PHARMACOLOGY

THE MECHANISM OF ACTION OF HEXOBARBITAL

COMMUNICATION II. REFLEX INHIBITION OF CORTICAL MOTOR EFFECTS AND SPONTANEOUS MOTOR ACTIVITY OF THE ANIMAL RESULTING FROM THE ACTION OF HEXOBARBITAL ON THE INTEROCEPTORS OF THE INTESTINE

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In a previous report [4] experimental results were given showing that perfusion of the intestine with hexobarbital in concentrations close to those determined in the blood during hexobarbital narcosis (2-5 mg%) is accompanied by lowering of the excitability of the interoceptors. Introduction of larger doses of the narcotic (100, 200, 300 mg) causes at first strong stimulation of the interoceptors and then subsequently depresses them.

Since one of the essential signs of the narcotic state is depression of the motor activity of the animal, we looked into the possibility of reflex inhibition of motor reactions by the application of evipan to the interoceptors of the small intestine. The results of 29 experiments are described below.

EXPERIMENTAL METHOD

Experiments were performed on cats under urethane narcosis in the usual dose — 1 g per 1 k g body weight of the animal. In part of the experiments we used a dose of urethane reduced to 1/5 to 1/10 of the narcotic dose. Under these conditions we observed continuous or periodic motor activity on the part of the animal.

In the course of the investigation we recorded the contractions of the right semitendinosus muscle resulting from stimulation of the left motor area of the cerebral cortex. This stimulation was carried out through an opening in the skull made with a special burr in the left frontal bone and in the posterior bony wall of the frontal sinus. With an approach of this sort to the motor area it was possible to avoid hemorrage from the venous sinuses. The dura mater was opened. Stimulation was by means of an induction current from an induction apparatus, using bipolar silver electrodes, immovably fixed to the skull of the cat. The current in the primary coil of the inductor was obtained from the town supply through a voltage stabilizer and a step-down transformer (4 v). The strength of the stimulus was counted in centimeters on the scale of the inductor.

Evipan sodium was injected from a syringe into the artery of a loop of bowel isolated from the animal in respect to its circulation, but with its nerve connections intact, or it was added to the perfusion of the intestine with Ringer-Locke solution containing 50-100 mg% of narcotic. The blood pressure in the carotid artery was recorded by a mercury manometer and the respiration by a Marey's tambour connected to the trachea of the animal.

EXPERIMENTAL RESULTS

In 17 experiments the effect of injection into the vessels of the intestinal loop of 10 % evipan sodium on the cortical motor reactions and on the "spontaneous" motor activity of the animal was studied.

Altogether 38 injections of various amounts of the narcotic — from 30 to 500 mg — were given.

The results obtained in this series are shown in the Table.

Change in the Motor Reactions of an Animal Resulting From the Action of Evipan Sodium (Hexobarbital) on the Interoceptors of an Isolated Portion of the Small Intestine

Dose of narcotic (in mg)	Number of injections	A			B		
		Cortical motor effects			"Spontaneous" motor activity		
		Intensification	Depression	No change	Intensification	Depression	No change
30	1	–	1	–	–	–	–
50	9	–	3	4	–	2	–
100	8	–	3	4	–	1	–
200	11	–	6	3	–	2	–
300	7	1	3	1	1	1	–
500	2	–	–	2	–	–	–
Total . . .	38	1	16	14	1	6	–

As seen from the table, in 16 out of 31 cases after application of the narcotic to the receptors in the intestine, inhibition of the cortical motor effects was observed. After denervation of the intestine these changes did not arise, which proves their reflex nature.

One of these experiments is illustrated in Fig. 1. Stimulation of the left motor area with a coil distance (CD) of the induction apparatus of 17 cm produced clear contractions of the semitendinosus muscle (A). Injection into the blood vessels of the cat of 2 ml of 10 % evipan sodium was accompanied by a reflex rise in the blood pressure, stimulation of respiration and contraction of the semitendinosus muscle (the so-called "spring" reaction). Stimulation of the motor area with a stimulus of the same strength or stronger (CD = 17, 16.5, 16, 15.5 cm) 35 seconds after injection of narcotic was found to be ineffective. A contraction of the muscle was produced only by increasing the strength of the stimulus to 2 cm on the scale (CD = 15 cm). After 7 minutes the reaction of the muscle was restored to a stimulus of CD- 16 cm. Full restoration of the motor effect was observed 22 minutes after the injection of evipan sodium (B).

After division of the nerves supplying the loop of bowel, injection of evipan sodium caused no reflex changes in the blood pressure or respiration and did not modify the character of the cortical motor effect (C).

Such inhibition of muscular contractions was not observed in all the experiments. In 14 out of the 31 experiments (see Table, A) the character of the motor reactions to stimulation of the motor area did not change. There were also variations in the intensity and duration of the inhibition. In some experiments there occurred merely a diminution in the motor reaction, while in others it was completely absent.

The presence or absence of reflex influences on cortical motor effects by the interoceptors of the intestine as a result of the action of evipan sodium depends on two conditions at least.

The first condition is the strength of the stimulation of the motor centers, which in turn depends on (in our experiments) the depth of the urethane narcosis. Usually we selected an intensity of stimulation of the motor area which would give clear muscular contractions for a certain length of time (25-30 minutes). In most of our experiments this was from 0.25 to 0.5 cm above the threshold value. In cases where in response to such feeble stimuli the muscular contractions became irregular (usually in light narcosis), we had to increase the strength of stimulation to 1-1.5 cm above the threshold level. It was, in fact, in these cases where most commonly reflex influences from the receptors in the intestine were absent. To this group, for example, belongs the experiment illustrated in the table (A), where two injections of 5 ml of 10 % evipan sodium did not alter the course of the motor reactions.

The importance of the functional state of the central apparatus controlling the motor reactions was shown particularly clearly in those cases where the experiment was performed on cats given preliminary large doses of urethane (100-200 mg/kg). Because of sharp variations in the excitability of the motor area, stimulation was not carried out under these conditions. "Spontaneous" contractions alone were recorded.

Injections of different doses of evipan sodium produced in 6 cases out of 7 (see Table, B) after an initial short stimulation, a prolonged inhibition of the "spontaneous" muscular contractions, lasting on the average for

3 to 12 minutes (Fig. 2). In only one experiment did injection of the narcotic produce purely intensification of both motor reactions of the animal, without subsequent inhibition.

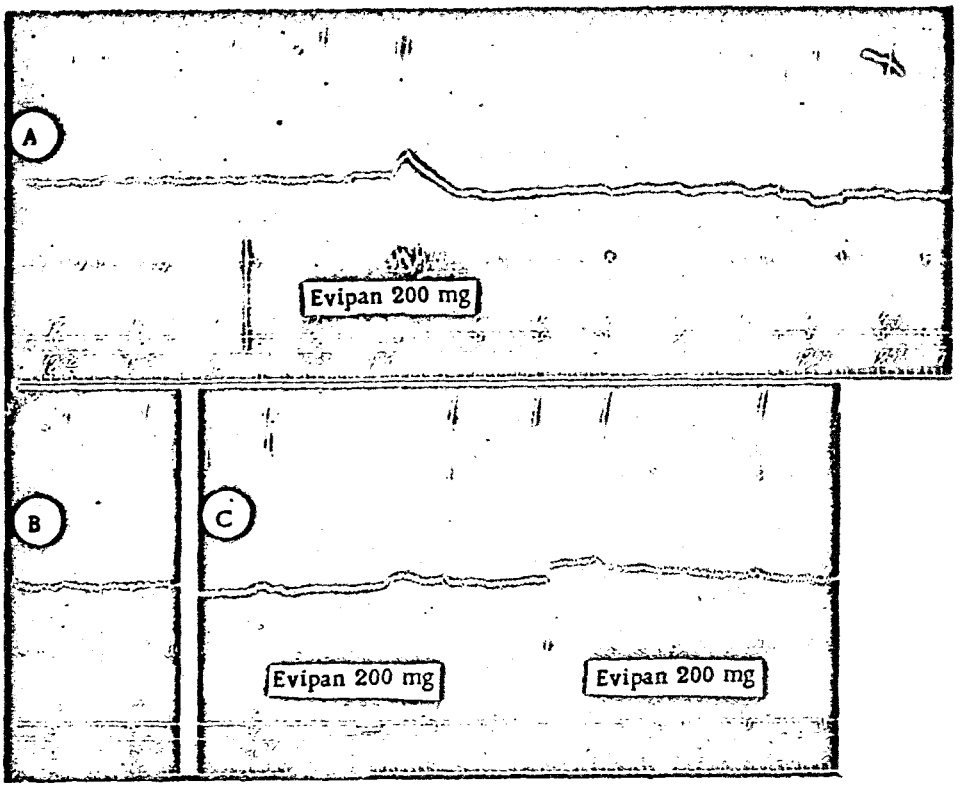

Fig. 1. Changes in the cortical motor reactions of the cat due to the action of evipan sodium on the interoceptors of the isolated intestinal loop. Experiment.
A) inhibition of cortical motor effects after injection of 2 ml of 10 % evipan into the intestinal vessels of the cat (urethane narcosis); B) restoration of muscular contraction 22 minutes after injection of the narcotic; C) the same dose of narcotic injected into the vessels of a denervated loop of intestine causes no change in cortical motor effects. Interpretation (from above downwards): contractions of the right semitendinosus muscle, blood pressure in the carotid artery, respiration, record of stimulation of the left motor area of the cerebral cortex (the figures represent the distances between the coils on the inductor scale) and injections of narcotic into the intestine, the zero line of the mercury manometer and the time record (5 seconds).

Comparison of the experimental results shown in the table (A and B) shows that the inhibition of the "spontaneous" motor reactions resulting from the action of evipan sodium on the interoceptors of the intestine appears relatively more often then inhibition of the cortical motor effects. This depends, evidently, not so much on differences in the mechanism of "spontaneous" movements of the animal and of cortical motor effects as on differences in the original functional state of the central nervous system (depth of narcosis).

The second condition affecting the frequency of inhibitory influences from the interoceptors of the intestine on the cortical motor effects is the dose of the injected narcotic.

As shown in the Table (A), on injection of evipan sodium in doses of 30-100 mg inhibition was observed in 7 out of 15 cases and in 8 it was absent; on injection of 2-3 ml of a 10 % solution of evipan sodium (200-300 mg) the muscular contractions remained constant in only 4 out of 14 cases, while in 9 cases clear inhibition was observed. In one experiment, after injection of 300 mg of evipan sodium the muscular contractions were strengthened.

The intensity of inhibition also varied with the dose of narcotic: in response to the injection of 30-50 mg of evipan into the vessels of the loop of intestine, the muscular contractions were merely diminished, while on injection of larger doses complete inhibition of motor reactions was observed.

In a second series of experiments (12 experiments) we investigated the influence on cortical motor effects of prolonged perfusion of the intestine with Ringer-Locke solution containing 50 or 100 mg% of evipan sodium.

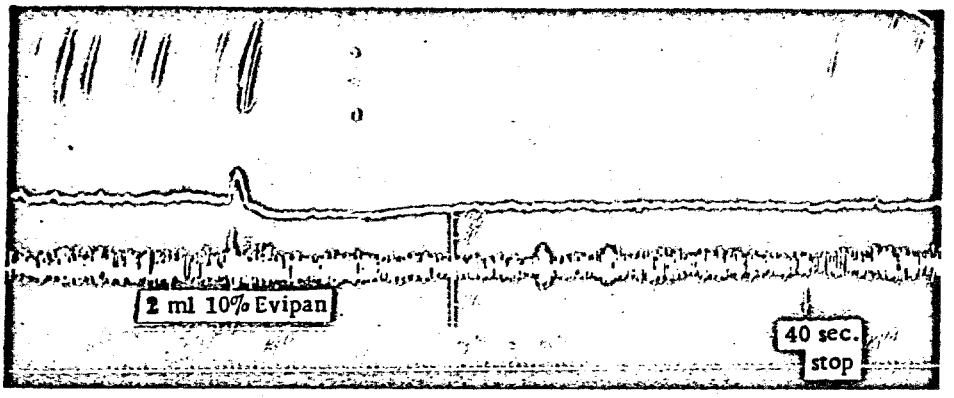

Fig. 2. Inhibition of spontaneous motor activity by injection of 200 mg of evipan into the vessels of an isolated loop of small intestine.
Interpretation (from above downwards): contraction of the semitendinosus muscle, blood pressure, respiration, record of injection of narcotic, zero line of the mercury manometer, record of time (5 seconds). The arrow indicates stopping of the drum for 40 seconds. Muscular contractions were absent at this time.

The intestine was perfused twice in the course of 20 minutes with the solution containing a concentration of 100 mg%. In each case there was observed a clear inhibition of muscular contraction on stimulation of the motor centers of the cerebral cortex. On perfusion lasting from 3 to 21 minutes with the solution containing 50 mg% of narcotic, clear inhibition of cortical motor effects was observed in 12 cases out of 17, there being no change in the remaining 5.

The results of one experiment in this series are shown in the form of a kymogram in Fig. 3. During the 30 minutes before perfusion of the intestine with evipan solution, muscular contractions in response to stimulation of the motor area were constant at CD equal to 11 and 11.25 cm.

Fig. 3 shows the effects of two successive stimuli (2, 3). In order to check the excitability of the chemoreceptors of the intestine, control injections of 50 γ of nicotine were given. Its administration (1) was accompanied by increase in the arterial blood pressure, stimulation of respiration and contraction of the semitendinosus muscle. Perfusion of the loop of intestine with a 0.05% solution of evipan was continued for 5 minutes 46 seconds. During this time 200 ml of solution passed through the blood vessels of the intestinal loop, corresponding to 100 mg of narcotic. At the beginning of perfusion the arterial blood pressure rose and respiration was strengthened. Later the level of the blood pressure fell and the amplitude and rate of respiration diminished. One minute after the beginning of perfusion with evipan the effect of stimulation of the motor area at CD equal to 11.25 cm was intensified (5), after perfusion for 4 minutes it was considerably reduced (6), and then it died out (8). At this time the vegetative and motor reflexes in response to stimulation of the interoceptors of the intestine with nicotine were absent (7). Contractions of the muscle did not occur in response to stimulation of the motor area (9, 11, 12) for some time (14-17 minutes) after flushing out the narcotic, in spite of the restoration of the excitability of the receptors to nicotine (10). The motor effects were only fully restored 27 minutes after the end of perfusion with narcotic (13, 14, 15).

The results of these experiments show the possibility of reflex inhibition of the cortical motor effects arising in consequence to prolonged action of evipan on the interoceptors of the intestine.

We consider noteworthy the feature which we were able to observe in two experiments (during a second perfusion with narcotic in the experiment described and twice in another experiment), that is the more rapid restoration of the "spring" reaction in the muscle during stimulation of the receptors in the intestine with nicotine (Fig. 3, 10) compared with the restoration of muscular contraction in response to stimulation of the motor area of the cortex (13, 14, 15). This shows that all the links in the reflex arc from the interoceptors of the intestine to the muscle may be freed sooner from the inhibitory process than the motor effect resulting from stimulation of the

neurones in the motor area of the cerebral cortex. Consequently reflex inhibition of the cortical motor effects, arising as a result of changes in afferent impulses from the interoceptors in the intestine from the action of evipan, is localized, evidently, somewhere above the level of establishment of the reflex from the intestinal receptors to the muscle. It may be due either to a direct lowering of the excitability of the neurones in the motor area of the cerebral cortex, or to the appearance of a focus of inhibition at a lower level in the central nervous system.

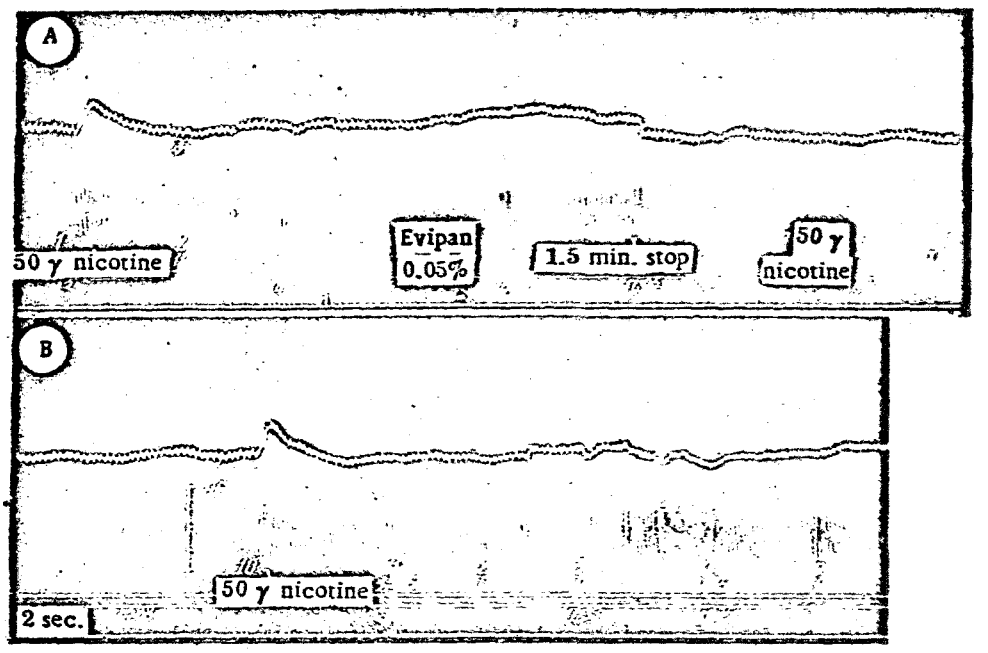

Fig. 3. Change in the cortical motor reactions of the cat during perfusion of an isolated part of the intestine with a 0.05 % solution of evipan sodium. Experiment. (Cat. Urethane narcosis).
1,7, 10) reflexes to the injection into the blood vessels of the intestine of 50 γ of nicotine; 2, 12, 13, 15) effects of stimulation of the left motor area at CD equal to 11 cm; 3, 5, 6, 8, 9, 11, 14) effects of stimulation at lower strength, at CD equal to 11.25 cm; 4) beginning of perfusion of the intestinal loop with evipan in a concentration of 0.05 %; first arrow) drum stopped for 1 $^{1}/_{2}$ minutes; second arrow) end of perfusion of intestine with evipan. Interpretation as in Fig. 1. Time intervals recorded every 2 seconds.

The problem of the localization of the reflex inhibition which we have observed requires further experimental study, especially since after flushing out the narcotic the motor effect is usually restored sooner than the excitability of the interoceptors of the intestine.

Control experiments involving denervation of the intestine, in this series of experiments, showed that the inhibition which we have described did not depend on the appearance of evipan in the general circulation, but was reflex in nature.

CONSIDERATION OF THE RESULTS

The behavior and the mechanisms of influences from the receptors in the internal organs on the motor reactions have been studied by many workers [1, 2, 3, 5, 8 and others].

Inhibition of cortical motor effects by stimulation of receptors in the rectum was observed by A. A. Ukhtomskii [6]. In experiments by Danielopolu [9] and V. N. Chernigovskii [7] it was shown that stimulation of the sinus and depressor nerve enhances muscular contractions caused by stimulation of the motor area of the cerebral cortex.

According to the findings of O. S. Merkulova [5], application to the chemoreceptors of the intestine of chemical stimulants of different natures (acetylcholine, nicorine, carbon dioxide) is accompanied by a variety of effects on the activity of the skeletal musculature.

The mainly inhibitory reflex action of evipan, shown by our experiments, on the course of motor reactions may be to some extent accounted for by its narcotic action on the interoceptors. In contrast to the other chemical stimulants evipan at first gives rise to a brief stimulation of the interoceptors, followed by prolonged depression of their activity. In accordance with this, the stream of afferent impulses to the center, intensified at first, is diminished in the second phase of action of the narcotic. It is possible, therefore, that inhibition, at first developing in the motor center in connection with their excitation, is later maintained by the reduction in afferent interoceptive impulses. We put forward this consideration purely as a working hypothesis which is in need of further experimental verification.

SUMMARY

Experiments were performed on cats. It was established that when evipan-sodium (arpal) acts on intestinal interoceptors there is usually a reflex inhibition of the cortical motor effects and "spontaneous" motor activity of the animal (in 22 cases out of 38). The dependence of this effect on the initial functional condition of the central nervous system and the dose of narcotic introduced was studied.

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* In Russian

** Original Russian pagination. See C. B. translation.