Dietary Protein as a Regulator of Lipid Metabolism: State of the Art and New Perspectives

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Summary August 28 and 29, 1989, a workshop entitled "Dietary protein as a regulator of lipid metabolism" was held in Fukuoka. This workshop highlighted the progress that has been made since 1909, the year that Ignatowski put forward that animal proteins in the diet can induce atherosclerosis in rabbits. It is now clear that humans respond to dietary soybean protein *versus* animal proteins, such as casein, with a decrease of serum cholesterol concentrations. However, the response in humans is not as pronounced as it is in various animal models. The mechanism by which the type of dietary protein affects serum cholesterol concentrations is still a matter of debate but various elegant concepts have been launched. These concepts have contributed significantly to our current understanding of the regulation of cholesterol metabolism. Future work will concentrate on further unravelling the mechanisms involved, with special reference to proteins other than those used generally, that is soybean protein and casein.

Key Words dietary proteins, serum cholesterol, lipid metabolism

Introduction

When the workshop entitled "Dietary protein as a regulator of lipid metabolism" was held in Fukuoka, August 28–29, 1989, it was 80 years ago that Ignatowski (1) put forward that dietary animal proteins such as those in milk, eggs and meat can induce atherosclerosis in rabbits. Since Ignatowski's paper of 1909 (1), various groups of investigators (2–4) have shown in rabbits that casein is more atherogenic and produces higher serum

cholesterol concentrations than soybean protein. For these studies, cholesterol-free diets were used in which the type of protein was the only variable. Although differential effects on serum cholesterol levels have been observed with diets containing a variety of proteins (3), most studies have examined the effects of casein and soybean protein.

The papers that were presented during the workshop in Fukuoka are published in this supplement to the *Journal of Nutritional Science and Vitaminology*. It is clear that many investigators are still fascinated by the fact that dietary proteins influence lipid metabolism. It is also clear that although much progress has been made, there is considerable controversy as to the mechanisms underlying the differential cholesterolemic effects of dietary proteins. For details of the presentations during the workshop, we refer to the papers published. Here, we wish to briefly review the state of art and point to new perspectives in research on dietary proteins and cholesterol metabolism.

Why research on dietary proteins and cholesterol metabolism?

Increased concentrations of serum total and low density lipoprotein cholesterol can cause atherosclerosis and ischemic heart disease in man. Lowering serum cholesterol concentrations will delay manifestations of atherosclerosis. This applies to the entire population of Westernized countries, and especially to many hypercholesterolemic patients, in whom lowering of low density lipoprotein cholesterol will delay the occurrence of new ischemic events. The ultimate aim of research on dietary

proteins and cholesterol metabolism is to provide further insight into practical means of decreasing serum cholesterol in man through changes in dietary habits. Thus, the crucial question is whether the type of dietary protein influences serum cholesterol concentrations in man.

Sirtori *et al.* (5) reported that soybean protein feeding *versus* consumption of mixed animal proteins in type II hypercholesterolemic patients reduced the level of serum cholesterol by up to 20%. However, the consumption of the soybean protein diet in these studies also involved other changes in the diet, including the elimination of cholesterol. It is thus not possible from these studies to assess the effect of the dietary protein independently. Quite a number of studies have been published in which the type of protein was the only variable. These studies (6–11) reported either a small or no effect of the type of dietary protein on serum lipoproteins in normolipidemic subjects, and a slightly larger effect in hyperlipidemic patients. There is suggestive evidence that the cholesterol-lowering effect of soybean protein *versus* casein becomes more pronounced against a dietary background relatively high in cholesterol (11).

When all experiments with humans are considered, it would appear that soybean protein, when compared with casein, slightly lowers serum cholesterol in man. The young, growing rabbit, the most favorite animal model for studies on dietary proteins, cholesterol metabolism and atherosclerosis, certainly is more sensitive than humans. This has been demonstrated elegantly in experiments in which young rabbits were fed on the same diets as humans (7). It is conceivable that young, rapidly growing infants are more sensitive to the type of dietary protein than adults. The hypercholester-

olemic effect of casein was only observed in young growing rabbits and not in their mature counterparts (12). Indeed, Tseng *et al.* (13) reported that the type of protein in milk formulas fed from birth had pronounced effects on serum lipids of infants in a randomized, double-blind trial (Table 1). Thus, it would appear that casein produces higher serum lipid concentrations than whey protein in infants. This does not agree with studies in rabbits showing that casein and whey protein produce similar serum cholesterol concentrations (14, 15). In any event, it seems that further studies on dietary proteins in formula-fed infants may provide useful information.

Apart from practical relevance, studies on dietary proteins and cholesterol metabolism, especially those using animal models and focussing on the mechanisms involved, are important so as to broaden our insight into the regulation of cholesterol metabolism. Animal data can also be used to assist in predicting effects in humans that are not experimentally accessible in humans themselves. Furthermore, the value of the use of animal models in human research lies in the generation of ideas and hypotheses and the speeding up of the process of discovery. Perhaps the most important contribution of the use of animals concerns the widening of our basic knowledge of interactions between diet and metabolism. Comparative studies with different animal species are very useful in this respect.

Progress in research on dietary proteins and cholesterol metabolism

Since the publication of Ignatowski's hypothesis (1), a vast amount of data has been collected. The effects of various dietary proteins on serum cholesterol concentrations have been described

Table 1. Serum cholesterol and triglyceride concentrations in infants fed formulas with varying casein-to-whey protein ratios.

Casein : whey ratio	Serum cholesterol (mmol/liter)		Serum triglycerides (mmol/liter)	
	4 weeks ¹	8 weeks	4 weeks	8 weeks
82 : 18	3.5 ± 0.1	4.3 ± 0.1	1.3 ± 0.1	1.8 ± 0.1
66 : 34	3.2 ± 0.1	3.1 ± 0.1	0.9 ± 0.1	1.3 ± 0.1
50 : 50	3.3 ± 0.1	3.3 ± 0.1	0.8 ± 0.1	1.1 ± 0.1

Means ± SE for 10 infants (5 males and 5 females). The formulas were fed from birth to 8 weeks of age. ¹ Age. Adapted from Tseng *et al.* (13).

in different animal species including man. The mechanism by which the type of dietary protein influences serum cholesterol concentrations is a matter of debate. Nevertheless, many interesting concepts have been developed (16), and have contributed to our understanding of cholesterol metabolism, often reaching beyond the topic of dietary proteins.

The hypocholesterolemic effect of soybean protein *versus* casein in experimental animals is associated with increased excretion of bile acids and neutral steroids in feces, decreased liver cholesterol concentrations, increased rates of hepatic cholesterol and bile acid synthesis, increased number of lipoprotein (apo B/E) receptors on liver membranes and decreased rates of lipoprotein cholesterol output by the liver (16). How can these effects of soybean protein be explained in molecular terms, or rather, what is the initial link between dietary protein and cholesterol metabolism? It is this initial link that is seen differently by different groups of investigators. Some feel that it is at the level of the intestine, whereas others propose that dietary proteins first interact with cholesterol metabolism at the post-absorptive level. Future work should both prove and disprove one of the 2 views. While on its way, such work will have significant spin-off towards our general understanding of the regulation of cholesterol metabolism.

Future studies on dietary proteins and cholesterol metabolism

In discussions during the workshop, a few lines of future research emerged. First, there is still uncertainty about possible cholesterol effects of non-protein components in the protein preparations. Even the purest protein preparations such as soybean protein isolate and casein contain up to 20% of non-protein material. Although there is no solid evidence that non-protein components have substantial effects on serum cholesterol, it will be important to further pursue this issue. In any event, investigators should use experimental diets that are balanced with respect to different amounts of non-protein components in the protein preparations. Secondly, it is anticipated that studies using single amino acids, which may have marked effects on serum cholesterol concentrations, will shed more light on the regulation of cholesterol metabolism. On the other hand, it is questionable whether studies

with mixtures of amino acids can provide information about the effects of intact proteins (17). Thirdly, further studies on the mechanism of action of dietary proteins will involve proteins other than casein and soybean protein. Current concepts may hold only for casein and soybean protein and may not be extended to other dietary proteins. There is evidence that different animal proteins influence serum cholesterol concentrations through different mechanisms (15).

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