STRAIN DIFFERENCES IN THE RESPONSE OF SERUM CHOLESTEROL TO DIET IN INBRED RABBITS, RATS AND MICE

A.C. Beynen[1], M.B. Katan[2] and L.F.M. van Zutphen[1]

[1]Department of Laboratory Animal Science, State University, P.O. Box 80.166, 3508 TD Utrecht, [2]Department of Human Nutrition, Agricultural University, De Dreijen 12, 6703 BC Wageningen (The Netherlands).

ABSTRACT

Both in man and various animal species differences have been observed between individuals in the response of serum cholesterol to changes in the diet. We have employed inbred strains of laboratory animals with defined, but different cholesterolemic responses to diet to study this phenomenon. In male rabbits of six inbred strains we observed a 5-fold range of differences between strains in the response of plasma cholesterol to the addition of 0.5% (w/w) cholesterol to the diet. Male animals of 10 inbred strains of rats and 7 strains of mice were challenged with a diet containing 2% (w/w) cholesterol, 0.5% cholate and 5% olive oil. A 8 to 10-fold range of between-strain differences in the cholesterolemic responses of the mice and rats was found. Further studies were performed with two selected rabbit strains that differed in the sensitivity to dietary cholesterol. The hyperresponsive strain was also found to be more sensitive to hypercholesterolemia induced by animal protein (casein versus soybean protein) and by saturated fat (coconut fat versus corn oil). The diets used were cholesterol-free and consisted of semipurified components; either the protein or fat type were the only dietary variables. Two rat strains previously found to be hyperresponsive to a diet containing cholesterol, cholate and olive oil, were now fed a semipurified diet containing 1% of cholesterol and 20% of fat, and so were two hyperresponsive strains. The responses of serum cholesterol to the semipurified diet (when compared with a commercial diet) in the hyporesponsive strains were similar to those in the hyperresponsive strains. Thus, in these rat strains clear differences in responsiveness are seen only on diets containing both cholesterol and cholate.

INTRODUCTION

The type of fat and the amount of cholesterol in the diet affect the level of serum cholesterol in man. The effects of these dietary components can be predicted using emperical formulas (1). However, such predictions of serum cholesterol changes only hold for group means and not for individual subjects. Evidence has been presented that persons exist with a consistently high response (hyperresponders) or low response (hyporesponders) of the concentration of serum cholesterol to increased intakes of cholesterol (2) or to replacement of polyunsaturated dietary fatty acids by saturated fats (3). The mechanisms underlying hypo- and hyperresponsiveness have not yet been unraveled (4). The availability of inbred strains of laboratory animals with defined, but different cholesterolemic responses to changes in diet, may be of great importance in order to shed more light on the mechanisms involved.

Cholesterol Metabolism in Health and Disease: Studies in the Netherlands, edited by A. C. Beynen, M. J. H. Geelen, M. B. Katan, and J. A. Schouten. Ponsen & Looijen, Wageningen 1985

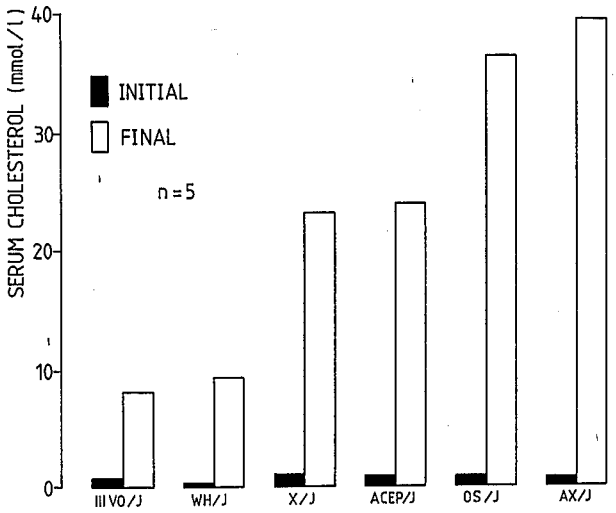

Fig. 1. Serum cholesterol levels in inbred strains of rabbits before and after feeding a diet containing 0.5% (w/w) cholesterol for 28 days (5).

Fig. 1 shows the levels of serum cholesterol in male rabbits of six inbred strains. The animals were sampled while they were on a commercial rabbit chow diet and also after 28 days of receiving the same diet to which 0.5% (w/w) cholesterol had been added. The animals with the most extreme response (AX/J) showed a 5-fold higher increase in serum cholesterol than the strain with the lowest response (IIIVO/J). These two strains are at present maintained at the Department of Laboratory Animal Science, Utrecht.

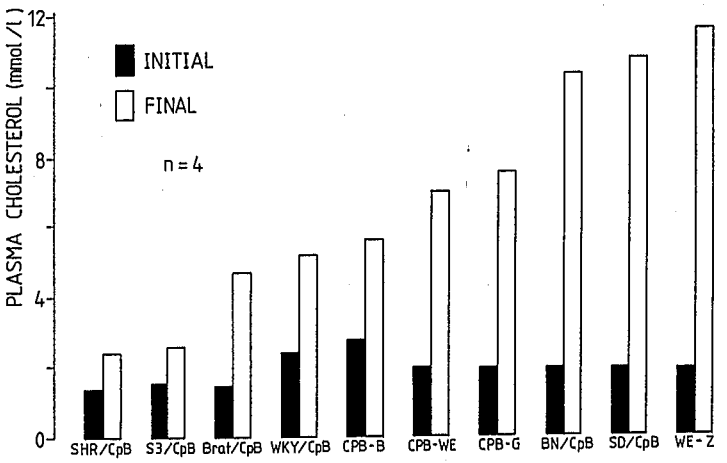

Fig. 2. Plasma cholesterol levels in inbred strains of rats sampled before and 21 days after feeding a diet containing 2% cholesterol, 0.5% cholate and 5% olive oil (6).

For cholesterol loading studies with rats and mice we have used a commercial diet to which 2% (w/w) cholesterol, 0.5% cholate and 5% olive oil had been added. Fig. 2 shows that transfer of male, inbred rats from a commercial diet (which contains about 20 mg of cholesterol per 100 g) to the high-cholesterol diet revealed inter-strain differences in the response of plasma cholesterol. The increase in plasma cholesterol varied from 75% (SHR/CpB) to 500% (WE-Z). Strain differences in the response of plasma cholesterol to the high-cholesterol diet were also seen in male inbred mice (Fig. 3).

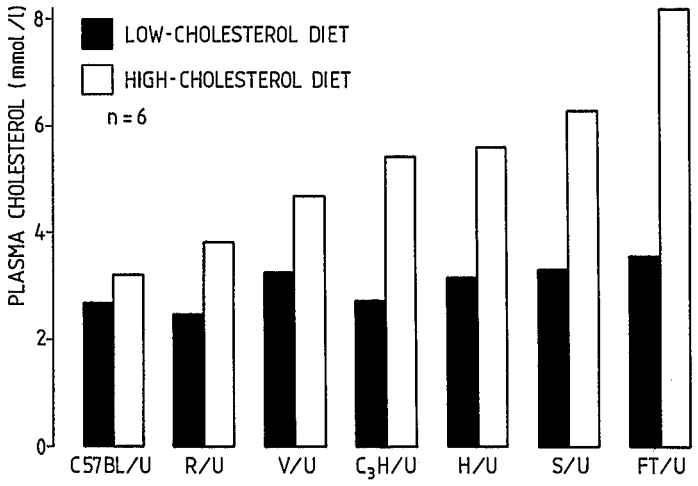

Fig. 3. Plasma cholesterol levels in inbred strains of mice fed either a commercial diet or a diet containing 2% cholesterol, 0.5% cholate and 5% olive oil for 28 days.

EFFECTS OF DIETARY COMPONENTS OTHER THAN CHOLESTEROL

It is important to know whether hyperresponders to dietary cholesterol are also hyperresponsive to other dietary components, as such information may provide further clues to the mechanisms underlying the differences in cholesterolemic response to cholesterol. It is well-known that cholesterol-free, semipurified diets containing casein as a protein source produce hypercholesterolemia in rabbits, and that no such effect is observed with soybean protein. The replacement of polyunsaturated fat (corn oil) by saturated fat (coconut fat) also elevates serum cholesterol levels in rabbits. Fig. 4 shows that the inbred rabbits hyperresponsive to dietary cholesterol (AX/Ju) are also more sensitive to the type of protein and type of fat in the diet compared with the hyporesponders (IIIVO/Ju). The diets were essentially cholesterol-free and consisted of semipurified components (cf. ref. 7 and 8); the protein or fat type were the only dietary variables. Fig. 4 also shows the response of plasma cholesterol in the two rabbit strains to the consumption of a commercial diet to which 0.3% of cholesterol had been added.

Although rats are notoriously insensitive to dietary cholesterol, we still found (9) that in male rats of a hyperresponsive strain (SD/CpB) the addition of 1% of cholesterol to a semipurified diet induced a significantly higher increase in serum cholesterol than in a hyporesponsive strain (SHR/CpB).

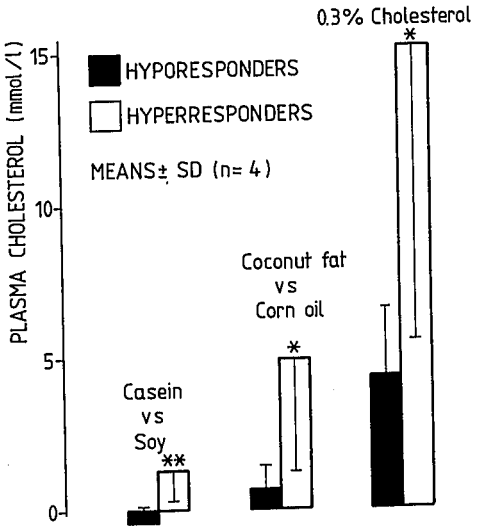

Fig. 4. Plasma cholesterol responses to different hypercholesterolemic dietary components in the same male rabbits of two inbred strains. All diets were fed for 4 weeks.

However, the absolute responses (0.17 ± 0.12 mmol/l in the hypo- and 0.45 ± 0.27 in the hyperresponders; means ± SD, n=6) were much lower than on the hypercholesterolemic diet containing both cholesterol and cholate (Fig. 2). Thus cholate intensifies the difference in cholesterolemic response between the rat strains. However, we have found indirect evidence that rats develop liver disease on the cholate-containing diet, which makes this model for diet-induced hypercholesterolemia less suitable.

We also made comparisons of the effects of soybean protein and casein and of pectin and cellulose in these two rat strains (SD/CpB and SHR/CpB) using cholesterol-free semipurified diets. Casein caused higher serum cholesterol levels than soybean protein and cellulose caused higher cholesterol levels than pectin. These effects were somewhat greater in the hyper- than in the hyporesponsive strain, but the difference between the strains did not reach statistical significance (9).

In another attempt to develop a suitable model of diet-induced hypercholesterolemia in rats, we used male rats of two hyperresponsive strains (SD/CpB and BN/CpB) and of two hyporesponsive strains (SHR/CpB and Brat/CpB), the classification being based on the data shown in Fig. 2. The rats were now fed a commercial diet and a semipurified diet containing 1% of cholesterol and 20% of fat, but no cholate. Fig. 5 shows that the absolute serum cholesterol levels on the high-fat, high-cholesterol semipurified diet were highest in the hyporesponsive strains (BN/CpB and SD/CpB). However, baseline levels were also elevated in these strains, and as a result, the increase of serum cholesterol on the semipurified diet compared with the commercial diet in the hypo- and hyperresponsive strains were similar. The responses to a commercial diet containing cholesterol (2%), cholate (0.5%) and olive oil (5%) were checked in the same experiment, and the results were almost identical to those

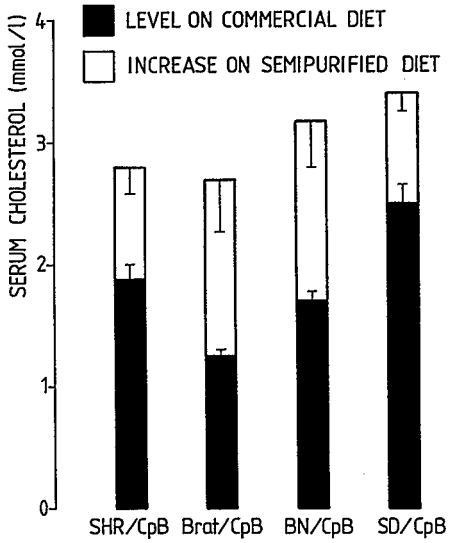

Fig. 5. Serum cholesterol levels in 4 inbred strains of rats (means ± SD, n=6) fed for 26 days either a commercial diet or a semipurified diet containing 1% of cholesterol and 20% of fat. The differences in serum cholesterol for the commercial and semipurified diet are also given.

presented in Fig. 2. Thus in these rat strains clear differences in responsiveness are seen only on diets containing both cholesterol and cholate.

CONCLUSION

We have identified inbred strains of rabbits which are hypo- or hyperresponsive to dietary cholesterol, and such strains are also hypo- or hyperresponsive to the type of dietary protein and to the fatty acid composition of dietary fat. Inbred strains of rats and mice were found to differ with respect to their cholesterolemic response to the combination of cholesterol, cholate and olive oil, but it is difficult to reproduce these differences with diets that are less extreme. Thus for the time being, the inbred rabbit strains are a superior model for studying individual differences in diet-induced hypercholesterolemia in man.

ACKNOWLEDGEMENT

M.B.K. is an established investigator of the Netherlands Heart Foundation.

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