PHARMACOLOGY

THE EFFECT OF CORAZOLE* ON THE PERIODIC ACITIVITY OF A "HUNGRY" STOMACH

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Extra-digestive gastric contractions were first observed by A. M. Cheshkov [7], in experiments on dogs. V. N. Boldyrev [1] studied this activity of the gastrointestinal tract systematically and in detail. V. N. Boldryev and other authors have shown that the increased motor activity in the body of a hungry animal or man is connected with a series of physiological reactions. The regular appearance and accurate alternation of the active and resting periods of all the periodic activity components indicates that these periodic changes in the body are regulated by one central mechanism.

The existence of central influences on the stomach has been proved by direct experiments with mechanical denervation of the stomach. It was established that the periodic gastric activity ceases when the vagus nerves are cut. As the vagus nerves regenerate, the "hungry" movements of the stomach are restored [6].

Therefore, according to contemporary opinion, the periodic activity of the stomach is regulated by the central nervous system. The regularity and inertia in the appearance of this function suggest that it is the lower sections of the central nervous system which directly regulate the periodic activity of the stomach. The cerebral cortex can adjust and modify the function in question according to environmental conditions and to the condition of the body [2, 3, 5].

Studying the periodic contractions of the stomach can be quite helpful in ascertaining the mechanism and typical effect of therapeutic substances on the lower sections of the central nervous system.

In this work, we studied the effect of corazole, which has a stimulating effect on the central nervous system, on the periodic activity of a "hungry" stomach.

EXPERIMENTAL METHODS

The experiments were done on two dogs, Secret and Tarzan, which had Basov's gastric fistula. The animals were experimented upon 18-20 hours after their last meal. Any food that still remained in the stomach was washed out with a lukewarm physiological solution. The contractions were recorded with a rubber balloon, which was connected to Marey's capsule by a water-air transmission with a system of rubber tubes. The gastric contractions were registered on a kymograph-smoked tape, with a slow cylinder rotation (1 turn per 6-8 hours). This slow rotation was accomplished with the help of a small, synchronized Warren's motor, which was joined with the rotating mechanism of the kymograph by a system of cog-wheels. The low speed of the kymograph cylinder's rotation made it possible to record an entire experiment or most of it on one tape (duration of experiment: 6-10 hours).

* Russian trade name.

Fourteen control experiments were done and thirty-five with the corazole injection.

In the dog Secret, the active and resting periods occurred with a strict rhythmicity in the control series of experiments. Four to five active periods occurred, lasting from 16-25 minutes during 7-8 hours of observation. The resting periods lasted from 70-95 minutes.

Slightly more variation in the duration of the active periods and the intervening pauses was observed in the control experiments with Tarzan. The contraction periods lasted 14-30 minutes, and the resting periods, 65-100 minutes.

In view of the fluctuating indices of periodic gastric activity in the control experiments, we conducted preliminary observations for a period of 3-4 hours before each experiment, as well as those done in the control experiments, and only administered the preparation to be tested after we knew the character of the contractions on the day of the experiment. Corazole was injected subcutaneously during the pause between the contractions, 15-25 minutes after the end of the last active period.

EXPERIMENTAL RESULTS

We first examined the effect of corazole in a dose of 20 mg/kg, which, according to data in the literature, has a marked stimulatory effect on the central nervous system. The injection of this dose of corazole caused such a considerable protraction of the resting period that, in some experiments, the alternating action period disappeared completely. In some experiments, the contraction periods became much shorter, and the amplitude of the contractions decreased. Often the action period succeeding the protracted pause also was lengthened (see Table and Fig. 1).

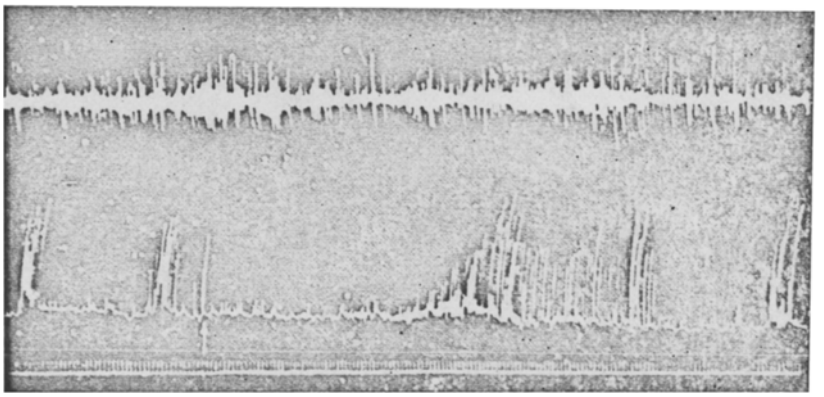

Fig. 1. Effect of 20 mg/kg of corazole on periodic gastric activity in Tarzan. Curves from top to bottom show: respiration, periodic gastric contractions; indication of time (in 4 minute marks). The arrow shows the corazole injection.

Therefore, when testing the effect of 20 mg/kg of corazole on the "hungry" movements of the stomach, we discovered that this dose first suppressed motoricity up to complete inhibition of the periodic contractions for 2-4 hours, but then increased gastric motor activity.

There are indications in the literature that corazole can paralyze the postural reflexes, the labyrinth reflexes and the righting reflex [8, 9]. However, since this type of effect was only observed when very large, convulsive doses of the preparation were administered, the inhibition observed may have been due to the paralysis of the nerve centers.

An inhibitory effect on models of periodic activity was obtained from a comparatively small dose of corazole, which did not cause convulsions or any change in the outward behavior of the animals. In this case, it is difficult to believe that gastric motor activity was inhibited because of nerve center paralysis. It is more probable that, in our experiments, pessimal inhibition was caused by the addition of corazole's stimulatory effect to the already stimulated centers regulating the "hungry" motoricity of the stomach. If our proposition is correct,

then smaller doses of corazole should also have a stimulating effect on this function. There was no noticeable effect on the character of the periodic gastric contractions in either of the dogs caused by a dose of 5 mg/kg of corazole. When 10 mg/kg was injected, changes were observed in the dog Tarzan, but they were unstable in character: in three out of five experiments, the pause either became shorter or the action periods longer.

TABLE

Duration of Resting and Action Periods in Minutes in the Dog Tarzan with 20 mg/kg of Corazole Injected

No. experiments	Duration of resting period		Duration of action period	
	Before corazole injection	After corazole injection	Before corazole injection	After corazole injection
1	102	228	18	80
2	108	156	19	43
3	94	116	21	19
4	88	216	16	132
5	88	220	16	50
6	86	260	25	40

The stimulating effect of corazole on the "hungry" movements of the stomach was clearly manifested in the dog Tarzan when a dose of 15 mg/kg was used: the contraction periods became 5-38 minutes longer, an average of 21 minutes for five experiments (Fig. 2).

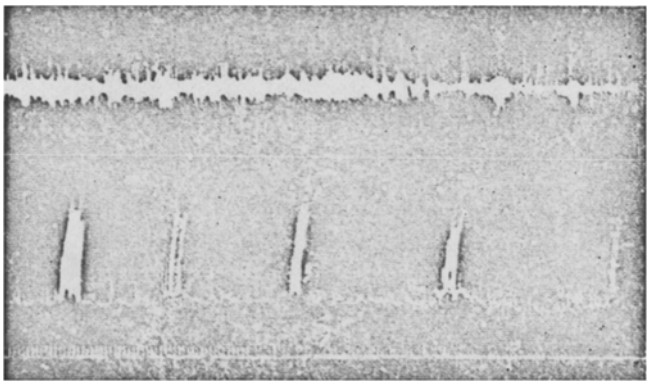

Fig. 2. Effect of 15 mg/kg of corazole on periodic gastric activity in Tarzan. The curves are the same as in Figure 1.

In Secret, unlike Tarzan, this dose of corazole did not have this type of effect in any of the experiments. In two out of four experiments, this analeptic had an immediate inhibitory effect of the gastric motoricity, which was indicated by a certain decrease in the duration of the action period (7-9 minutes).

Therefore, the experiments with the injection of corazole in small doses showed that this analeptic can have a stimulating effect on the periodic activity of a "hungry" stomach, within a definite range of doses, which was shown most clearly in the experiments on Tarzan.

Therefore, the use of periodic gastric activity as an index of the typical action of corazole shows the diphasic character of its effect on the central nervous system. It is particularly certain that small doses of corazole (15-20 mg/kg), which do not have a convulsive effect, can have both a stimulating and an inhibitory effect on the central nervous system. It is possible that the inhibitory effect depends on the development of pessimal

inhibition in the centers regulating the periodic activity of the "hungry" stomach. It is interesting that, in conformity with our data, the inhibitory effect of corazole could also be observed on a model of calomel hypersecretion. The centers of the brain stem which regulate intestinal secretion appeared in a condition of maximal stimulation when an intestinal loop, isolated according to Thiry-Bella, was stimulated with calomel [4]. In both cases, the existing condition of preliminary stimulation evidently aided the development of the inhibitory phase of corazole's effect on the central nervous system.

SUMMARY

It has been experimentally shown that the effect of corazole on the "hungry" movements of the stomach depends on the dose given. Large but not convulsive doses (20 mg/kg) cause an inhibitory effect resulting, probably, in pessimal inhibition developing in the central nervous system. Smaller doses (10-15 mg/kg) exert a stimulating effect leading to prolonged peristalsis.

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