PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 151, 368-371 (1976)

Effect of Low Calorie Diet on the Hyperlipidemia, Hypertension, and Life Span of Genetically Obese Rats[1] (39212)

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A new strain of genetically obese rat was recently obtained in our laboratory (1, 2). The abnormal phenotype is inherited as a homozygous recessive trait. Along with obesity the animal develops a hyperlipidemia, which consists of a marked hypertriglyceridemia and a moderate hypercholesterolemia and is independent of high dietary fat intake. The electrophoretic pattern usually contains a prominent prebeta band (VLD lipoproteins) and resembles that of human type 4 hyperlipoproteinemia. The obese animals also develop proteinuria and spontaneous hypertension. Their average life span is only 10 months, and most deaths are due to kidney failure or to the complications of atherosclerosis.

Because the obese rats exhibit hyperphagia a study was made of the effect of a low caloric diet on the various abnormalities, especially the obese state, the hyperlipidemia, and the high blood pressure, and also on the longevity of the animals.

Methods. Genetically obese rats, 3 months old and of both sexes, were divided into two groups. One group was offered food (Purina chow) *ad libitum* while the other was placed on a daily intake of 12 g of Purina chow, which is approximately one third the amount eaten on an *ad libitum* basis. All animals received tap water *ad libitum* for drinking.

Body weight, plasma lipids, electrophoretic pattern, proteinuria, and blood pressure were obtained just prior to instituting these regimens and then subsequently according to the following schedule and methods: body weight weekly, plasma lipids by autoanalyzer every 2 months after overnight fast, electrophoretic pattern by the polyacrylamide gel technique (Canalco, Rockville, Maryland, QDL reagent kit), proteinuria every 2 months by the method of Shevsky and Stafford (3), and blood pressure monthly under anesthesia (0.2 ml of a 2% nembutal solution/100 g of body weight) by inserting a polyethylene cannula into a femoral or brachial artery and connecting it to a Hg manometer.

Results. The effect of the *ad libitum* and restricted diets on the body weights of the genetically obese rats is shown in Fig. 1. While the animals fed *ad libitum* became progressively larger throughout their lifetime, those on low caloric intake showed a marked reduction in weight. The latter declined continually during the first 2 months of diet and by the end of this period the animals had lost about one third their predietary weight. Thereafter the weight stabilized within a narrow range. With the loss in weight the obesity diminished and body habitus gradually reverted toward lean. This evidently resulted from depletion of lipid stores which were used to meet the energy requirements of the body.

The animals on low caloric diet remained in fairly good condition in spite of marked weight loss. Their fur was cleaner and they were more active than their counterparts on unrestricted diet. Also they did not develop decubiti in the pubic and cervical regions, such as occurred frequently among the control animals as a result of pressure from obesity and immobility.

The low dietary intake uniformly resulted in a substantial lowering of plasma triglycerides. The latter declined from a mean predietary level of 300 mg/100 ml to 94 mg/100 ml by 2 months and then remained permanently reduced and at levels which usually were only slightly above normal (Fig. 2). With the fall in triglycerides the plasma changed from turbid or cloudy to clear, and the prominent prebeta band in the electrophoretic pattern became faint or absent.

[1] Supported by Grant No. 74-852 from American Heart Association.

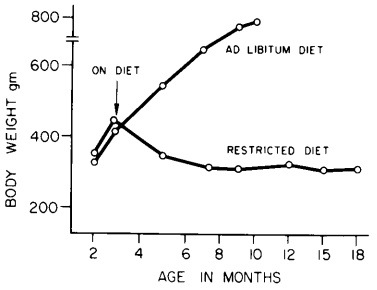

FIG. 1. Body weight of genetically obese rats. N = 20 rats in each diet group.

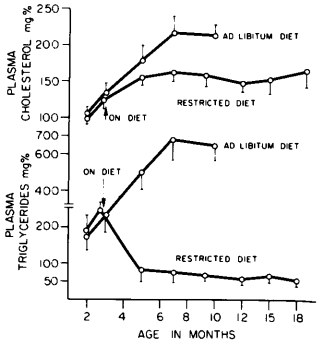

FIG. 2. Plasma lipids of genetically obese rats. N = 20 rats in each diet group.

In contrast to the behavior of the triglycerides the plasma cholesterol of the obese rats continued to rise above the predietary level in spite of low caloric intake. The increase continued for the first few months of diet before stabilizing at levels which were slightly to moderately above normal. However, the elevation in plasma cholesterol was distinctly less than in animals receiving food *ad libitum* (Fig. 2). After 4 and 6 months of low caloric intake the mean plasma cholesterol was 28% lower (162 mg/100 ml as compared to 224 mg/100 ml) and 25% lower (157 mg/100 ml compared to 212 mg/100 ml), respectively, in animals on restricted food intake. The reductions at these intervals are significant ($P < 0.01$).

Due to a membranous glomerulopathy the obese rats fed *ad libitum* showed proteinuria when 2–3 months old, and this progressed so that by 7 months of age up to 800 mg of protein were excreted daily in the urine. The proteinuria was uniformly abolished in the animals placed on a low caloric diet. After 2 months of this regimen the urinary excretion of proteins was either within normal limits or only slightly elevated, and thereafter did not exceed 50 mg daily.

As shown in Table I reduction in caloric intake and loss of weight failed to lower the blood pressure and alleviate the hypertensive state even in animals maintained on diet for 15 months. In fact, the rats on restricted diet tended to have higher pressures than did those on *ad libitum* regimen.

The longevity of the obese animals maintained on a low calorie diet was greatly increased. Whereas the rats on *ad libitum* food lived an average of 10 months those on restricted diet have already lived over 18 months.

Discussion. Restricted food intake was highly beneficial to the genetically obese rats, i.e., the body weight of the animals dropped sharply, obesity gradually diminished, the hypertriglyceridemia was almost eliminated, the hypercholesterolemia was reduced and longevity was substantially increased.

Genetically obese rats subjected to a low calorie diet showed a substantial loss of body weight, and this was accompanied by a marked reduction in plasma triglycerides. The latter declined to normal levels in some instances, although usually there was a slight residual hypertriglyceridemia. In a similar way, restricted caloric intake also reduces the hypertriglyceridemia of humans with type 4 hyperlipoproteinemia (4–6). Treatment of the latter consists of reduction to

TABLE I. BLOOD PRESSURE OF GENETICALLY OBESE RATS.[a]

Age (months)	Blood Pressure (mmHg)	
	Ad libitum diet (20)	Low calorie diet (20)
3 (control)	150 ± 14	154 ± 18
5	160 ± 18	185 ± 19
7	172 ± 16	196 ± 22
9	185 ± 20	192 ± 20
10[b]	176 ± 22	185 ± 18
12		200 ± 24
15		204 ± 16
18		188 ± 12

[a] Values are mean ± SD. Number of animals in parentheses.

[b] Average life span of obese rats on *ad libitum* diet is 10 months.

ideal body weight by means of a restricted diet which is low in amount of carbohydrate and preferably low in content of saturated fats and cholesterol. In our study of genetically obese rats these requirements were met by utilizing small amounts of Purina chow which has only a 5% content of fat.

The behavior of the plasma cholesterol in obese rats subjected to low caloric intake differed from that of the triglycerides. This was not surprising since the level of plasma cholesterol depends on both endogenous and exogenous dietary factors. In spite of restricted food intake the plasma cholesterol continued to rise for a brief interval and then stabilized at slightly to moderately elevated levels. However, the latter were significantly lower than those for obese animals on *ad libitum* diet. This finding parallels that of Olefsky *et al.* (7) who maintained 30 obese hyperlipidemic individuals (17 with type 4, 10 with type 2, and 3 with type 3) on low caloric intake for 2–10 months (average 4.3 months) in order to achieve a weight loss of 11 kg and found that the decline in weight was accompanied by a 21% reduction in the level of plasma cholesterol. However, Wilson and Lees (8) reported that the plasma cholesterol was unchanged in six hyperlipidemic individuals (five with type 4 and one with type 3) following dietary restriction and weight loss.

At present the concensus is that in humans the caloric content of the diet affects the concentration of blood cholesterol (9–11). The latter generally rises following overconsumption of food and falls during intervals of low caloric intake and weight loss. In the presence of a diet low in total calories even a high cholesterol intake did not result in elevated levels of blood cholesterol (10).

The restricted diet eliminated the proteinuria of the obese animals apparently by arresting the glomerulopathy responsible for excretion of protein. How such arrest was achieved is not clear, although the beneficial effect may have resulted, at least in part, from reduction in the excretory load of the kidneys. A similar glomerulonephropathy and proteinuria occurs in rats rendered obese by hypothalamic injury (12, 13), as well as in aging normal rats (14–16), and in each instance the renal lesion was shown to be enhanced by overconsumption of food and retarded by a restricted diet. An association between obesity and proteinuria (17–20) and of both of these with glomerular nephropathy (19, 20) has also been noted in the human. In such individuals loss of weight by dietary means was accompanied by a remission of the proteinuria.

The restricted diet failed to alleviate the hypertensive state of the obese animals. This result is at variance with the apparently widespread notion that weight reduction will lower the blood pressure of obese hypertensive individuals (21). While the high blood pressure of the obese animals is genetically based, its precise cause is not known. However, it is clearly independent of the obesity and hyperlipidemia exhibited by the rats.

The obese rats which were permitted to eat *ad libitum* died prematurely at about 10 months of age, mainly of renal failure due to glomerulonephritis or of intra-abdominal hemorrhage from a ruptured atherosclerotic artery. A low calorie diet eliminated premature death. On such a regimen the life span of the animals has nearly doubled and may ultimately approach or equal that of normal rats. Undoubtedly the restricted diet served to prevent or arrest the development of renal and vascular disease in these animals.

Summary. A new strain of genetically obese rat recently obtained in our laboratory exhibits endogenous hyperlipidemia (marked hypertriglyceridemia and moderate hypercholesterolemia) and spontaneous hypertension. The animals die prematurely from kidney failure or from the complications of atherosclerosis. A low calorie diet proved to be highly beneficial to these rats. Body weight declined, obesity diminished, the hypertriglyceridemia was almost eliminated, and the hypercholesterolemia was reduced. However, the hypertensive state was not alleviated. Since the life span of the rats was greatly prolonged by a low calorie diet, the latter undoubtedly served to prevent or arrest the development of renal and vascular disease in these obese animals.

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Received September 8, 1975. P.S.E.B.M. 1976, Vol. 151.