# THE EFFECT OF NOVOCAIN HYDROLYSIS PRODUCTS ON THE COURSE AND REVERSE DEVELOPMENT OF ATHEROSCLEROSIS UNDER EXPERIMENTAL CONDITIONS

A. F. Ryzhova

From the Department of Pharmacology (Head – Prof. T. A. Mel'nikova)
of the Leningrad Chemico-Pharmaceutical Institute
(Presented by Active Member of the Akad. Med. Nauk SSSR S. V. Anichkov)
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A number of investigations [2-8] have demonstrated that novocain, used both for therapeutic and prophylactic purposes, manifests a favorable influence on the course of experimental atherosclerosis. It is known that when novocain enters the vascular bed it is quickly split into its components – paraaminobenzoic acid (PABA) and diethylaminoethanol (DAE). In this case, the novocain completely loses its anaesthetic properties, but retains its pharmacotherapeutic ones [1].

This work was devoted to studying the activity of novocain hydrolysis products (as compared with its intact molecule) on the course of atherosclerosis under experimental conditions.

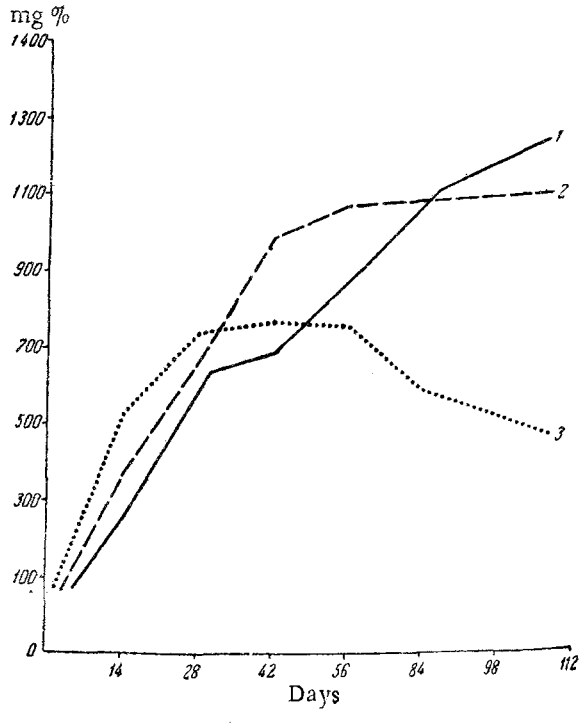


Fig. 1. Curves of cholesterolemia in the control rabbits (1), and in rabbits that received DAE (2) and PABA (3).

## EXPERIMENTAL METHOD

Experimental atherosclerosis was obtained in male rabbits, weighing from 2 to 3 kg, by means of daily feeding with cholesterol, using 0.5 g/kg in 30 g of tertaya carrot, over a period of 4 months. The presence of the atherosclerotic process, and its severity, were judged from the level of cholesterol in the serum (by the method of Grigo) and the level of phospholipids (by the method of Fisko-Sabborou, according to inorganic phosphorous). At the end of the experiments, the experimental and control animals were sacrificed by air embolism. We studied the morphological changes in the wall of the aorta, determining the total amount of lipids in it by the method of Buck and Rossiter [9].

## EXPERIMENTAL RESULTS

The experiments were carried out on 32 rabbits.

In the first series of experiments, we investigated 3 groups of rabbits (18 animals). The rabbits of the control group received only cholesterol, administered perorally in a dose of 0.5 g/kg for a period of 16 weeks. The serum concentration of cholesterol quickly rose in the animals – up to 1279 ± 217 mg % at the end of the experiment, with simultaneous lowering of the phospholipid level to 298 ± 7 mg %. The colesterol/phospholipids index was equal to 4.3 (Fig. 1 and 2).

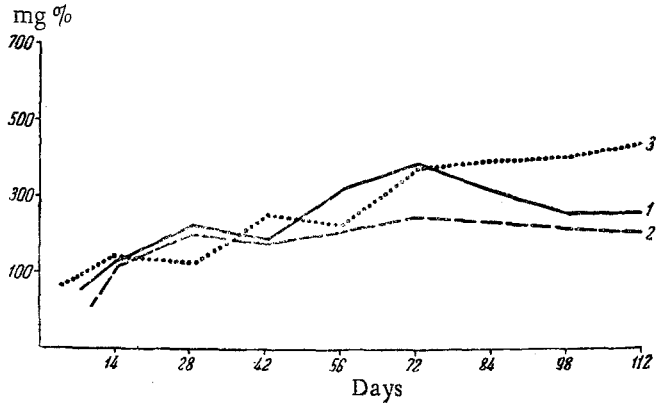


Fig. 2. Curves for the concentration of phospholipids in the serum of the control rabbits (1), and rabbits that received DAE (2) and PABA (3).

TABLE 1. The Concentration of Lipids in the Aortic Wall of Rabbits (Mean Data in mg)

| Substance administered | Weight of the aorta | Amount of lipids in the aortic wall | |
|---|---|---|---|
| | | mean | per 100 mg of aortic tissue |
| Control | 982 | 118 | 12 |
| PABA | 980 | 74.1 | 7.3 |
| DAE | 791 | 112 | 14.1 |
| Novocain [6] | 611 | 35.6 | 5.6 |

Macroscopic investigation of the aortic wall showed that, in the majority of the control rabbits, it was thickened, due to the development of large, confluent, atheromatous plaques, which projected into the lumen of the vessels. The intima was tuberculated, due to deposits of lipids, especially in the thoracic section, An accumulation of atheromatous plaques was also observed on the aortic valves.

Upon microscopic investigation of aortic sections, stained with sudan III, in all the animals of the control group we observed uneven thickening of the intima, due to lipid deposits, with involvement of the muscular layer. The amount of lipids per 100 mg of aortic tissue was equal to 12 ± 1.15 mg (Table 1).

Simultaneously with the cholesterol (0.5 g/kg), the rabbits of the second group (7) were injected subcutaneously with PABA in a dose of 5 mg/kg twice a day, in the form of a 1% solution, for a period of 16 weeks. In this case, we began to inject to PABA 2 weeks after the cholesterol feeding (for the purpose of demonstrating, and excluding from the experiment, cholesterol-resistant animals).

The serum cholesterol concentration in the animals of this group rose less intensely in the first few weeks of the experiment, and in comparison with the control animals, it was equal to an average of 697 ± 65 mg %. Beginning with the 8th week of the experiment, the cholesterol level, in the majority of the animals, fell considerably on the average, and by the end of the experiment it reached a figure of 510 mg %, while in the control animals, at these intervals, it continued to remain at a high level (see Fig. 1).

The phospholipid curve showed analogous changes: an initial lowering of their concentration in the serum, with a subsequent rise in the second half of the experiment, to an average of 420 ± 59.4 mg % (see Fig. 2). The cholesterol/phospholipids index in the rabbits of this group was equal to an average of 1.2.

The atheromatous changes in the aortas of the experimental animals were significantly less manifest than in the control. Macroscopic investigation of the aortic wall showed that, in the majority of animals that received PABA, the wall was not thickened, the intima was shiny on a large portion of its expanse, and only in the aortic arch, at the mouths of the large arteries, was there a certain accumulation of atheromatous plaques, projecting over the surface of neighboring portions of the intima.

In the majority of rabbits, microscopic investigation of the aortic wall demonstrated only small accumulations of lipids in the internal mambrane of the aorta, and atheromatous deposits were found in the muscle layer in the aorta of only one animal. The amount of lipids per 100 mg of aortic tissue was equal to 7.3 ± 0.46 mg (see Table 1).

TABLE 2. Comparative Concentration of Lipids in the Aortic Wall of Rabbits Following Treatment with PABA and Novocain (Mean Data in mg)

| Control | | | PABA | | | Novocain | | |
|---|---|---|---|---|---|---|---|---|
| weight of the aorta | total amount in the entire aorta | per 100 mg of aortic tissue | weight of the aorta | total amount in the entire aorta | per 100 mg of aortic tissue | weight of the aorta | per 100 mg of aortic tissue | weight of the aorta |
| 969 ± 69.5 | 114 ± 14.9 | 11.5 ± 0.9 | 819 ± 28.7 | 45 ± 14 | 5.4 ± 0.36 | 685 ± 70 | 42.7 ± 5.7 | 4.7 ± 0.56 |

The rabbits of the third group (6 animals) were simultaneously treated with cholesterol (0.5 g/kg) and rectally administered diethylaminoethanol, the latter in a dose of 5 mg/kg containing lubricant, over a course of 16 weeks. In these rabbits, the blood cholesterol concentration was high (an average of 1137 ± 225 mg %) throughout the course of the entire experiment, and the phospholipids – relatively low (an average of 241 ± 38.4 mg %). The cholesterol/phospholipids index was as high as in the control – 4.7. It should be noted that soon after the application of DAE, the general condition of the animals worsened, they became sluggish, lost weight, and often the developing intoxication led to their deaths. On macro- and microscopic investigation, aortic atheromatosis was markedly manifested in all the animals, and the degree of the disease process did not differ from that observed in the control animals. The amount of lipids per 100 mg of aortic tissue was equal to 14.1 ± 0.87 mg % (see Table 1).

The second series of experiments was carried out on 14 rabbits, which were fed cholesterol for four months, and then, after cessation of these feedings, were injected with PABA for a period of 16 weeks, for the purpose of studying its action on the reverse development of atherosclerosis. The duration of this series of experiments was 8 months.

After stopping the cholesterol feedings, rabbits of the control group (7) received daily subcutaneous injections of physiological saline. The concentration of cholesterol in their sera fell slowly, and by the end of the experiment was equal to 876.5 ± 137 mg%, with the phospholipids equal to 245.7 ± 27.8 mg %, and the cholesterol/phospholipids index equal to 3.5.

The amount of lipids per 100 mg of aortic tissue was equal to 11.5 ± 0.9 (Table 2).

The rabbits of the second group (7) were injected subcutaneously with PABA over a course of 4 months, in a dose of 5 mg/kg twice a day. In the majority of rabbits, 30-35 days after PABA injection was begun, we noted a significant clearing of the serum, and a drop in the cholesterol concentration from 928.5 to 593.3 mg %.

In 5 of the 7 rabbits, 2 months after treatment with PABA, the concentration of cholesterol and phospholipids in the serum went back to normal. Atheromatosis of the aorta was weakly manifested in the majority of rabbits. We observed only small accumulations of lipids in the aorta arch, at the mouths of the large vessels; in the remaining expanse, the aorta was clean, and the intima, shiny. The amount of lipids per 100 mg of aortic tissue was equal to 5.4 ± 0.36 mg (see Table 2).

Thus, PABA, as well as novocain, inhibits the development of lipoidosis in the aorta of rabbits, and manifests a positive effect on the process of reverse development of atherosclerosis in the animals. All this provides a basis for concluding that the active component of the novocain molecule, as pertains to its antiatherosclerotic action, is para-aminobenzoic acid.

As far as the second component of the novocain molecule, namely diethylaminoethanol, is concerned, it does not prevent the development of lipoidosis in the aorta and other vessels, and causes an intoxication in the animals.

## SUMMARY

The work is devoted to the study of the effect produced by products of novocain hydrolysis (as compared to its whole molecule) on the course and resolution of experimental atherosclerosis in rabbits. Two series of experiments were staged: the first one investigated the effect of para-aminobenzoic acid (PABA) and diethylaminoethanol (DAE) on the course of experimental atherosclerosis; the second one examined the effect of PABA on the process of atherosclerosis resolution in rabbits.

From comparative evaluation of the main indices (the level of cholesterol phospholipids, cholesterol-lecithin index, morphological changes and the amount of lipids in the aortic wall) it follows that PABA and novocain retard the development of lipoidosis in the aorta and accelerate the process of resolution of lipoid infiltration during the retrograde development of lipoidosis in the aorta and accelerate the process of resolution of lipoid infiltration during the retrograde development. All the aforementioned leads to a supposition that paraaminobenzoic acid is the active part of the novocain molecule in its antisclerotic action. Diethylaminoethanol does not retard the development of atherosclerotic process in experimental conditions.

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