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Letter to the Editors

Differences in the underlying mechanisms of cholesterol- and casein-induced hypercholesterolemia in rabbit and rat

Dear Editors,

Hypercholesterolemia and atherosclerosis are easily produced in rabbits given cholesterol-free, semipurified diets with casein (or other animal proteins) instead of soy protein (or other vegetable proteins). This is, however, less so in many other animal species, where particular experimental conditions, for example dietary cholesterol supplements, are required to elicit such a pronounced differential effect of dietary proteins.

The events which lead to the observed changes in plasma cholesterol levels may be classified as gastrointestinal or metabolic. Among the gastrointestinal events are changes of steroid absorption and excretion, intestinal bile acid pool size and bile acid binding in the intestine. The observed metabolic events are changes of VLDL secretion, VLDL turnover, hepatic apo-B,E (LDL) receptor activity and hepatic HMG-CoA reductase activity [1,2].

These events may be triggered by protein amino acid composition, leading to different plasma amino acid levels and differences of endocrine response.

Metabolic changes brought about by hypothyroidism parallel the whole pattern of metabolic changes caused by casein. Low thyroid hormone levels increase hepatic cholesterol secretion [3], but decrease HMG-CoA reductase activity [4], hepatic and extrahepatic LDL receptor activity [5,6], bile acid synthesis, fecal steroid excretion, and lipoprotein lipase activity [6]. Lower thyroxine concentrations have in fact been observed with casein feeding as compared to soy protein feeding in gerbils [7] and as compared to gluten feeding in rats [8].

The reason for the particular susceptibility of the rabbit towards dietary cholesterol is the fact that rabbit liver responds to an enlarged liver cholesterol pool not with an appropriate increase in cholesterol and bile acid excretion but with a decrease of cholesterol synthesis [9], an enhanced β-VLDL secretion [10] and, most important, down-regulation of LDL receptors [11]. Down-regulation of LDL receptors causes (i) a delayed uptake of VLDL remnants via this receptor and subsequently a pronounced rise of plasma VLDL cholesterol levels [10], and (ii) an enhanced conversion of VLDL and IDL to LDL [12] and therefore also a rise of LDL.

As casein feeding, as compared to soy protein, leads to a higher cholesterol (re-)absorption [13], similar metabolic events may occur. Both an increased hepatic secretion of cholesterol ester-enriched β-VLDL [14] and a delayed turnover of IDL [15] have been reported in casein-fed as compared to soy protein-fed animals, subsequently leading to increased LDL cholesterol levels [14,16]. No accumulation of β-VLDL was found in the plasma of casein-fed rabbits [17], though this was not always confirmed [16]. It cannot be decided yet whether the enhanced cholesterol absorption per se [13] or a hypothyroid state is the prime effector for the casein-induced change of VLDL secretion and LDL receptor down-regulation.

A quantitatively different response towards dietary cholesterol or casein is seen in the rat. The homeostatic regulation of rat liver cholesterol metabolism is predominantly achieved by variation of cholesterol synthesis [18]. Cholesterol feeding causes only moderate hypercholesterolemia [19], as cholesterol synthesis is markedly decreased [18,20], but LDL receptor mediated lipoprotein uptake is unimpaired [12,18,20]. Remnants of tri-

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glyceride-rich lipoproteins are quickly taken up by the liver before conversion [21] and therefore LDL cholesterol levels are usually low in the rat.

It is assumed that casein feeding leads to hypothyroidism, a metabolic state in which the LDL receptor is down-regulated [4,5,12]. A delayed turnover of VLDL has, in fact, been observed in casein-fed rats [22]. But even in the hypothyroid state there is no delay of chylomicron [23] or VLDL remnant [5] uptake in the rat, but only of LDL uptake, leading to somewhat increased LDL-cholesterol levels [5]. Therefore the enhanced cholesterol absorption and decreased cholesterol excretion [24] and stimulation of VLDL secretion [25,26], brought about by casein feeding, are obviously not strong enough to overwhelm the regulatory capacity and to provoke pronounced hypercholesterolemia in this animal.

Pronounced hypercholesterolemia develops in rats only if cholesterol feeding is coupled with hypothyroidism. Due to a high secretion of cholesterol-enriched β-VLDL brought about by cholesterol feeding [3] and due to a delayed clearance of these particles via the LDL receptor in the hypothyroid state [23] plasma VLDL-cholesterol levels are markedly increased [3,19]. The same pronounced increase of plasma VLDL-cholesterol levels has been shown in rats fed casein plus cholesterol as compared to their counterparts fed soy protein plus cholesterol [27].

The presence of β-VLDL in plasma has been linked with the development of atherosclerosis. β-VLDL are rapidly taken up by macrophages via a specific β-VLDL receptor [28]. As casein feeding on its own enhances VLDL secretion [25,26] it is assumed that there is also a higher production of β-VLDL with casein-cholesterol feeding. This may explain why macrophages incubated with plasma of casein-cholesterol fed rats contained more cholesterol ester as compared to those incubated with plasma of soy protein-cholesterol fed rats [29]. Casein or soy protein feeding on their own had no such effect.

The rabbit and the rat are apparently two extremes in their ability to regulate LDL receptor activity [12]. In the rat only the combination of two interfering events, cholesterol feeding and hypothyroidism or casein feeding, produces marked hypercholesterolemia.

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