ON THE MECHANISM OF ACTION OF HEXENAL

COMMUNICATION 1. THE ACTION OF HEXENAL ON THE INTEROCEPTORS OF THE INTESTINE

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In spite of numerous investigations of the pharmacology of hexenal [6, 10, 16], its mechanism of action, both as concerns its basic narcotic effect, and its side effects on the circulation and respiration, remains in many ways obscure.

Certain clinical observations and experimental data are hard to explain on the basis of the generally accepted concept of a direct depressive influence of barbiturates on different portions of the central nervous system (cerebral cortex, reticular formation, spinal cord).

To such facts belong, for example, observations indicating a different effect of intravenous and intraarterial injection of hexenal. V. S. Galkin and N. C. Misyuk [4], carrying out hexenal tests on hypertensive patients, observed that the injection of 10 ml of 10% hexenal into the peripheral portion of the femoral artery did not cause a fall in blood pressure nor a state of narcosis. Intravenous injection of the same dose produced a temporary hypotensive effect and the development of a state of general anesthesia. Repeating these observations on animals, A. G. Bukhtiyarov [3] confirmed them and showed in addition that the narcotic and toxic effect of hexenal was more marked when the narcotic was introduced into the external jugular vein towards the heart than when the same dose was introduced into the carotid artery to the brain. These and many other facts led to the idea of a possible role in the mechanism of hexenal anesthesia of reflex effects from receptors of internal organs.

Direct demonstration of action of various narcotics on the receptors of the carotid sinus was obtained by numerous authors [2, 8, 12, 13, 15]. The electrophysiological investigations of D. Whitteridge and E. Bulbring [17] and later A. S. Paintal [14] demonstrated changes in the condition of the expansion receptors of the lungs following inhalation of ether and chloroform.

In the present work the results of 28 experiments on the action of hexenal on the intestinal interoceptors were observed.

METHODS

We carried out our experiments on cats anesthetized with 20% urethane. We transfused a loop of the small intestine, circulatorily isolated, through the superior mesenteric artery and vein with oxygenated Ringer-Locke solution at 38-39°. The innervation of the intestine was completely intact. We administered hexenal in large doses (50, 100, 200 mg), injecting it into the artery of the loop with a syringe (1-2 ml of a 5-10% solution). We investigated the action of smaller doses under conditions of prolonged perfusion of the organ with the same solution, containing from 2 to 100 mg% of hexenal. We recorded the reflex changes in blood pressure (mercury manometer in the carotid artery) and respiration (Marey's capsule attached to the animal's trachea). In addition, in all experiments we verified the responsiveness of the interoceptors to other chemical preparations (acetyl-

choline, Na Evipan (Bayer, Farbenindustrie) and Avipal (Winthrop Chemical Co.). No important differences in their action on the interoceptors were observed.

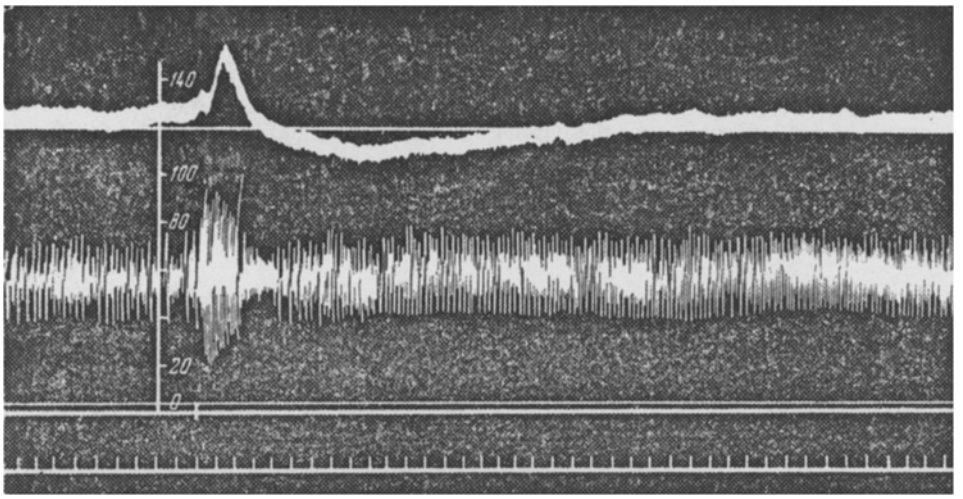

Fig. 1. Reflex changes of blood pressure and respiration in experiments involving injection of Evipan into the blood vessels of an intestinal loop.
Meaning of curves (from top to bottom): Blood pressure in mm of mercury, initial level of blood pressure, respiration, stimulus mark (injection of 1 ml of 10% Evipan), zero line of manometer, time signals (5 seconds).

RESULTS

First we studied (in 7 experiments) the action of 10% hexenal, generally used in surgical and experimental practice. As a rule, the injection into the vessels of an intestinal loop of 1-2 ml of 10% hexenal was accompanied by a two-phase change in blood pressure and respiration (Fig. 1). At the moment of injection of the hexenal the blood pressure rose sharply, then fell below the initial level and returned to normal after various intervals of time (from 1 to 10 minutes). After the initial sharp increase the respiration also decreased somewhat, then was restored to the original level.

Section of the nerves innervating the intestinal loop completely abolished the circulatory and respiratory effect, which demonstrates the reflex nature of these changes.

Later on we attempted to ascertain the minimal active concentration of hexenal, and also study the effect of prolonged perfusion with small doses of the narcotic on the excitability of the interoceptors. Twenty-one experiments were carried out in which the intestine was perfused with hexenal solutions of the following concentrations: 2 mg % (2 experiments), 5 mg % (6 experiments), 10-20 mg % (6 experiments), and 50-100 mg % (7 experiments).

Fifteen to 20 minute perfusion of the intestine with a hexenal solution of concentration 2 mg % had no effect, either on the blood pressure or the amplitude of the respiration. There was only observed a negligible decrease of the vascular pressor reflexes, appearing in response to a small dose of nicotine (2 γ). The reflexes to large doses of the irritant (10 and 20 γ) did not change.

More definite results were obtained on using a 5 mg % solution of hexenal. In spite of the fact that in all experiments reflex changes in blood pressure and respiration were absent following administration of the narcotic, its action was clearly evident in a lowering of the sensitivity of the receptors to other chemical stimuli. One of the experiments is presented in Fig. 2. Three minute perfusion with Evipan in a concentration of 5 mg % [2, 3] led to a significant decrease of blood pressure and respiratory reflexes, elicited by the administration of 10 γ of

nicotine [4]. The rate of perfusion in this experiment was 33-34 ml per minute. Subsequently, three minutes after this, 5 mg hexenal in 100 ml of solution was injected into the circulation of the small intestine. Restoration of reflexes was observed only about 28 minutes after washing out the narcotic.

If the duration of perfusion with hexenal of a given concentration was increased to 20-30 minutes, then reflexes to weak stimuli (5-10 γ acetylcholine and nicotine) disappeared completely, reflexes to strong stimuli (50-100 γ) were however preserved, but their intensity was markedly decreased.

More significant alterations of the functional characteristics of the receptor apparatus were observed on increasing the concentration of narcotic in the perfusion fluid to 10-20 mg %. Reflexes to weak stimuli disappeared in the course of 5-10 minutes after the beginning of perfusion, and somewhat later, after about 20-30 minutes, there was observed a complete absence of reflex reactions to the administration of large doses of nicotine and acetylcholine (100 γ). On stopping the perfusion with the "narcotic" solution the reflexes were generally completely restored in the course of half an hour (Fig. 3). As a rule during the action of 10-20 mg%

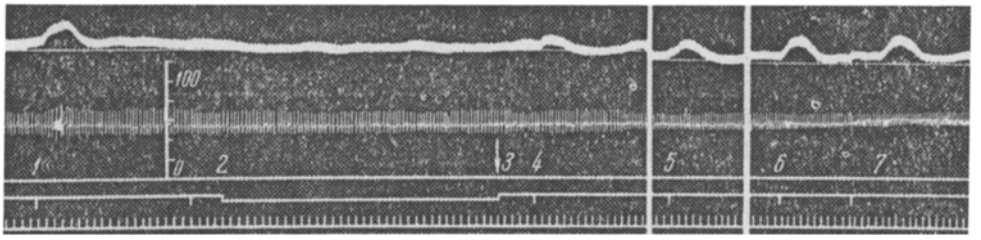

Fig. 2. Reflex changes in blood pressure and respiration inexperiments with perfusion of intestinal loop with Evipan in a concentration of 5 mg %.
Meaning of curves (from top to bottom): blood pressure in mm of mercury, initial blood pressure level, respiration, zero line, records of stimuli (injection of 10 γ of nicotine, 5 γ acetylcholine, time signals (5 seconds).

hexenal on the interoceptors of the intestine the blood pressure dropped somewhat and respiration was slowed.

V. N. Chernigovsky [7] and V. A. Lebedeva [5] observed an analogous effect after injecting a 1-2 % novocaine solution into the intestinal circulation. The electrophysiological investigations of N. Ya. Anikina [1] supported the original explanation, that novocaine, depressing the activity of the interoceptors, produces a decrease in tonic impulses, acting through the afferent fibers of the intestine on the vasomotor and respiratory centers. This same mechanism evidently underlies the reflex lowering of blood pressure and slowing of respiration which are observed during perfusion of the intestine with hexenal.

Further increase of the concentration of hexenal in the perfusion fluid to 50-100 mg % caused complete disappearance of reflexes, both to weak and strong stimuli, after a very short time, from 1 to 5 minutes. Such doses first produced a negligible elevation of the blood pressure (10-20 mm of mercury) and a moderate strengthening of respiration, which then changed to a hypotensive effect and a decrease in amplitude and frequency of respiration.

DISCUSSION

Hexenal, therefore, in very small concentrations (2-5 mg %) acts on the interoceptors of the intestine, producing on prolonged contact a gradual decrease in their excitability. With larger concentrations of hexenal (10 %) there is observed an initial strong irritability of the receptors with a subsequent depression of their activity.

Since there is no basis for suggesting a specific sensitivity of the interoceptors to hexenal, the latter probably exerts from the first moment an equally strong general influence on all the receptors in its path. It is possible that on intravenous injection the receptor fields of the heart and lungs have special significance [9],

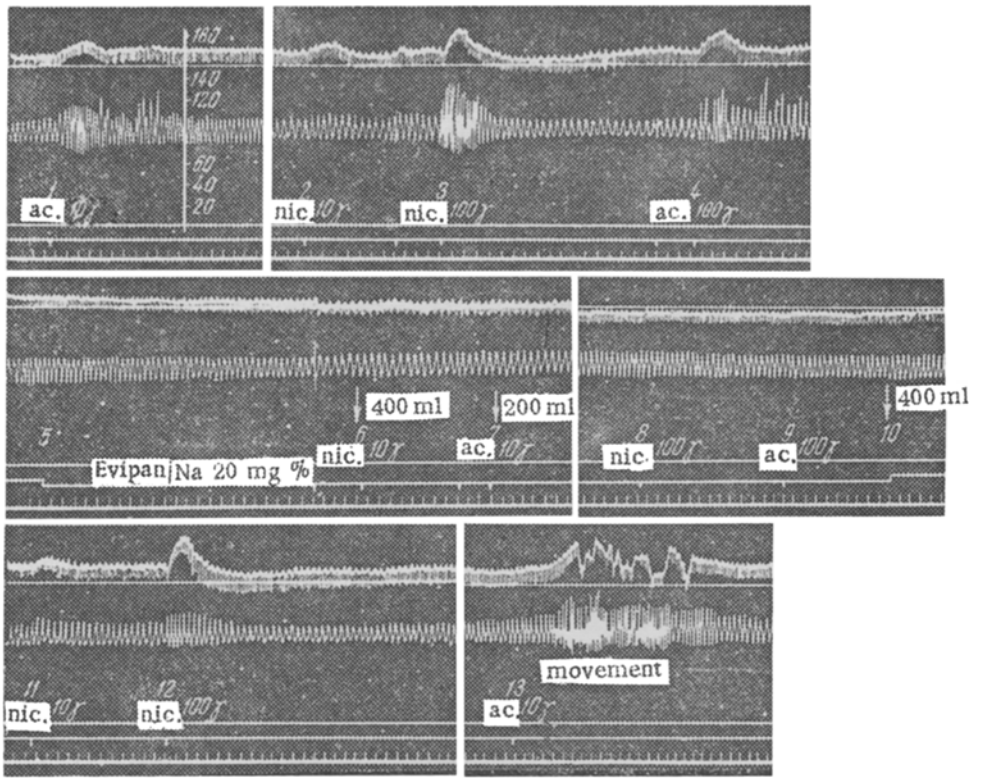

Fig. 3. Reflex changes in blood pressure and respiration in experiments with perfusion of intestinal loop with Evipan in a concentration of 10-20 mg %.
Meaning of curves (from top to bottom): blood pressure in mm of mercury, initial blood pressure level, respiration, records of stimuli [injection of 10 γ acetylcholine (1, 7, 13); 100 γ acetylcholine (4, 9)]; 10 γ nicotine (2, 6, 11); 100 γ (3, 8, 12). Time signals (5 seconds).

being subjected before all others to the action of the narcotic. The prolonged action of hexenal on other interoceptors would depend, naturally, on the rapidity of destruction of hexenal and its excretion.

According to the data of H. Genuit and K. Labenz [11], the narcotic concentration of hexenal in the blood is approximately 1.4-1.5 mg %. We did not succeed in detecting a decrease in the excitability of the receptors of the intestine from the action of solutions of hexenal in concentrations of 2-5 mg %. Taking into account the possible disturbance of the functional state of the reflex apparatus produced under the conditions of the experiment (narcosis, perfusion), it must be recognized that the concentrations of hexenal employed by the authors referred to and by us are quantities of the same order of magnitude.

Consequently the interoceptors present themselves as one of the target organs on which hexenal can act when it is administered to animals or man. Therefore the assumption of a possible role of an interoceptor component in the mechanism of hexenal narcosis receives still further confirmation.

SUMMARY

By perfusing an isolated intestinal loop in cats anesthetized by urethane, reflex changes of blood pressure and respiration produced by hexenal, acetylcholine and nicotine on intestinal interoceptors were studied. Strong (10%) and weak 2-5 mg %) solutions of hexenal affect the interoceptors, lowering their excitability after prolonged contact. A reflex from the interoceptors probably plays a part in the mechanism of hexenal anesthesia.

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