The antibiotic activity of tetracycline in different portions of the perfusing fluid leaving the intestinal loop was determined by diffusion in agar, in order to decide the importance of antibiotic inactivation. These experiments proved that tetracycline activity persisted during both the period of well-marked increase and the period of subsequent decline of arterial pressure.

The decline of the reflex could not, therefore, be linked either with slowing of the perfusion flow and consequent reduced entry of tetracycline or with change in the concentration of tetracycline in the perfusing fluid. No relationship could be observed between the rapidity with which signs of adaptation appeared, the rapidity with which it developed, the degree of adaptation and particular form of tetracycline. Nor was there any obvious connection between the rapidity with which adaptation developed and the strength of response reactions.

The features of the development of adaptation of interoceptive reflexes to antibiotics observed in this investigation are in accord with the features of adaptation of interoceptive reflexes to other stimuli, as described by several authors [9, 11, 12]. Most investigators are of the opinion that this phenomenon is connected with active reduction of excitability (inhibition) of the vasomotor center. According to Chernigovskii [13], "adaptation, the basis of which is an inhibitory reaction, protects receptor cells from exhaustion by making it possible for the body to adjust itself to altered environmental conditions."

Adaptation of interoceptive reflexes to tetracyclines helps to explain certain phenomena observed in the course of their clinical employment. It is possibly because of this that the side-effects involving the gastrointestinal tract, seen in some patients, occur mainly in the early part of treatment and diminish or disappear later.

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All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.