EXPERIMENTAL ATHEROSCLEROSIS PRODUCED BY DRUG INHIBITION OF THE THYROID GLAND

K. Mircheva, Z. Kemileva, M. Shtereva

The numerous investigations on animals, carried out with the model of atherosclerosis as suggested by Anichkov, prove that changes in the cholesterol metabolism (1, 2, 3, 4, 9, 11) are the basic cause for atherosclerotic processes. Some writers discard the possibility that charging of the organism with cholesterol might play an essential role in the etiology of this condition, and accept a diversity of effects presumably accounting for the alterations in the metabolism of endogenic cholesterol (5, 7, 8). The question concerning the type of experimental animals in which experimental atherosclerosis could be produced is likewise disputable. Some support the statement that certain animal species are not susceptible to atherosclerosis, as for instance rats (30, 11). At the same time, others present data demonstrating the development of atherosclerosis in rats (4, 6, 9, 13, 14). The participation of the thyroid gland in the development of atherosclerosis is likewise a controversial issue. The pertinent literature abounds in reports on accelerated development of experimental atherosclerosis following inhibition of the thyroid function (4, 5, 9, 13). On the other hand, data are presented, though scarce, proving that the thyroid gland inhibition exerts insignificant effect upon the development of experimenal atherosclerosis, even leading to attenuation of the development of atherosclerosis (5, 10, 11).

Proceeding from the controversial data just listed, we performed the present study with the objective of determining the influence of the thyroid gland in experimental cholesterol atherosclerosis in rats.

Experimental material and method

The experiments were carried out on a group of 40 white albino rats in the first month of life; the younger age was selected by virtue of the fact that the model we wished to create was to be furthermore used in influences mainly exerted on young animals. The animals were equally distributed into four groups — the first group, in addition to the general diet, received a 5% cholesterol dose with the daily ration. The second group received the general diet plus 0.02 mg daily dose of thymidazol (1-methyl-2-mercaptoimidazol) per os for thyroid function inhibition. The third group, in addition to the general diet, received also 5% cholesterol with the daily ration and 0.02 mg thymidazol for inhibiting the thyroid gland. The fourth group consisted of control animals on general diet. In about 2 1/2 months since

the beginning of the experiments, the diet of all the animals was suppl mented with 1 gr daily dose lard, with the purpose to increase the quantit of saturated fatty acids in the organism. The feeding and observations c the animals continued for 6 months and thereafter they were killed ar material was obtained for investigating the total cholesterol in the serun aorta, liver, kidneys and spleen after the slightly modified method of Bloc (8a). For greater convenience and with a view to reducing the expenditure reagents, the investigations were carried out on tissues, obtained from tw animals of the same group, taking the mean value. The values received fro the different groups were subjected to statistical elaboration after the me hod of Student Fischer.

Results and Discussion

The changes in the quantity of the total cholesterol in the serum and i the organs investigated of the various animal groups differ in compliance with the experimental background.

Table

Mean Values of Cholesterol Content in mg % in the Serum and Some Organs

Groups	Serum	Aorta	Liver	Spleen	Kidneys
1. Fed on cholesterol diet	105	1725	736	562	577
2. Hypothyroidism	80.6	618	347	532	521
3. Hypothyroidism + cholesterol	123	436	1265	597	644
4. Controls	117	841	482	510	588

The quantity of cholesterol in the serum does not exhibit great difference in the separate groups as compared to that of the control group (Fig. 1) Merely in the animals of the group with cholesterol added to the diet an supplemented with thymidazol for inhibiting the thyroid function, a sligh increase was noted (Table 1, fig. 1), but with no statistical significance. I the remainder two animal groups, the cholesterol quantity was decreased most strongly pronounced in the animals treated only with thymidazo It is of interest to notice, that the decrease is rather substantial as compare to control animals and affords reliability of results during statistical ela boration: $(0.99 < P_t < 0.999)$. In this respect our data disagree with the thos reported by Boyd (1959—9), who claimed an increased cholesterol level i the plasma durirg drug inhibition of the thyroid function with thiouraci The explanation of these facts is rather difficult, but it could possibly b assumed that it is due to the different experimental animal species (h employed rabbits), or to the difference in the drugs used.

A greater than two-fold increase is observed in the cholesterol content i the wall of the aorta (Fig. 2) in the animals of the group fed on cholestero $(0.99 < P_t < 0.999)$, whereas in the remaining groups it is lowered. Thi reduction is quite apparent and statistically reliable in the group with thy midazol inhibition of the thyroid gland and cholesterol diet $(0.90 < P_t <$

0.95). These findings are of interest firstly, because there is no conformity between the cholesterol content in the serum and in the wall of the aorta, and secondly, because even the slightest deposit of cholesterol in the wall of the aorta is registered in the animals with combined hypothyroidism and cholesterol diet. Up to a great extent these facts are controversial to the findings reported by other authors. It may be, that the age of ihe animals also has some importance in this respect, accounting for the altered reaction insofar treatment is concerned. The accumulation of cholesterol in the liver is reverse to its deposit in the aorta (Fig. 2).The highest cholesterol content is recorded in animals fed on cholesterol with simultaneously produced drug hypothyroidism. The cholesterol quantity is three times higher than in the control animals. Lesser, but statistically reliable is the increase of cholesterol in the liver of the animals from the group fed merely on cholesterol with no hypothyroidism. The animals treated only with thymidazol display a reduction of cholesterol content in the liver, which, compared to the controls, gives statistical reliability ($P_t = 0.95$). The quantity of cholesterol in the spleen was increased in either group of animals, receiving cholesterol with the diet — both treated and not treated with thymidazol. The increase compared to controls, provides for statistical reliability of the results obtained. In the group treated merely with thymidazol without additional ration of cholesterol in the food, the quantity of total cholesterol in the spleen is reduced, but the difference is not statistically reliable. Fluctuations in the quantity of total cholesterol in the kidneys are insignificant. Merely the reduction of cholesterol in the thymidazol treated group is statistically reliable. The slight increase in the remaining two groups is deprived of statistical reliability.

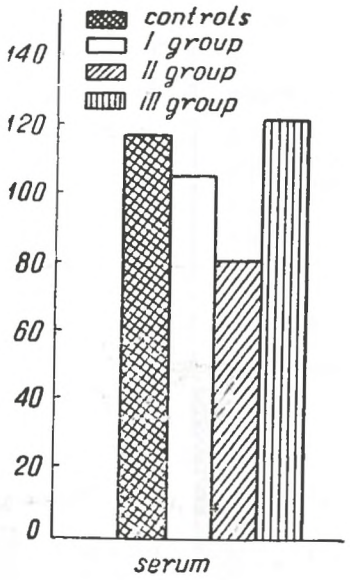

Fig. 1. Cholesterole content in the serum of white albino rats

It is evident from our findings that pronounced hypercholesteremia was produced in none of the individual groups. It is worth mentioning that a general reduction of the cholesterol values is produced in the serum as well as in the other organs studied of the animals with hypothyroidism without additional cholesterol ration. The explanation of this fact is not easy, especially if controversial literature reports are considered. It could possibly be assumed that age exerts a certain influence upon the metabolic processes and autoregulation of the cholesterol metabolism, thus resulting in a more rapid elimination and dissociation of the cholesterol. The overdose of cholesterol in the animals fed on strict cholesterol diet, leads to a considerable increase of the total cholesterol in the wall of the aorta, whereas the group fed on cholesterol in association with thymidazol treatment displays substantially lower values of total cholesterol in the wall of the aorta as compared to controls. It might be assumed that a certain interdependence exists bet-

ween the accumulation of cholesterol in the wall of the aorta and its con-
tent in the liver. In the animals, charged merely with cholesterol, the leve
of the cholesterol in the wall of the aorta is 1925 mg %, and in the liver i

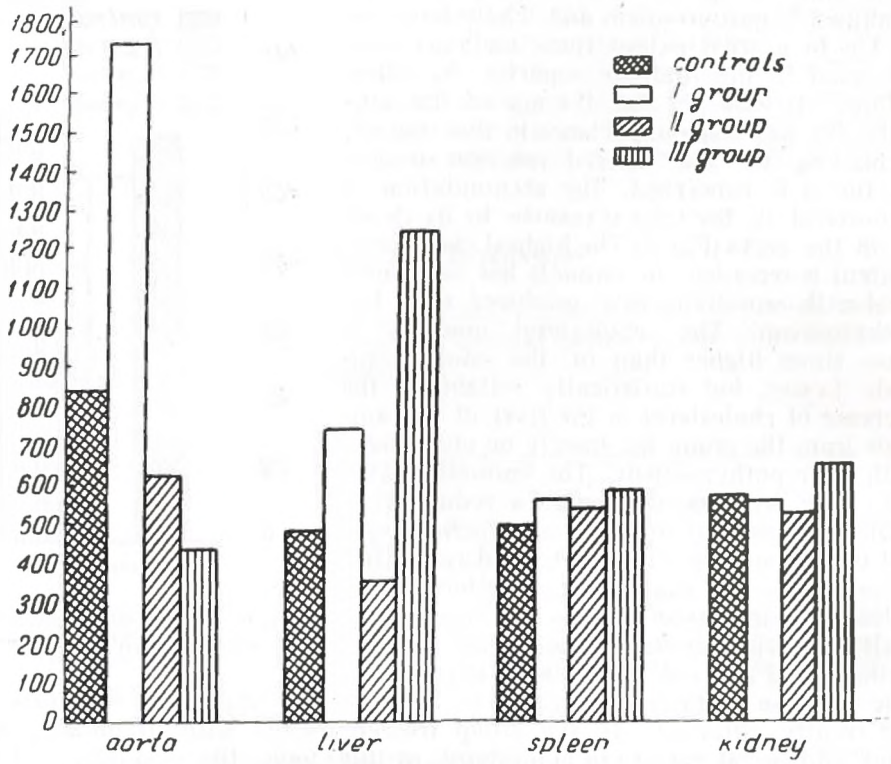

Fig. 2. Cholesterine content in the aorta, liver, spleen and kidney of white albino rats

is 736 mg %. The animals which in addition to being charged with choleste-
rol, were also treated with thymidazol, the cholesterol content in the aorta
is 436 mg % and in the liver — 1265 mg %. It could be assumed that under
the effect of hypothyroidism, the metabolic processes get attenuated, and
thereby the cholesterol is excreted from the organism through the liver.
The complexity of the interrelationships in the developing processes could
not be explained merely on the basis of the investigations herein described;
further studies are undoubtedly required.

On the basis of the data obtained, the following conclusions were reached:

1. The cholesterol charging of the organism leads to increased cholesterol deposit in the wall of the aorta and in the parenchymatous organs without pronounced hypercholesteremia.

2. Inhibition of the thyroid function with thymidazol reduces the cho-
lesterol concentration in the serum and in the parenchymatous organs stu-
died.

3. The cholesterol charging on the basis of thymidazol induced hypothyroidism results in a reduction of the cholesterol level in the wall of the aorta and increase in the parenchymatous organs investigated.

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ЭКСПЕРИМЕНТАЛЬНЫЙ АТЕРОСКЛЕРОЗ ПРИ МЕДИКАМЕНТОЗНОМ ПОДАВЛЕНИИ ФУНКЦИИ ЩИТОВИДНОЙ ЖЕЛЕЗЫ

К. Мирчева, З. Кемилева, М. Щерева

РЕЗЮМЕ

При экспериментальном холестериновом атеросклерозе прослежено влияние щитовидной железы на уровень холестерол в сыворотке крови, в аорте и в некоторых паренхиматозных органах. Опыты были проведены над четыремя группами крыс, в возрасте одного месяца. Первая группа получала по 5% холестерол ежедневного пищевого рациона, вторая группа получала к общей пище по 0,02 мг тимидазола в сутки через рот — в целях подавления функции щитовидной железы. Третья группа получала по 5% холестерол ежедневного пищевого рациона и по 0.02 мг тимидазола. Четвертая группа являлась контрольной и животные получали общую пищу. Через 2 1/2 месяца после начала опытов, к пище было

прибавлено по 1 г смальца в день. Животные кормились в течение 6 месяцев.

Установлено, что нагрузка холестеролом приводит к увеличенному отложению холестерола в стенку аорты и в паренхиматозные органы у крыс. При подавлении функции щитовидной железы тимидазолом, содержание холестерола в сыворотке крови и исследованных органах уменьшается. Холестероловая нагрузка на основе гипотиреоидизма вызванного тимидазолом приводит к уменьшению содержания холестерола в стенке аорты и к увеличению его в исследованных органах.