

THE RELATIONSHIP BETWEEN CERTAIN ELECTROLYTES AND THE MEDIATORS OF NERVOUS EXCITATION

Part I. The Relation of the Acetylcholine-Cholinesterase System to Calcium and Potassium in the Blood of Subtotally Pancreatectomized Dogs

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The enzymatic theory of nerve conduction is based on extensive experimental evidence [10]. According to this theory, excitation is associated with the liberation of chemically active substances, and, in particular, of the mediator acetylcholine. The action of acetylcholine is limited by its destruction by the enzyme cholinesterase [16, 19, 20, 21]. Equally numerous reports have pointed out the important part played by the ions of calcium and potassium in the excitatory process [1, 2, 5, 18].

A. V. Kibiyakov and his co-workers have shown that the pancreas plays an important part in regulating parasympathetic function. Partial extirpation of the pancreas leads to autonomic disturbances, and affects the participation of acetylcholine in nervous conduction [6-9, 11, 13]. We have previously demonstrated quantitative changes in the amounts of acetylcholine and in the activity of cholinesterase in the blood in this condition.

In the present work we have studied the relationship of the acetylcholine-cholinesterase system to the blood calcium and potassium in normal and in subtotally pancreatectomized animals.

METHOD

The experiments were carried out on chronic preparations of four dogs — Charka, Piratka, Pulek and Arma. Blood for analysis was collected from the saphenous vein. Acetylcholine was determined using the isolated frog lung and our modification [14] of Corsten's method [17]; cholinesterase was titrated using the method described by T. V. Pravdich-Neminskaya [12], and potassium and calcium were measured using the manganese method [3]. In each dog, for a month before the operation, 8-10 determinations were made of acetylcholine, cholinesterase activity and potassium and calcium. Then, two-thirds of the pancreas was removed from three of the animals (Piratka, Pulek, and Arma), and both ducts were tied off in order to prevent the formation of acetylcholine. One of the dogs (Arma) received daily injections

of 0.5 ml of $1 : 10^{-4}$ acetylcholine. The experiments were performed while the animals were in a fasting condition.

RESULTS

The results obtained confirmed our previous conclusions about the changes in the amount of acetylcholine and in the activity of cholinesterase in the blood after pancreatectomy. We will report the case of the dog Piratka. Before operation, the blood acetylcholine was $2 \cdot 10^{-7}$, and the cholinesterase activity varied between 8.38 and 24.57%. After operation, measurements were made from the fifth day onwards; on the fifth day, the acetylcholine concentration was $2 \cdot 10^{-6}$, on the sixth day it was $2 \cdot 10^{-9}$, and on the seventh, $2 \cdot 10^{-13}$. Subsequently the amount gradually increased, and by the 19th day it was $2 \cdot 10^{-6}$. Cholinesterase activity was measured at the same time as the acetylcholine determinations were made. It was found that the two quantities changed together; on the fifth day cholinesterase activity fell to 12.38%, on the sixth, to 10.92%, and on the seventh, to 7.28%. Subsequently it gradually rose, reaching 28.67% on the 19th day.

Before operation, the amount of potassium varied between 31.24 and 62.84 mg%. After the operation (from the seventh to the 19th day), it varied between 25.63 and 52.11 mg%. The low values occurred on the 10th, 15th, and 19th days. It can be seen, therefore, that potassium was maintained at a somewhat lower level than that obtaining before operation. However, the fluctuations in potassium concentration did not run parallel to those of acetylcholine or cholinesterase. Also, on the 19th day after the operation, during the period when amounts of acetylcholine and cholinesterase activity were recovering, potassium concentration was still low.

The calcium content of the unoperated dogs was 16-31 mg%. After operation it was raised, and varied between 24 and 45.4 mg%. It must be noted that the

greatest increase in calcium concentration occurred on the sixth day, that is, on the day when there was a considerable reduction in the acetylcholine and cholinesterase activities. The results of the experiments on Piratka are shown in Fig. 1.

The results obtained in the experiments on the second dog, Pulek, showed certain special features. The minimum value of acetylcholine was reached later, on the 23rd day. Recovery to the original level was effected by the 50th day. Frequently, an adrenergic effect was observed. There was a marked reduction in the cholinesterase activity, which reached a minimum on the seventh day, and remained at a value less than normal until the 71st day. In this dog there was no parallelism between the changes in acetylcholine and cholinesterase activities.

In Pulek, the changes in the acetylcholine-cholinesterase system just described were associated with changes in the electrolytes. Before the operation, the potassium content of the blood was 22.65-30.81 mg%, and afterward it was higher and varied between 27.26 and 47.72 mg%. The greatest concentration was reached on the sixth day after the operation. Before the operation, the calcium level was 31.6-32.4 mg%, and in the first few days after the operation it was reduced, reaching 26.2 mg% on the seventh day. Subsequently the level rose once more, reaching 44 mg% on the ninth day and 35 mg% on the 23rd day. By the 50th day it had fallen to 21 mg%, but on the 71st day the concentration was 33 mg%. Thus, on days when the acetylcholine concentration was low, the calcium content was high. The results of these experiments are shown in Fig. 2.

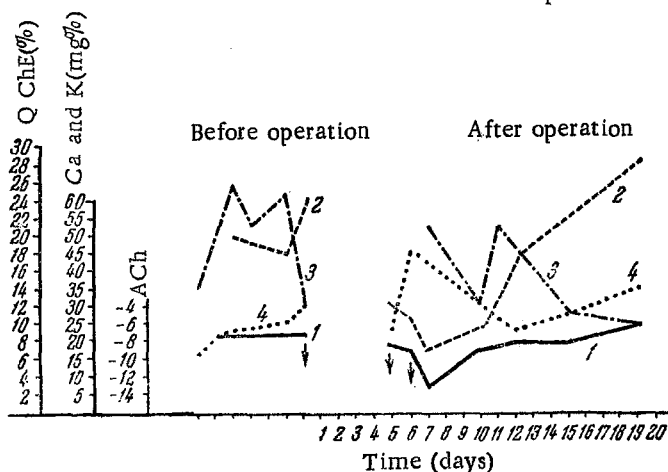


Fig. 1. Blood changes in Piratka after removing 2/3 of the pancreas, and after tying off both ducts. 1) acetylcholine (ACh); 2) cholinesterase activity (Q ChE); 3) potassium (K); 4) Calcium (Ca); the arrows indicate the adrenergic effect.

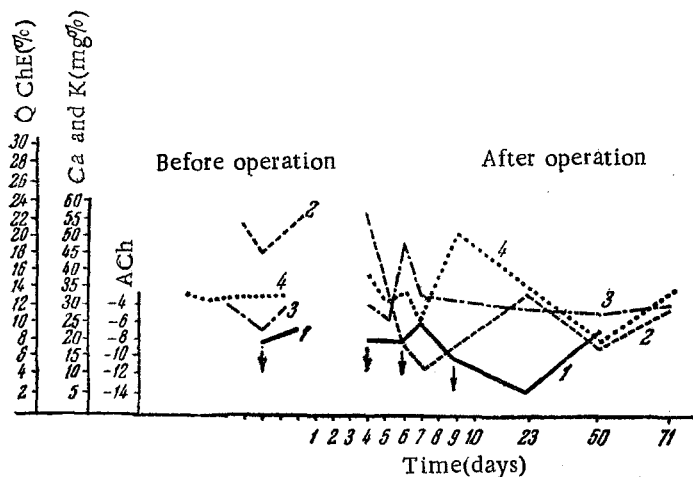


Fig. 2. Blood changes in Pulek after removing 2/3 of the pancreas, and tying off both ducts. Indications as in Fig. 1.

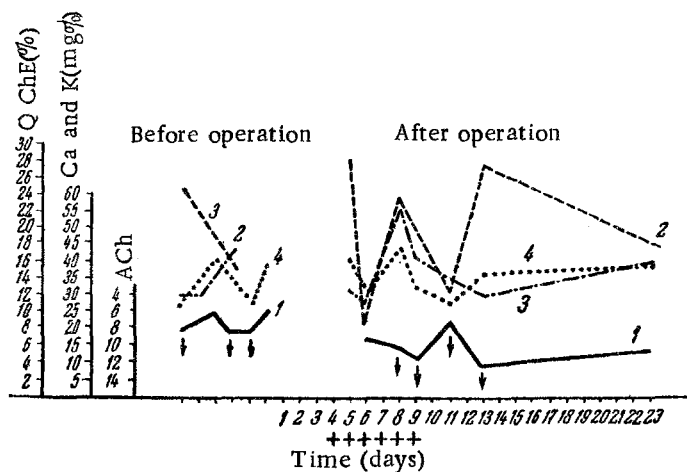


Fig. 3. Blood changes in the dog Arma after removing 2/3 of the pancreas, and tying off both ducts. Indications as in Fig. 1; a "+" indicates compensation by acetylcholine.

The different course of the postoperational changes of the factors measured was probably due to the animals having different types of nervous activity. The dog Piratka reacted much less forcefully to external stimuli, whereas Pulek was highly excitable.

The third dog, Arma, who in behavior resembled Piratka, was given acetylcholine daily from the fourth to the ninth day for the purpose of compensating the autonomic changes induced by pancreatectomy. The results of the experiments on this dog are shown in Fig. 3. In the first days after the operation, there was only a small reduction in the acetylcholine blood concentration. By the 11th day, the acetylcholine was completely restored. Subsequently, no further acetylcholine injections were given, and its concentration in the blood again fell. Cholinesterase activity measurements showed it to be low only on the sixth day after the operation, and on other days, in most of the experiments, it varied between normal limits.

As a rule, no marked differences in potassium concentration, as compared with the preoperative period, were recorded, and only on the eighth day was any increase in concentration observed. No appreciable variation from the norm was discovered in the amount of calcium.

It can be seen, therefore, that partial pancreatectomy causes marked changes in blood acetylcholine and a considerable reduction in cholinesterase activity. There is also a reduction in the amount of potassium. However, the change in the amount of potassium is not so great, and is more variable. The amount of calcium remains comparatively constant, though, as a rule, it was somewhat increased. Compensatory injections may restore the level of acetylcholine and bring about a rapid return to normal of cholinesterase activity, as well as of potassium and calcium levels.

The results obtained show that the extent of the functional autonomic disturbance induced by pancreatectomy is determined by the change in the amount of the nervous-conduction mediator acetylcholine liberated, and by the extent to which it is destroyed by the enzyme cholinesterase, and that the changes are accompanied by variation in the blood potassium and calcium levels.

SUMMARY

The acetylcholine and cholinesterase levels, and the amounts of potassium and calcium in the blood, were studied in chronic experiments on dogs. It was found that partial removal of the pancreas and the ligation of its ducts caused a considerable reduction in both acetylcholine and cholinesterase activities. Blood calcium was increased, and the amount of potassium differed in different animals.

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