VEGETABLE PROTEINS AS DRUGS

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Received in final form 15 June 1987

INTRODUCTION

The physicians' armoury for attacking the problem of hypercholesterolemia in individual patients generally includes drugs. A wide variety of hypocholesterolemic drugs is marketed, and the prescribing physician must always assess the risk:benefit ratio of a given drug. As with any pharmacological intervention, there are risks and side-effects associated with the use of cholesterol-lowering drugs. The side-effects, which vary between patients, often lead to poor compliance. Drug efficacy in the recipient depends on compliance, and possibly also on the individual sensitivity to the drug (Sirtori et al., 1977b). Thus, physicians have to deal with the problem of selecting drugs and tailoring the drug regimen to their patients' requirements.

In this communication we propose that vegetable proteins, especially soybean protein, should be considered as hypocholesterolemic drugs or as a substitute for convential drugs. A diet rich in soybean protein effectively lowers serum cholesterol levels in patients with type II

0031-6989/87/060387-08/$03.00/0

hypercholesterolemia. As a rule foodstuffs containing soybean protein are well accepted, and side-effects, if any, are minimal.

EFFICACY

In 1977 Sirtori et al. reported the hypocholesterolemic activity of the soybean-protein diet in type II hypercholesterolemic patients. The soybean-protein diet contained 13% of energy as soybean protein, 6% as other vegetable protein and 1.5% as animal protein. When compared to a diet containing 8% of energy as vegetable protein and 13% as animal protein, the soybean-protein diet reduced serum total cholesterol by about 20% after three weeks. Further studies from the same laboratory (Sirtori et al., 1979) and from other laboratories (Descovich et al., 1980; Wolfe et al., 1981; Vessby et al., 1982; Widhalm, 1986) have confirmed the cholesterol-lowering activity. Diets rich in protein from other beans such as Vicia faba also exert cholesterol lowering activity in type II hypercholesterolemic patients (Weck et al., 1983). The soybean-protein diet specifically lowers cholesterol in the atherogenic low-density lipoproteins (LDL) whereas that in the anti-atherogenic high-density lipoproteins (HDL) is left unchanged or somewhat increased. The soybean-protein diet is not effective in normocholesterolemic subjects (Sirtori et al., 1977a; Carroll et al., 1978). Moreover, it has been shown that purified soybean protein preparations exert negligible anti-hypercholesterolemic activity (Van Raaij et al., 1982).

Thus there is evidence that soybean-protein diets cause a decrease in serum cholesterol, on average, by about 20% in hypercholesterolemic patients. This effect is similar to that achieved by cholesterol-lowering drugs such as clofibrate and its analogs, nicotinic acid, and the bile acid sequestrants cholestyramine and colestipol. Only combined drug regimens are

more effective. The combination of nicotinic acid and bile acid sequestrants may reduce serum cholesterol by up to 50% (Kane et al., 1981). Such a decrease normalizes serum cholesterol concentrations in heterozygous familial type II patients. Recent work has demonstrated that serum cholesterol normalization in these patients can now be achieved by a single drug regimen by using inhibitors of the key enzyme in cholesterol biosynthesis, 3-hydroxy-3-methylglutaryl Co-enzyme A (HMG-CoA) reductase. After treatment with the inhibitors, mevinolin (Illingworth and Sexton, 1984), compactin (Mabuchi et al., 1983) and synvinolin (Mol et al., 1986) serum cholesterol levels fell towards almost normal values. Thus, as to efficacy, the soybean-protein diet is as effective as single drug regimens except for HMG-CoA reductase inhibitors.

SIDE-EFFECTS

Side-effects of drugs generally have an adverse influence on compliance, and consequently also on efficacy. In addition, side-effects can deteriorate the health status of the patient. The side-effects of the classical drugs are well-known. Clofibrate and its analogs increase the lithogenic risk, as well as the potential for a variety of side effects (WHO Cooperative Trial, 1980). There is evidence that some of these drugs produce peroxisomal proliferation in rodents and possibly in man, the sequalae of which are not fully understood. Many patients using nicotinic acid develop flushing. Bile acid sequestrants have to be taken in very large quantities (up to 20 g/day) which in itself reduces patients' compliance. In addition, the sequestrants cause constipation, flatulence and nausea of varying degrees in about a quarter of the patients. Probucol lowers HDL cholesterol levels, which may be considered disadvantageous (Kesaniemi and Grundy, 1984). So far, the studies with HMG-CoA inhibitors

have not shown serious side-effects. However, it should be emphasized that no solid conclusions can be drawn yet because these studies lasted only up to 24 months (Illingworth, 1984). Effective treatment of heterozygous familial type II hypercholesterolemia is a commitment for life. Immediately after withdrawal of drug therapy, serum cholesterol concentrations will rise towards pre-treatment values.

The soybean-protein diet is generally well tolerated. It is however critically important that efforts are being made to make the soybean-protein containing foodstuffs as palatable as possible. Side-effects, if any, are increased flatulence. It is unlikely that life-long consumption of a diet enriched with soybean-protein would negatively affect health. However, absolute proof cannot be given. There is some evidence that diets enriched with soybean protein cause elevated concentrations of urate in serum (Van Raaij, 1982). Hyperuricemia could increase the risk for gout.

MECHANISM OF ACTION

The cholesterol lowering properties of soybean protein have also been demonstrated in various animal models such as the rat, hamster, rabbit, pig and monkey (West and Beynen, 1986). The rabbit is the most popular model for studying the differential cholesterolemic effects of dietary proteins. In most studies soybean protein has been compared with the prototypical animal protein, casein. Using cholesterol-free, semipurified diets with the protein source as the only variable, soybean protein induces no hypercholesterolemia and atherosclerosis, whereas casein does (Kritchevsky, 1979). Likewise, on diets containing other vegetable proteins such as cottonseed protein, sunflowerseed protein and peanut protein, rabbits also maintain low concentrations of serum cholesterol (Carroll, 1982).

For the rabbit model the mechanism underlying the cholesterol lowering activity of soybean protein, when compared to casein, can be described as follows (Beynen et al., 1986 a, b). Soybean protein decreases the absorption of intestinal cholesterol (Huff and Carroll, 1980), which is of endogenous and/or exogenous origin, and probably also reduces the re-absorption of bile acids. This results in the observed increase in fecal excretion of neutral steroids and bile acids (Huff and Carroll, 1980; Kuyvenhoven et al., 1986). Thus soybean protein causes a diminished feed-back inhibition of the hepatic conversion of cholesterol into bile acids. Thus more cholesterol will be chanelled into the bile acid synthetic pathway. This in turn tends to deplete liver cholesterol pools. Liver cholesterol concentrations have indeed been shown to be lower in rabbits fed a soybean-protein diet than in their counterparts fed casein (Huff and Carroll, 1980; Beynen et al., 1983).

Thus dietary soybean protein reduces liver cholesterol in rabbits. The liver responds by an increase in the number of LDL receptors and by enhancing de novo cholesterol synthesis. Indeed, Sirtori et al. (1984) have shown that the binding of apoprotein B containing β-VLDL particles to liver membranes of rats is increased when the donor animals had been fed a cholesterol-rich diet containing soybean protein, compared to casein. Stimulation of hepatic cholesterol synthesis in soybean-protein fed animals has been demonstrated both directly and indirectly. Liver microsomal HMG-CoA reductase activity has been found to be increased in rats fed soybean protein when compared to casein (Nagata et al., 1982; Sirtori et al., 1984). Cholesterol turnover is much faster in rabbits fed soybean protein when compared with casein (Huff and Carroll, 1980).

The increased number of LDL receptors induced by soybean protein is responsible for the fall in serum cholesterol. The LDL cholesterol taken up by the liver can be used for bile acid synthesis. However, in order to

prevent the body from depletion of cholesterol, de novo synthesis has to be activated. A new steady-state will be reached, at which hepatic cholesterol synthesis is increased and fecal excretion of bile acids is also increased. Thus, cholesterol turnover is enhanced. At this new steady-state serum cholesterol is low and the number of LDL receptors high. It can be concluded, from the rabbit studies, that the cholesterol lowering activity of soybean protein may well reside in its ability to interrupt the entero-hepatic cycle of cholesterol and bile acids. How this effect is brought about is not yet known. The mechanism of action of soybean protein may be partly assimilated to that of bile acid sequestrants specifically stimulating the elimination of bile acids (Grundy, 1986), and possibly to that of neomycin (Samuel, 1979), which affects to a larger extent the excretion of neutral sterols. Other absorbable drugs, act through different mechanisms (Shepherd and Packard, 1983).

It has not yet been proven that the soybean-protein diet in type II hypercholesterolemic patients acts via the same mechanism as described for animal models. On the contrary, Fumagalli et al. (1982) reported that the soybean-protein diet did not affect the fecal excretion of neutral steroids and bile acids in type II patients. In this study the hypocholesterolemic effect was similar to that seen in previous work. Another possible mechanism involves the effects of certain amino acids or peptides in the protein on cholesterol metabolism. Among the amino acids, arginine is a likely candidate. Consumption of the soybean-protein diet will be associated by an increase of arginine intake by about 1.5 g/day. At this level of intake arginine in capsule form has been shown to lower serum cholesterol in healthy subjects by about 13% (Kohls et al., 1987). The mechanism underlying this effect of arginine is by no means clear, but it may involve release of glucagon (Noseda and Fragiacomo, 1980). Clearly, the

mechanism of action of the soybean-protein diet in type II patients remains to be established.

CONCLUSION

The soybean-protein diet has been shown to be clinically useful in the treatment of type II hypercholesterolemia. The diet is generally well accepted and has no consistent side-effects. Although the metabolic basis for its hypocholesterolemic effect has not yet been unravelled, the soybean-protein diet deserves a place in the physicians armoury for attacking the problem of type II hypercholesterolemia.

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THE ORIGINAL STUDIES REPORTED IN THIS PAPER WERE PARTLY SUPPORTED BY A COLLABORATIVE RESEARCH GRANT FROM NATO