INSULIN ACTION IN EXPERIMENTAL ATHEROSCLEROSIS

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A study of the effects of insulin on the development of atherosclerosis is called for by the necessity for therapeutic administration of insulin to many diabetics who also have atherosclerosis.

Among the reasons for the predisposition toward atherosclerosis in diabetes, the most important is the disruption of lipid metabolism [1, 7, 8, 10]. This disruption is particularly great in more decompensated diabetes [4, 11]. Insulin treatment, by improving the course of diabetes, stabilizes the lipid content in the blood and thereby possibly prevents the progression of atherosclerosis [3, 5, 6]. When insulin is injected into healthy rabbits, lipemia decreases [9]. Experiments in birds indicate that insulin does not affect the development of alimentary atherosclerosis, but its use hampers the reverse development of experimental coronary atherosclerosis in birds [12].

The present article is a study of the effect of insulin on the development of alimentary hypercholesterolemia and on the cholesterol content of the aorta, liver and adrenal glands in rabbits during the development of experimental atherosclerosis.

METHODS

Experiments were performed on 24 male chinchilla rabbits of 2.5 to 3 kg in weight. The animals were divided into 3 equal groups. Rabbits of Group I were the controls, maintained on the usual diet. Rabbits of Group II received 0.12 mg of cholesterol per kg of animal weight in their feed for 45 days. Rabbits of the Group III were given cholesterol in the same doses and simultaneously were injected subcutaneously with 4 units of protamine-zinc insulin daily for 45 days. The total serum cholesterol was measured at the beginning and at the end of the experiment. On the 46th day the rabbits were killed by air emboli. At necropsy the aorta, liver and adrenals were taken for measurement of the total cholesterol content. The organs were washed free of blood by perfusion, carefully freed from surrounding tissues, the adventitia removed from the aorta. The organs were dehydrated to constant weight in a vacuum with heating and then were dissolved in alkali. The total cholesterol content was measured per 100 mg dry tissue weight. The cholesterol was extracted by a mixture of chloroform and methanol in 2 : 1 ratio. The quantity of cholesterol extracted was determined colorimetrically using the Liebermann-Burchard reaction.

RESULTS

In rabbits kept on the customary diet the total blood serum cholesterol during the observation period did not change. At the start of the experiment it was an average of 68 ± 5.7 mg% and at the end—70 ± 4.6 mg%. In rabbits given cholesterol, i.e., kept under conditions which reproduce alimentary atherosclerosis, the blood serum cholesterol level toward the end of the experiment had markedly increased (mean rising from 80 ± 5.1 to 1670 ± 141 mg%). In animals receiving insulin at the same time as cholesterol the increase in serum cholesterol content on the 45th day of the experiment was less marked (rise from 71 ± 5.2 to 1044 ± 124 mg% mean values). Consequently, the injection of insulin deters development of alimentary hypercholesterolemia.

At necropsy of the animals which had been given cholesterol alone, solitary lipid patches were visible to the eye in all cases in the aorta, mainly in the arch and in parts of the main arteries arising therefrom. In rabbits which had received insulin and cholesterol, no macroscopic changes were detected in the aorta. Evidently insulin inhibits

Effect of Insulin on Cholesterol Content of Blood Serum and of Organs

Rabbits	No. of rabbits	Aver. level of cholesterol in blood at end of expt. (in mg%)	Aver. cholesterol content (per 100 mg of tissue dry weight		
			aorta	liver	adrenals
Healthy	8	70 ± 4,6	0,08 ± 0,00	0,25 ± 0,03	1,8 ± 0,4
Treated with cholesterol	8	1 670 ± 141	0,39 ± 0,05	1,44 ± 0,3	10,3 ± 1,1
Treated with cholesterol and insulin	8	1 044 ± 124	0,23 ± 0,03	2,74 ± 0,4	14,5 ± 1,5

the formation of alimentary lipoidosis of the aorta. The cholesterol content in the aortas of rabbits which had received cholesterol only was also higher than in rabbits which had received the combination of cholesterol and insulin (see table).

The cholesterol content of the liver and adrenal glands in rabbits with experimental atherosclerosis was considerably greater than in healthy rabbits, and was even more significantly elevated in these organs in animals receiving the combination of cholesterol and insulin.

Thus, the administration of insulin under conditions which reproduce alimentary atherosclerosis leads, together with inhibition of the development of hypercholesterolemia, to a sharp increase in the cholesterol content of the liver and adrenals. The accumulation of cholesterol in the liver and adrenals as the result of insulin administration may be one reason for the lower blood cholesterol level. In turn, this possibly controls the decrease in aortic lipoidosis and leads to more moderate total cholesterol content in the aortas of animals given insulin in the period of atherosclerosis production. The experiments showed that the administration of insulin in atherosclerosis prevents the development of vascular injury because of its effect on the blood cholesterol level. Significant accumulation of cholesterol in the liver and adrenals evidently indicates an increase in cholesterol catabolism since these very organs are the main sites for cholesterol transformation and secretion. The experiments here performed indirectly confirm the advisability of using rational insulin therapy in diabetic patients with atherosclerosis.

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