

EFFECT OF AGE ON DEVELOPMENT OF EXPERIMENTAL ATHEROSCLEROSIS IN CASTRATED RABBITS

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The least marked changes in lipid metabolism after castration develop in rabbits of reproductive age (8-12 months); atherosclerotic lesions of the aorta likewise are absent in this group.

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The object of the present investigation was to examine the incompletely studied problem of the role of age in the action of estrogens in atherosclerosis [1-11, 13].

EXPERIMENTAL METHOD

Experiments were carried out on 72 female rabbits. Castration was performed on 33 sexually immature females aged one month and weighing about 700 g and 25 rabbits of reproductive age (8-12 months) weighing 2.5-3.5 kg. Three months after castration the rabbits were divided into four groups depending on the character of the experiments carried out during the next 3 months: castrated animals (group 1); castrated rabbits receiving estradiol dipropionate (group 2); castrated animals receiving cholesterol (group 3), and castrated rabbits receiving both cholesterol and estradiol dipropionate (group 4). In addition, rabbits aged 4 years and weighing 4-4.5 kg also were castrated. At the same time as the castrated animals were fed with cholesterol, noncastrated rabbits received cholesterol for 3 months: 9 animals aged 4 months, corresponding in age to the castrated sexually immature rabbits, and 5 aged about 1 year, corresponding to the age of the castrated sexually mature animals. The experiment lasted for 6 months. Cholesterol was given with chopped carrot in a dose of 0.12 g/kg body weight daily. Estradiol dipropionate was injected intramuscularly three times a week in a dose of 0.02 mg/kg body weight. Five noncastrated rabbits not receiving cholesterol, corresponding in age to the sexually immature animals, and five rabbits aged 10-13 months were investigated. The serum concentrations of cholesterol and phospholipids were determined and the cholesterol/phospholipids ratio calculated. At autopsy the uterus was weighed. The aorta was stained in toto with Scharlach red and examined macroscopically.

EXPERIMENTAL RESULTS

The mean serum cholesterol concentration throughout the experiments is given in Table 1. The phospholipid concentration changed in the same direction as the serum cholesterol, but the change was less marked so that the cholesterol/phospholipids ratio corresponded to the change in cholesterol concentration.

In all the old rabbits, at several places in the aorta marks of lipid deposits slightly elevated above the surface of the intima and brightly stained with Scharlach red were found. No information could be obtained in the literature concerning such massive deposition of lipids in the aortic wall after castration [4, 8, 12]. In our experiments the deposition of lipids in the aortic walls of the castrated old rabbits took place in association with a comparatively small and brief increase in the serum cholesterol concentration.

After castration of sexually mature rabbits of reproductive age deposition of lipids in the aorta could not be detected macroscopically. In the castrated sexually immature rabbits, small lipid spots stained with Scharlach red were found in the initial part of the thoracic aorta in only two cases: in one castrated rabbit and one castrated rabbit receiving estradiol dipropionate. In these two rabbits the serum cholesterol concentration was highest two months after castration (140 and 150 mg%).

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TABLE 1. Serum Cholesterol Concentration and Severity of Aortic Lesions in Castrated Rabbits of Different Ages

Age of animals at beginning of experiment	Experimental conditions	No. of animals	Serum cholesterol concentration (in mg%)			Severity of aortic atherosclerosis in each rabbit	
			before experiment	6 mos. after castration (3 mos. feeding with cholesterol, administration of estradiol dipropionate)			
1 month	Castration	9	50±2,3	101±10,4	P>0,5	+	—
	Castration + estradiol propionate	8	66±4,5	141±15,4	P<0,02	+	—
	Castration + cholesterol	8	54±4,3	479±27	P<0,001	++++	++
	Castration + cholesterol + estradiol dipropionate	7	56±4,5	320±33	P<0,001	++++	++
8-12 months	Castration	7	56±3	91±5	P>0,5	—	—
	Castration + estradiol propionate	6	63±7	62±4	P<0,05	—	—
	Castration + cholesterol	7	59±4	247±6	P<0,05	+++	+
	Castration + cholesterol + estradiol dipropionate	6	50±7	207±25	P<0,001	+++	+
More than 4 years	Castration	4	84±2,4	143±20	P<0,05	+++	++
4 months	Cholesterol	10	82±7,6	158±11	P<0,001	++++	++
	Control	5	80±5	53±2,4		—	—
12 months	Cholesterol	5	72±6	234±30	P>0,05	+++	+
	Control	5	53±2,6	65±8		++	—

Note. P determined relative to initial data of this same group, and in all other cases relative to control groups of corresponding age.

It is important to note that the dose of estradiol dipropionate given in our experiments to the sexually immature castrated rabbits evidently gave rise to a blood level of estrogens close to the physiological level for animals of this age, because the weight of the uterus of the castrated rabbits receiving estradiol dipropionate was almost equal to the weight of the uterus of noncastrated rabbits of the same age. In rabbits castrated in the reproductive age the weight of the uterus after administration of the same dose of estradiol dipropionate was 50-100% higher than the weight of the uterus of the control rabbits.

It may be concluded from a generalization of the results of these experiments that castrated sexually mature female rabbits of reproductive age are the most resistant to changes in the lipid indices after castration. Even in animals fed with cholesterol, ovarioectomy did not cause an increase in the blood cholesterol level in rabbits of reproductive age (Table 1). These observations strongly demonstrate the reliability of the mechanisms controlling lipid metabolism in young animals of reproductive age. The mechanisms regulating lipid metabolism in females before reaching the age of sexual maturity are evidently less reliable.

The group of old animals in our experiments was too few in number to allow the results obtained in experiments on them to be regarded as anything more than preliminary. However, the consistency of the changes in all the rabbits of this small group suggests that the mechanisms controlling lipid metabolism in old rabbits are the least reliable of all.

Clearly, the most important factor determining deposition of lipids in the aortic wall after castration is the state of the vascular wall itself, reacting differently to castration of animals of different age groups.

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