# CHANGES IN VASCULAR REACTIVITY IN EXPERIMENTAL ATHEROSCLEROSIS

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Elevated blood pressure promotes the development of arterial atherosclerosis [1, 9]. Numerous data indicate that the development of atherosclerosis affects vascular tonus. Thus, a marked change in the vascular reactions to administration of a number of drugs is observed in rabbits with experimentally induced atherosclerosis [4-7].

However, the problem of the influence of atherosclerosis on the reactivity of the peripheral blood vessels has not been sufficiently well studied. The majority of the investigations have been conducted under acute experimental conditions and even on isolated organs. No research has been done on vascular reactivity in response to the action of factors characteristic of the ordinary living conditions of animals, such as temperature, in the presence of atherosclerosis. No elucidation has been made of the immediate cause of the change in vascular reactions in this disease: whether it is the lipids administered to produce atherosclerosis, the vascular atherosclerosis itself, or other changes in the organism caused by the lipid stress.

Our work was conducted as an approach to the clarification of these problems.

## EXPERIMENTAL METHOD

The experiments were conducted on 56 rabbits, each of which was subjected to repeated observation. Vascular reactivity was studied from the character of the vascular reactions to cold stimulation. The character of the vascular reaction was evaluated from the readings of an electrothermometer, whose sensor was fastened to the rabbit's ear. The temperature measurements were made at the same point throughout the entire experiment; this is very important, since the temperatures of different sections of the rabbit ear differs greatly. The temperature was recorded every 2 min for 10-15 min before and $1\frac{1}{2}$-2 h after cold stimulation of the ear by 2-min application of a cylindrical thermode filled with chunks of ice; this device had a cooling surface with a diameter of 3 cm. Taking into account the daily periodicity of the temperature of the rabbit ear [3], the experiments were always carried out at the same time of day.

Atherosclerosis was induced by feeding the animals cholesterol (0.2 g/kg) dissolved in sunflower oil.

## EXPERIMENTAL RESULTS

In the experiments of series I we studied the influence of cold stimulation on the state of the blood vessels of the ears of healthy rabbits. It was found that the temperature of both ears changes during cooling of one. It decreases markedly during cooling, rises rather rapidly to its initial level after the cold stimulus ceases to act (within 2-4 min in the majority of experiments), and then continues to rise, which results in its reaching values 10-15° above the initial level in the majority of experiments. The ear temperature decreases for 30-50 min after exposure to cold and reverts to its initial value 60-90 min after stimulation. The experiment whose results are shown in Fig. 1 (Curves A and C) is an illustration of this. An analogous pattern was observed in the other experiments of this series.

These data enable us to conclude that brief local cooling of one ear causes a reflex reaction of the vessels of both ears, which takes the form of brief constriction and subsequent prolonged dilatation.

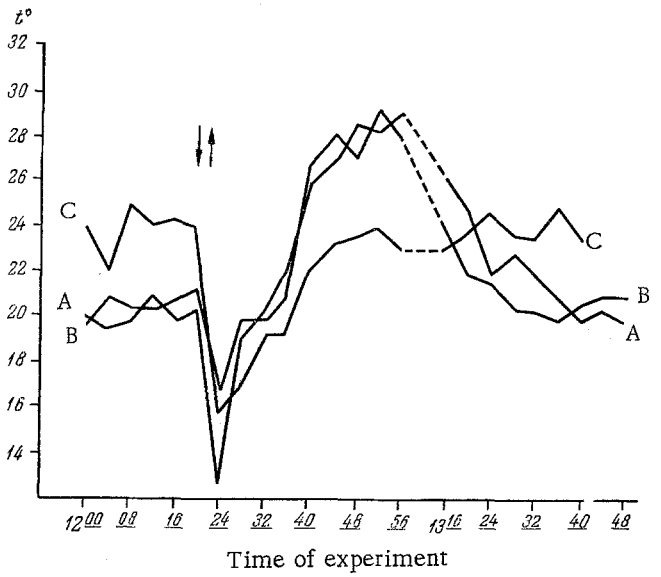


Fig. 1. Reactions of the vessels of the ears of normal rabbits and of animals which received a 5% solution of cholesterol in sunflower oil. A) Temperature curve for stimulated ear of healthy rabbit in response to cold stimulation; B) Other ear of same animal; C) Ear of rabbit which received cholesterol solution for 80 days. The arrows indicate the time of cold stimulation of the ear.

In the experiments of series II we studied vascular reactivity in rabbits with alimentary atherosclerosis.

Cold stimulation of the ears of these rabbits did not cause the vasodilative effect observed on exposure of the ears of healthy rabbits to cold. As may be seen in Fig. 1C, the vessels of the rabbits which received cholesterol for an extended period did not dilatate in response to cold stimulation of the ear; this is indicated by the absence of any marked rise in ear temperature after cold stimulation, as was observed in the healthy rabbits.

Prolonged administration of cholesterol dissolved in sunflower oil thus has a manifest influence on the reactivity of the peripheral blood vessels, attenuating the vasodilative effect of cold stimulation.

We were faced with the question of which of the lipids administered—cholesterol or sunflower oil—exerts this influence. Two further series of experiments were conducted to clarify this problem. In one (series III) vascular reactions were studied in rabbits which received cholesterol only (in a dose of 1 g daily), while in the other (series IV) these reactions were studied in rabbits which were given sunflower oil only (in a dose of 2.5 ml/kg daily).

The animals which received cholesterol alone exhibited the same change in vascular reactions to cold stimulation as the rabbits which received cholesterol and sunflower oil. However, the change in vascular reactivity extended over a more prolonged stress period when cholesterol was administered alone than when it was given in conjunction with sunflower oil. Thus, while the vasodilative effect of cold stimulation could not be detected on the 80th day of stress under the influence of cholesterol administered in conjunction with sunflower oil, this reaction did not disappear until about the 120th day when cholesterol was given in pure form.

As the experiments of series IV showed, sunflower oil does not affect the character of the vascular reactions which develop in response to cold stimulation. After administration of sunflower oil for 80 and 120 days cold stimulation of the ear produced the vascular reaction normal for healthy rabbits: vascular constriction during application of the thermode and subsequent prolonged vascular dilatation.

It may consequently be assumed that the disappearance of the vascular reaction to cold stimulation observed after application of lipid stress results from the intake of cholesterol and not from that of sunflower oil.

The results of our experiments do not give a direct answer to the question of the immediate mechanisms of the influence of cholesterol on vascular reactivity. However, we must take into account the fact that the reactions of the peripheral vessels disappeared in all the rabbits which received cholesterol for a certain time, regardless of

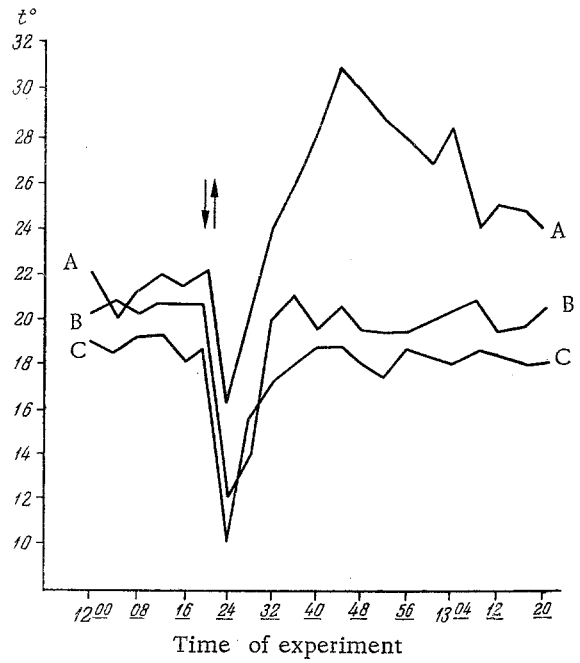


Fig. 2. Influence of crystalline cholesterol and methylthiouracil on the vascular reactivity of the rabbit ear. A) Temperature curve for rabbit ear in response to cold stimulation after administration of cholesterol for 80 days; B) After administration of cholesterol for 120 days C) After administration of methylthiouracil for 30 days. The arrows indicate the time of cold stimulation.

whether or not there were morphological changes in the vascular walls. There was not a single case in which atherosclerotic lesions were detected in the aural vessels. This enables us to conclude that the changes in vascular reactivity which occur in atherosclerosis do not result from morphological changes in the vascular walls. There are many grounds for assuming the disappearance of normal vascular reactivity in atherosclerosis to be caused by disruptions of neurohumoral regulation and, particularly, a decrease in the functional activity of the thyroid. The correctness of this hypothesis is shown by the results of the experiments of series V, in which we studied the vascular reactions of rabbits which had preliminarily been given 0.3 g of methylthiouracil daily for 30 days. It is well known [2] that the action of such an agent on the organism completely blocks the thyroxinogenic function of the thyroid. Determination of the basal metabolism of the rabbits of this series showed that their oxygen consumption dropped by 25-30% after administration of methylthiouracil in the aforementioned dose for 30 days, which corresponds to the alteration of gaseous interchange which occurs in rabbits after complete thyroidectomy [10].

These experiments showed that, just as in rabbits fed cholesterol for an extended period, a vasodilative reaction does not develop in response to cold stimulation of the ear in animals which have received methylthiouracil. As may be seen from Fig. 2C, the ear temperature did not rise above its initial level after cold stimulation as was the case in the healthy rabbits (see Fig. 1A and C Fig. 2A).

The results of our work and the data in the literature, which show that cholesterol administered in excess reduced the basal metabolism level [8] and can inactivate thyroxin [11], give us reason to believe that the change in the normal reactivity of the peripheral vessles which occurs in experimental atherosclerosis is caused by the influence of cholesterol on the neurohumoral regulation of vascular activity, including the functional state of the thyroid, which plays a very substantial role in this regulation.

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