THE EFFECT OF EPILEPTOGENIC EXCITANTS—CAMPHORATED OIL AND PYRAMIDON (AMIDOPYRINE) — ON CHEMORECEPTORS OF THE SMALL INTESTINE

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I. P. Pavlov considered that an outburst of excitation in an isolated pathological point of the cerebral cortex was the basis of a human epileptic seizure. This point – differing from one patient to another – should not necessarily be considered as a gross morphological lesion. It may also arise as a result of functional disturbance, or even merely be the sequel of the breakdown of a dynamic complex [5]. The outburst of excitation at the pathological point originates as a result of an afferent impulse from the periphery, i.e., by the reflex path.

Reflex provocation of a seizure can be illustrated clinically by extensive case material. However, to date, the reflex nature of the mechanism has been demonstrated experimentally only to a small extent [3,6,7,8,9,-11,12].

The reflex nature of a seizure stands out clearly in so-called "bell epilepsy" [3]. Material on the reflex nature of an epileptic seizure is given in the works of V. S. Galkin and co-workers (see summary in dissertation of L. P. Kokorev, 1952).

For the purpose of inducing experimental epilepsy, many of the chemical epileptogenic agents have been administered parenterally.

In order to reveal the mechanisms in the development of epilepsy induced by such substances it seemed to us necessary to answer the following question: "what influence do these substances exert on the interoceptors with which they inevitably come into contact on entering the organism?"

To begin with, we studied the influence of two epileptogenic excitants – camphorated oil and Pyramidon – on the chemoreceptors of the small intestine. It seemed to us essential to conduct experiments along these lines in order to make a fuller and complete analysis of the effect on the organism of these substances, which as is well known are widely used in therapeutic medicine.

EXPERIMENTAL

20 experiments were performed on cats, anesthetized by means of intravenous injection of urethane, with perfusion of a segment of the small intestine according to the method of V. N. Chernigovsky. We studied the reflex influence on blood pressure in the carotid artery and on respiration following administration of camphorated oil and Pyramidon into the vessels of the perfused segment of the small intestine. We made use of a 20% solution of camphor in peach oil and a 4% aqueous solution of Pyramidon. It proved necessary to verify in subsequent experiments the influence of these substances on the excitability of the chemoreceptors of the small intestine. For this purpose nicotine at doses of 50-200 γ was injected into the vessels of the intestines before and after the chemoreceptors had been subjected to the influence of camphorated oil and Pyramidon.

EXPERIMENTAL RESULTS

On administration of camphorated oil into the vessels of the small intestine, pressor reactions were seen (in blood pressure) and respiration was stimulated (Fig. 1). These pressor reactions were of a protracted "tonic" character. The threshold doses required to bring about these reflexes amounted to 2-4 mg camphor. With increased dosage of the excitant the pressor effect at first grew in amplitude but later only a protraction of the effect was observed. In one experiment out of six, reflex responses involving skeletal muscles – so-called "actuating" influences – were obtained.

Denervation of the perfused intestinal segment and also preliminary injection of novocaine into the intestinal vessels removed reflex influences. After the novocaine had been washed off with nutrient solution the reactions were restored.

In order to ensure that the results obtained were not the consequence of an oil embolism, we conducted control experiments in which we injected peach oil – the solvent of camphor in the preparation of camphorated oil – into the vessels of the perfused intestinal segment.

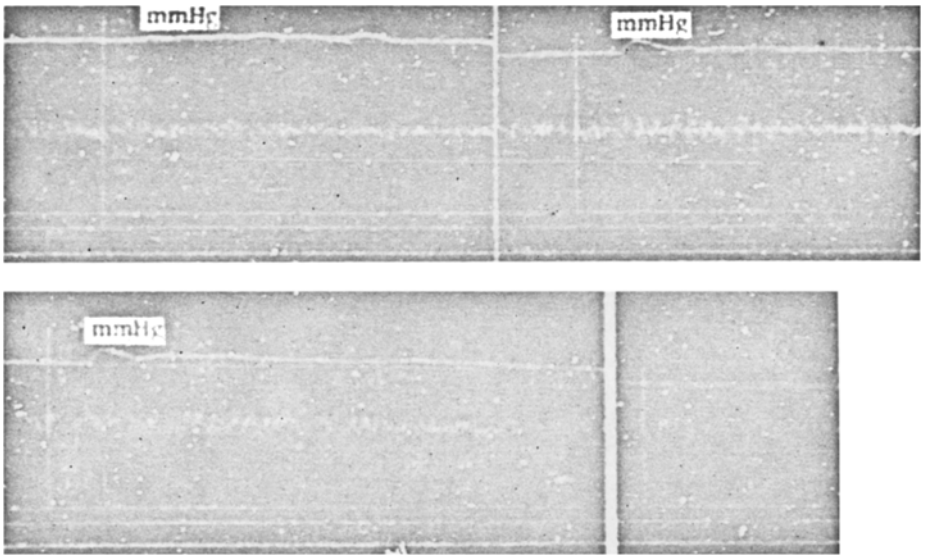

Fig. 1. Stimulation of chemoreceptors of small intestine in cats by camphorated oil. Tracings – top to bottom: blood pressure in carotid artery, line of original level of blood pressure, respiration, base line for mercury manometer, indication of stimulation, time interval (5 sec). Administration of camphorated oil: 1) 12 hours 3 minutes, 0.01 ml; 2) 12 hours 15 minutes, 0.05 ml; 3) 12 hours 32 minutes, 0.2 ml; 4) 12 hours 55 minutes, 0.2 ml peach oil.

Introduction of appropriate quantities of peach oil was not accompanied by reflex effects on blood pressure and respiration (Fig. 1, 4).

Another interesting feature of these experiments was that following administration of peach oil the blood pressure reflex reactions in response to administration of camphor were extremely protracted. Thus, in the experiment of December 4, 1955, 40 mg camphor introduced 17 minutes after administration of 0.2 ml peach oil produced a rise in blood pressure for 12 minutes.

In six experiments, we made a study of the influence of camphorated oil on the excitability of the chemoreceptors of the small intestine, the excitability being determined according to reflex responses to nicotine. Following administration of camphorated oil at doses of 0.1-0.5 ml (20-100 mg camphor), prolonged inhibition of reflex responses to nicotine was observed (Fig. 2), and in some experiments (with use of large doses) there was

Fig. 2. Influence of camphorated oil and peach oil on excitability of chemoreceptors in cat. Tracings - as in Fig. 1. 1) Administration 50 γ nicotine before administration of camphorated oil; 2) administration of 0.2 ml camphorated oil; 3,4,5,6,7) repeat administration of nicotine following administration of camphorated oil - 50 γ per administration.

even irreversible inhibition – the reflexes were not restored at all during 1-2 hours. Even when they were restored, the responses to nicotine were sometimes very protracted. Small doses of camphorated oil (0.03-0.05 ml) did not exert an inhibitory effect on reflex responses to nicotine; however occasionally within 20-50 minutes the responses became very protracted in character. It is characteristic that camphor, while inhibiting reflex responses to nicotine, did not influence the responses to repeated administration of camphor itself.

No inhibition of reflex responses to nicotine was observed following adminstration of peach oil.

For comparison purposes, camphorated oil was introduced into the femoral vein and always a depressor response was seen in blood pressure and inhibition of respiration. This fact is not new; it was established in the work of V.G.Baranoff and E. N. Speranskaja [10] and confirmed in the work of A. G. Bukhtiyarov [1].

Introduction of even very large doses of Pyramidon (up to 150 mg) into the vessels of the perfused segment of the small intestine did not produce distinct changes in blood pressure and respiration. However, as verified by the reactions to nicotine, the excitability of the intestinal chemoreceptors was subject to considerable change. There was either complete disappearance or marked inhibition of the reflex responses to nicotine after treatment of the intestinal receptors with Pyramidon (Fig. 3). 5-10 minutes after washing off the Pyramidon, reflex responses to nicotine were completely restored. Analogous results were obtained not only with administration of a single specific dose of Pyramidon (40-150 mg), but also when the liquid used to perfuse the small intestinal segment was changed from the normal Tyrode solution to this same solution plus a given amount of Pyramidon so that, for example, a 100 mg % Pyramidon solution was obtained.

In two experiments out of six, following introduction of Pyramidon (40-60 mg), a very insignificant decrease in the magnitude of the reflex responses to nicotine was observed. However 15-30 minutes after this there occurred an extreme prolongation of the pressor responses to nicotine – up to 6 minutes. Within 40-50 minutes the responses were again shortened.

The experiments conducted demonstrate that the interoceptors have a particular affinity for both substances investigated by us – camphorated oil and pyramidon – and that these substances exert on the interoceptors a completely specific effect.

Camphorated oil powerfully stimulates the chemoreceptors of the small intestine, the active factor being camphor and not the peach oil used as solvent. Furthermore, camphorated oil exerts a powerful inhibitory effect

on the excitability of the chemoreceptors of the small intestine. The active principle here also is camphor and not the peach oil.

Pyramidon at doses up to 150 mg although it does not itself produce distinct reflex changes in blood pressure and respiration, considerably diminishes the excitability of the chemoreceptors to nicotine. These findings are in agreement with the generally known sedative action of Pyramidon.

The protracted reactions in blood pressure observed in a number of the experiments are of particular interest. An analogous effect was observed by us in joint work with M. Ya. Ratner (1955) by treating the chemoreceptors of the small intestine with renin and by V. A. Lebedeva (1955) in work with Pentothal with application of the same experimental methods. Prolonged blood pressure reactions were observed by T. P. Yakimova in 1952 in experiments on cats with introduction of hot solution of alcohol (32°) and sodium chloride (20%) into the carotid artery and femoral vein. We venture to advance the hypothesis that the development of prolonged reactions of the "tonic" type from the chemoreceptors of internal organs is a type of general phenomenon the mechanism of which must be subjected to more thorough experimental analysis.

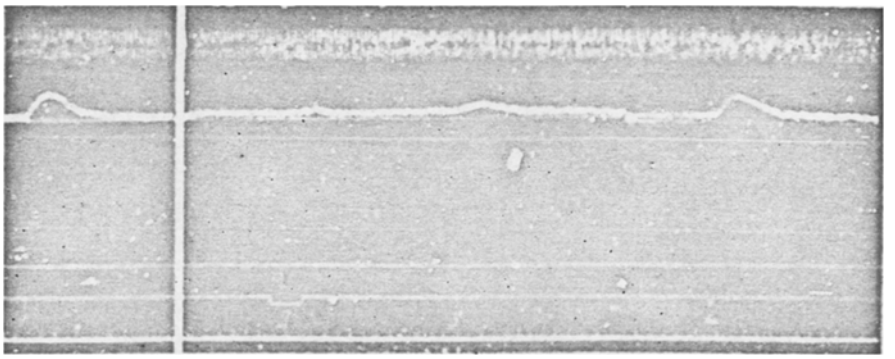

Fig. 3. Suppression of reflex responses from chemoreceptors of small intestine by Pyramidon in cats. Tracings – as in Fig. 1. 1) 13 hours 30 minutes – administration of 100 γ nicotine; 2) 13 hours 34 minutes – administration of 80 mg Pyramidon; 3) 13 hours 35 minutes – administration of 100 γ nicotine accompanied by decreased blood pressure reaction; 4) 13 hours 40 minutes – administration of 100 γ nicotine. Amplitude of reaction completely restored.

On the basis of the experiments conducted, it is possible to postulate that in the development of camphor- or Pyramidon - induced experimental epilepsy a definite role may be played by the reflex influences arising from the action of these substances on receptors in internal organs. This is all the more probable since the threshold epileptogenic dosage in cats of these substances (40 mg for camphor and 240 mg for Pyramidon) greatly exceeds the threshold dosage necessary to influence the chemoreceptors of the small intestine (2-4 mg for camphor and 40-60 for Pyramidon).

Consequently, with application of epileptogenic doses of these substances, the receptors of the internal organs undergo the most powerful stimulation and are the sources of a large number of nerve impulses.

SUMMARY

The influence of camphorated oil and Pyramidon on chemoreceptors of the small intestine was studied on cats under urethane anesthesia. After the injection of camphorated oil into the vessels of the small intestine by the method of perfusion a reflex increase of the blood pressure and stimulation of respiration was noted. Moreover, comphorated oil inhibited reflex reactions of chemoreceptors to nicotine. Injection of Pyramidon into the vessels of the small intestine did not effect any change in blood pressure and respiration, whereas the reactions to nicotine were greatly inhibited. The author surmises that reflexes play an important part in the development of experimental epilepsy.

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