EFFECT OF SUGAR ON ATHEROSCLEROSIS IN NONHUMAN PRIMATES

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FROM our laboratory^{1,2} it has been reported that high sucrose feeding is capable of producing wide-spread vascular lesions of aorta, heart and kidney in rabbits. The present paper deals with the effect of sucrose feeding on atherosclerosis in monkeys.

MATERIALS AND METHODS

Rats, rabbits and monkeys were fed experimental diets for a period of fourteen months, four eleven and 25 months, respectively. The basic diets were commercial products of Oriental Biochemicals, Tokyo. The amounts of sugar fed to animals were 19.5 gm for rats, 100 gm for rabbits and 40–80 gm for monkeys. Monkeys used averaged 2 kg in initial weight and consisted of 5 *Macaca irus*, 1 *Macacus rhesus* and 1 *Macacus fuscatus*. At the end of the feeding period the animals were bled and killed. The serum cholesterol, triglycerides and phospholipids were determined. Various serum enzymes and serum electrolytes were also measured. Microscopic examinations of aorta, brain, heart, kidney and liver were carried out by conventional histological methods.

RESULTS

In the previous reports we reported that sucrose-feeding to rabbits caused aneurysm-like lesions in the aorta, the thickening of the intima and the necrosis of the media of the aorta, coronary sclerosis, large scars in the myocardium and diabetic glomerulosclerosis-like lesions in the kidney. Furthermore, cataract and symmetric gangrene at the sole of the foot developed, and

abnormal glucose tolerance test was recognized. Although the mechanisms responsible for the development of sucrose-induced vascular lesions are not completely defined, it seems likely that an impairment of glucose metabolism is implicated in arterial lesions.

Sucrose-fed rabbits lost their body weight before their death (Fig. 1). Therefore, we divided the rabbits in 2 groups according to the degree of weightloss. In the animals whose loss of the body weight was more than 30% of their maximal weights, loss of hair, an abnormal scaly condition of the skin, dermatitis, disappearance of visceral fats, symmetric gangrene of a sole of foot, and cataract were observed more frequently than in those whose weightloss was not so significant (Fig. 2). The similar symptoms were reported to be produced by the rigid exclusion of fat from the diet in rats. Burr *et al.*^{3,4} reported that the whole tale in those animals became heavily scaled and ridged, resulting in the loss of one to three cm of the tail. When twenty rats were reared on Diet MF supplemented by 16 gm of sucrose, all of them lost their tails 1 to 3 cm within six weeks (Table I). It should be emphasized that the lesions produced by sucrose feeding in rabbits are quite similar to Burr's findings which is produced by the careful exclusions of fats from the diet and is readily prevented or cured by the addition of 2 per cent of fatty acids to the diet. These data led us to the

TABLE I LOSS OF THE TAILS OF SUCROSE-FED MONKEYS AND RATS

	Changes of the Tail Monkey 13 M.	Rat 6W.
Sucrose Group	4 / 4	20 / 20
Control Group	0 / 3	0 / 10

Key Words:

Atherosclerosis
Essential fatty acid deficiency
Sucrose-induced arteriosclerosis
Coronary heart disease

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Fig.1. Body weight of sucrose-fed rabbits.

Fig.2. Incidence of loss of hair, dermatitis, aortic atherosclerosis, disappearance of visceral fats, cataracta and symmetric gangrene of foot in sucrose-fed rabbits.

chromatographic comparison of fatty acid composition of cholesterol ester obtained from intact and scaly skin of the animals. Although the fatty acid composition of serum cholesterol ester was normal in sucrose-fed rabbits, percentages of oleic acid and linoleic acid were found to be low

for cholesterol ester obtained from the scalp skin and that of palmitoleic acid to be high (Fig. 3). Further studies should be performed to determine whether essential fatty acid deficiency is incriminated in the pathogenesis of arteriosclerosis.

Sucrose were given as lump sugar to 7 monkeys. Four of them who took much lump sugar than the other 3 animals, were sacrificed at the end of the experimental period of 26 months. Their body weight ranged from 2.1 to 2.4 kg at the start of the experiment and from 4.3 to 4.6 kg at autopsy. It seems that they arrived at puberty. Serum cholesterol levels ranged from 154 mg% to 264 mg% and triglyceride levels were within the normal range. Although glucose tolerance test was not carried out, the fasting blood sugar levels were slightly higher than those of control animals (130, 134, 168 mg%).

In previous works, we have found that there is a significant rise in serum SGOT, SGPT, LDH, CPK and alkaline phosphatase in sucrose fed rabbits. Sucrosefed monkeys also had elevated serum alkaline phosphatase, GOT, GPT, LDH and CPK. On the other hand, there were no changes in BUN, serum electrolytes, serum uric acid and serum creatine levels. The mechanism of elevation of serum enzymes was not defined.

The first change during sucrose feeding was loss of tail. It was not observed in the control animals (Table I). It was quite similar to the loss of the tail, just as observed in sucrose-fed rats.

Fig.3. Gas chromatography of cholesterol esters obtained from the normal and scalp skins of rabbits.

Fig.4. A photomicrograph of a tail from a monkey fed sucrose.

Microscopically, the skin was thickened and the subcutaneous tissue was fibrous. Larger arteries were severely occluded. The media of larger arteries in the tail became fibrous and increased in collagen and lost muscular cells. The intima was thickened and fibrous. In the smaller arteries the fibrosis of the media was observed, but the thickening of the intima was not so significant.

Arterioles revealed edematous intima and endothelial cells proliferation, resulting in the occlusion of the lumen (Fig. 4).

Atheroma was not detected by naked eye inspection in aortas. Microscopically, the intima was thickened and uneven and lots of foam cells were observed beneath the endothelium. Small number of foam cells were also observed in the

Fig. 5. A photomicrograph of aorta from a monkey fed sucrose.

depth of the intima. There were no significant changes in the media (Fig. 5).

In the heart scars were not observed macroscopically. Larger coronary arteries had thick intima and many foam cells. Some of the intima were fibrous and oedematous. In the same region lack of muscle cells was noted in the media. A small number of foam cells were present in the thickened media and AMPS were also accumulated in the same region. The intima of the smaller arteries displayed large, fibrous hillocks bathed with mucopolysaccharides. The smaller arteries in the myocardium did not show any significant changes. Microscopic examination of the myocardium revealed small foci of necrosis (Fig. 6).

The kidneys were normal except for diffuse swelling of the glomeruli.

DISCUSSION

The loss of tail was the first change observed during the experiment. It developed within 1 year. This was not true for the monkeys who did not like to take lump sugar. Furthermore, many arteries in the tail were found to be occluded. The loss of the tail was also observed in sucrose-fed rats. Therefore, it is possible that the loss of tail is due to the arterial lesions produced by sucrose-feeding.

Lesions of coronary arteries and aortas were found to be milder and differed in the nature in monkeys kept on a high sucrose diet, when compared to sucrose fed rabbits. The rabbits

developed aneurysm-like lesions of aortas with necrosis and calcification of the media and coronary sclerosis of elastofibrous type, while the intimal layers of aortas and coronary arteries of the monkeys kept on sucrose diet revealed deposition of fat and the media were not affected significantly. Some coronary arteries of the monkeys showed large amounts of mucopolysaccharides in the subendothelial spaces and inner media. A few of the rabbits developed infarction-like massive myocardial necrosis.

It is of great interest that rabbits and monkeys respond differently to the high sucrose diet. The mechanism by which this difference occurs has yet to be established. Using rats, some workers⁵⁻⁷ have noted elevations of lipid levels on sucrose administration compared with starch regimens; The converse has been found by others.⁸ *Kritchevsky et al*⁹ reported that in rabbits kept on diet with the carbohydrate component of 40% the average serum cholesterol level was 310 mg% and atheromata were observed in the aortas, whereas in our previous work serum cholesterol level remained to be about 60 mg% and lesions without participation of lipids were observed. In the present work serum cholesterol level of the monkeys was about 200 mg% at the end of the experiment. It is possible that serum cholesterol level might play some part in the different response of rabbits and monkeys to a high sucrose diet.

Vascular lesions noted above are likened to

Fig.6. A photomicrograph of coronary artery from a monkey fed sucrose.

spontaneous arterial lesions in monkeys. Thus, the question we are faced with is whether or not the vascular lesions mentioned above are spontaneous arterial lesions. The ages of the monkeys used were unknown, but they weighed about 2 kg at the start of the experiment and about 4 kg at its end. A body weight of 4.0 kg is considered to correspond to sexual maturation. Considering the data^{10,11} concerning spontaneous arteriosclerosis in monkeys, it is postulated that the severity of the above-mentioned vascular lesions are too severe for the age, and sucrose-feeding accelerates the development of arterial lesions. The loss of the tails and histologic findings in sucrose-fed monkeys support this conclusion. *Lang* and *Barthel*¹² studied the response of serum lipid levels and atherosclerosis to diets containing large amounts (66%) of either simple or complex carbohydrates for 16 months in monkeys and reported the high levels of serum cholesterol and triglycerides as well as the high incidence of atheromatous lesions. Their results correspond favorable with our results.

In our previous study we observed in sucrose-fed rabbits lesions which consist of deposition of the hyaline mass in the glomeruli, positive stained by PAS and are likened to diabetic glomerulosclerosis in man; on the other hand, in the present studies such lesions were not demonstrable in the kidney of sucrose-fed monkeys. In those rabbits glucose intolerance was established

and cataract and symmetric gangrene were also observed. Glucose tolerance tests, however, were not able to be performed in sucrose-fed monkeys, but the fasting blood sugar levels tended to be higher. Affection of large and small arteries in the tails and hearts in the monkeys led me to suggest that in sucrose-fed monkeys disturbed carbohydrate metabolism might play some part in the early appearance of arterial lesions. *Cohen* and *Rosemann*¹³ found an impaired glucose tolerance curve in 8 rats fed with a high sucrose diet and noted diffuse intercapillary glomerulosclerosis of the kidneys in 5 of them.

In 1969 *Yudkin*^{14,15} stated that there is now quite strong evidence that dietary sugar—sucrose—was an important factor in the etiology of coronary heart disease. The widely publicized theory has since been examined, but is not supported by acceptable clinical, epidemiological, theoretical or experimental evidence. The working Party on the Relationship between Dietary Sugar Intake and Arterial Disease¹⁶ has recently reported as follows: The sugar consumption of men with myocardial infarction was compared with that of matched controls in four different centers. The average sugar consumption was slightly greater in the patients with myocardial infarction than among the controls, but the differences were not statistically significant. Findings in one center suggested that the slightly higher sugar intake in patients with myocardial

infarction were likely to have been due to an association between the consumption of sugar and the smoking of cigarettes.

In the present study the loss of the tail and the early appearance of aortic and coronary atherosclerosis were established in sucrose-fed monkeys. Although Yudkin's claim was not supported, our data led me to postulate that extremely high intake of sucrose should be avoided. The risk of disturbance of carbohydrate metabolism induced by high intake of sugar gives support to this conclusion.

SUMMARY

In male monkeys, the response of serum lipid levels and atherosclerosis to diets containing large amounts of sucrose were studied for a period of 26 months. The first change during the experiment was the loss of tail which was also observed in sucrose-fed rats. Atheromatous lesions were observed in aorta and coronary arteries. The fasting blood sugar and cholesterol levels were increased.

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