Probucol was given to rats made diabetic by streptozotocin. Compared with diabetic rats not receiving probucol or with nondiabetic rats, probucol lowered the plasma concentrations of triglycerides, phospholipids, cholesterol, and apolipoprotein B. The concentrations of serum chylomicrons and very low density lipoprotein (VLDL) were also reduced. In control and diabetic rats, probucol enhanced the clearance of endogenously radiolabeled VLDL from the plasma. Clearances from the plasma of rat lymph chylomicrons or chylomicron-like emulsions were slow in diabetic rats. Probucol normalized chylomicron clearance in diabetic rats primarily by restoring hepatic uptake of remnants, which was decreased in diabetes. In diabetic rats, uptake of chylomicron remnants was increased in a number of extrahepatic tissues, including the heart and kidney. Probucol significantly decreased uptake in some extrahepatic tissues. Increased plasma clearance of VLDL and chylomicrons was associated with an increase in the apolipoprotein CH/CIII and apolipoprotein E/C ratios. Orally administered probucol was specifically incorporated into lymph chylomicrons, and clearance of probucol from the plasma exactly paralleled the clearance of chylomicron remnants, as traced with radiolabeled cholesteryl esters. Chylomicron-like emulsions incorporating probucol were exclusively cleared from the plasma by the liver in normal rats. We conclude that in streptozotocin diabetic rats, probucol is an effective hypolipidemic agent because it promotes the clearance of the triglyceride-rich lipoproteins. (Arteriosclerosis and Thrombosis 1993;13:231-239)

KEY WORDS • probucol • streptozotocin diabetic rats • plasma lipoproteins

Hypertriglyceridemia and hypercholesterolemia are frequently found in patients with diabetes mellitus. The hyperlipidemia primarily reflects slow clearance of plasma lipoproteins, although overproduction of lipoproteins may also be a contributing factor in non-insulin-dependent diabetes. A defective clearance from the plasma of chylomicrons and very low density lipoproteins (VLDLs) has been reported in human diabetic patients (for a review, see Howard) and in animal models of this disease. Hydrolysis of triglycerides may be compromised by severe insulin deficiency because insulin maintains the synthesis and secretion of lipoprotein lipase in some tissues. Posthydrolysis clearance of the remnant particles is also delayed, although the reasons for this are unclear. Elevated plasma concentrations of triglycerides and cholesterol are thought to contribute to the high incidence of atherosclerosis in diabetic patients, and so it is desirable to reduce the concentrations of these lipids.

Probucol is a potent hypolipidemic agent that reduces serum cholesterol level principally by increasing the fractional catabolic rate of low density lipoprotein (LDL). Probucol is an effective lipid antioxidant, but it is not clear whether its pharmacological actions on the metabolism of LDL are related to the prevention of oxidation. Lipoproteins from diabetic donors show increased amounts of oxidative products compared with lipoproteins of nondiabetic origin. Probucol has been shown to decrease oxidation of LDL and VLDL in streptozotocin diabetic rats and in VLDL from nephrotic rats. In this study we report the effects of probucol on the clearance from plasma and on organ uptake of triglyceride-rich lipoproteins in normal and diabetic rats.

Methods

Male Wistar rats (body weight, 220–250 g) were allowed free access to standard crushed rat chow and water. Rats were made diabetic with streptozotocin injected into a tail vein (55 mg/kg body wt in citrate buffer, pH 4.0). Diabetic rats were hyperglycemic, showed glucosuria, and had a low concentration of plasma immunoreactive insulin (IRI). Two weeks after streptozotocin injection, some diabetic rats were given chow containing 1% (wt/wt) probucol for either 3 weeks or 10 days. Diabetic rats failed to gain weight at the same rate as control animals (252±15 and 291±3.0 g, respectively, p<0.025), and probucol had no affect on body weight (256±9.1 g in the diabetic group receiving probucol and 293±7.3 g in the control group given...
Isolation and Radiolabeling of VLDL

Blood was collected from the abdominal aorta of anesthetized rats (pentobarbitone, 65 mg/kg body wt). EDTA (1 mM) was used to prevent coagulation of blood. Plasma was separated by low-speed centrifugation at 4°C. The plasma fraction containing chylomicrons and VLDL was isolated by ultracentrifugation at a density of 1.006 g/ml at 108,000g for 18 hours at 20°C. For radiolabeled VLDL, donor rats were injected with 100 μCi [14C]triolein, [3H]cholesterol, and [3H]cholesterol acetate in 0.4 ml each were taken from the carotid artery at regular intervals within a 30-minute period. After each sample withdrawal, an equivalent volume of physiological saline was injected. Animals were killed immediately after the final blood sample was taken with a lethal dose of pentobarbitone given intravenously. Organs and tissues were excised, weighed, and washed briefly in physiological saline. Samples of tissues were extracted according to the method of Polch et al, except that 0.03 M HCl replaced the water added to the solvent phase. After filtration and phase separation, an aliquot of the solvent phase was dried and radioactivity determined. Plasma and tissue radioactivities were measured in a Beckman liquid scintillation counter (model LS3800) set in dual-mode and with auto-quench correction. Total organ uptake was calculated by correcting for the sample of tissue as the percentage of total organ weight. Total body fat was calculated as 0.078 of body weight, muscle as 0.42 of body weight, and bone marrow as 0.30 of body weight.

Apolipoprotein Analysis

Chylomicrons and VLDLs were delipidated according to the method of Herbert et al and the soluble apolipoproteins separated by isoelectric focusing in polyacrylamide gels as previously described. Apolipoproteins were stained with a Coomassie R250/Coomassie G250 mixture (0.01% and 0.04% by weight, respectively, in 3.5% perchloric acid). The apolipoproteins were quantified as peak area percentages of total apolipoprotein absorbance after densitometric scanning at 600 nm (Bio-Rad model 620, Bio-Rad Australia). Lipoprotein Lipid Analysis

Plasma and lipoprotein triglycerides were measured with a commercially available test kit that corrected for free glycerol (Boehringer Mannheim, Mannheim, FRG). Cholesterol, phospholipid, and fatty acid contents were determined by commercial test kits (Wako Chemicals, Osaka, Japan). Apolipoprotein B was determined by radioimmunoassay with rabbit anti-rat apolipoprotein B.

Statistical Analysis

Lipoprotein clearance data, organ uptake, and apolipoprotein profiles were evaluated by one-way analysis of variance. Probability values less than 0.05 were accepted as significant.

Results

The effect of probucol on plasma lipids in normal and diabetic rats is shown in Table 1. In the fed state the plasma cholesterol level was significantly lower in con-
TABLE 1. Plasma Lipid, Glucose, and Apolipoprotein B Concentrations for Control and Diabetic Rats

<table>
<thead>
<tr>
<th>Plasma values (mg/dl)</th>
<th>Without probucol</th>
<th>With probucol</th>
<th>Without probucol</th>
<th>With probucol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fed state</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of animals</td>
<td>9</td>
<td>8</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Glucose</td>
<td>149±15</td>
<td>133±17</td>
<td>542±103</td>
<td>564±101</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>103±43</td>
<td>73±18*</td>
<td>147±84</td>
<td>53±22*</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>69±6</td>
<td>51±7*</td>
<td>79±23</td>
<td>55±15*</td>
</tr>
<tr>
<td>Phospholipid</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>2.1±0.3</td>
<td>1.8±0.5</td>
<td>7.5±2.6</td>
<td>4.1±1.2*</td>
</tr>
<tr>
<td>Lipoproteins &lt;1.006 g/ml</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglyceride</td>
<td>30±6</td>
<td>10±4*</td>
<td>52±23</td>
<td>10±5*</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>1.2±1.2</td>
<td>0.7±0.1*</td>
<td>5.0±4.3</td>
<td>1.3±1.3*</td>
</tr>
<tr>
<td>Phospholipid</td>
<td>2.6±1.8</td>
<td>0.7±0.1</td>
<td>14±9</td>
<td>3.9±6.8*</td>
</tr>
<tr>
<td>Apo B</td>
<td>ND</td>
<td></td>
<td>3.5±2.1</td>
<td>0.4±0.3*</td>
</tr>
</tbody>
</table>

HDL, high density lipoprotein; apo, apolipoprotein. The chylomicron and very low density lipoprotein lipoprotein fraction (d<1.006 g/ml) was isolated for measurement of lipids. HDL cholesterol was determined after precipitation of apo B-containing lipoproteins from plasma. Data are mean±SEM.

*Significantly different versus untreated group.

Control and diabetic rats receiving probucol compared with those not receiving probucol. No difference in cholesterol concentration was seen between control rats in the fasted state. Probucol reduced the plasma concentration of triglycerides in control and diabetic rats in either the fed or fasted state. The diabetic rats were not as hyperlipidemic as we have previously reported because a lower dose of streptozotocin was used. This was done to avoid severe ketoacidosis and prevent significant deterioration of physiological condition. Nevertheless, phospholipid and apolipoprotein B concentrations were greater in diabetic rats than in control rats, although this was significantly attenuated with probucol administration. Diabetic hyperlipidemia is usually reflected in the lipoproteins with a density <1.006 g/ml (chylomicrons and VLDL). The concentrations of triglycerides and cholesterol in the chylomicron+VLDL fraction were significantly reduced by probucol in control rats. In diabetic rats the concentrations of triglycerides, cholesterol, phospholipid, and apolipoprotein B were all reduced by probucol treatment.

The clearances in control and diabetic rats of radio-labeled VLDL triglyceride are shown in Figure 1. In each case VLDL was obtained from donor rats treated in a manner identical to the recipient animals (e.g., radio-labeled VLDL triglyceride injected into diabetic animals receiving probucol was isolated from diabetic rats receiving probucol). Clearance of VLDL triglyceride, which represents removal by lipolysis as well as particle clearance, was faster in probucol-treated normal rats than in control animals not receiving probucol. Diabetic rats had a slower clearance of VLDL triglyceride than did control rats. However, in probucol-treated diabetic rats, clearance was markedly enhanced.

To assess whether probucol altered clearance of chylomicrons, we monitored removal of lymph chylomicrons and lipid emulsions, which resemble chylomicrons in size and composition. The clearances of chylomicron-like lipid emulsions in control and diabetic rats are
shown in Figure 2. Probucol had no affect on triolein or cholesteryl oleate clearances in control rats, the latter being indicative of particle uptake. In contrast, the slow triolein and particle clearances observed in diabetic rats were completely normalized by probucol treatment. However, probucol given for a shorter duration (i.e., 10 days) was found to only partially ameliorate the slow triolein and particle remnant clearance in diabetic rats (Figure 3). Increased plasma clearance of emulsion lipid in diabetic rats was reflected in the organ and tissue uptake (Table 2). Diabetic rats had less liver uptake of emulsion cholesteryl oleate compared with control rats but greater uptake by a number of extrahepatic tissues, notably the heart and kidney. Probucol significantly increased liver uptake of emulsion cholesteryl oleate and decreased uptake by the spleen, heart, and muscle. Emulsion triolein uptake was increased in the liver of diabetic rats, indicative of remnants that were relatively enriched in triglycerides. In diabetic rats, the heart and kidney were also associated with more emulsion triolein than in control rats.

Analogous to the clearance pattern of emulsions, rat lymph chylomicrons appeared to have been removed more quickly in diabetic rats given probucol for only 10 days. However, this only became evident 15 minutes after injection. Changes in organ uptake after probucol
beled cholesterol were administered as a bolus injection of diabetic rats, which was not affected substantially by some of the extrahepatic tissues in diabetic rats and heart. The heart had a fourfold greater uptake in was completely normalized in rats that received probucol. Densitometric scanning of the apolipoproteins lipoproteins. Plasma VLDL and chylomicrons were iso-
tor-mediated clearance are processes regulated by apo-

tance of emulsions, there was less chylomicron cho-

colon. There was also a significant increase in cholesteryl ester uptake by adrenal and bone marrow tissues. Chylomicron triglyceride uptake increased uptake of triglycerides in the liver and heart of diabetic rats. This was measured. Of the total lymph probucol radioactiv-

clearance of chylomicron [3H]cholesteryl ester (Figure 5).

We synthesized chylomicron-like emulsions containing 3.5% of their total lipid mass as probucol. The appearance of these emulsions is shown in Figure 6. Probucol did not influence the rate of either triolein or cholesteryl oleate clearance from the plasma. On the other hand, cholesteryl oleate radioactivity was completely recovered in the liver (105±3%) compared with only 69±3% in the rats that received emulsion without probucol.

**Discussion**

In hyperlipidemic patients, probucol decreases LDL cholesterol (10–20%) and high density lipoprotein cholesterol (20–30%) concentrations without significant or
only modest changes in serum levels of VLDL cholesterol or triglycerides. In non-insulin-dependent diabetic patients, probucol significantly reduced the serum concentrations of cholesterol and triglyceride. We have now found in streptozotocin-induced diabetic rats that probucol effectively reduced the plasma concentration of cholesterol and triglyceride, principally by decreasing the concentration of chylomicrons and VLDL. Reductions in plasma lipids were seen even in control animals, as has been previously demonstrated. However, probucol increased the efficiency of VLDL triglyceride clearance in diabetic rats such that it was not different from that in untreated control animals. Probucol also enhanced VLDL triglyceride clearance in control rats.

In previous studies, we excluded slow hydrolysis of VLDL triglyceride by endothelial lipases as a cause of hypertriglyceridemia in streptozotocin diabetic rats. Recently, Homma et al found that probucol decreased lipoprotein lipase activity in postheparin plasma in humans while hepatic lipase activity in postheparin plasma remained unchanged. Therefore, the increased clearance rates after probucol treatment are unlikely to be due to increased hydrolysis of VLDL triglyceride.

We have established the existence of a defect in the clearance of chylomicron remnants in streptozotocin diabetic rats, and it may be that probucol improved the posthydrolysis phase of the clearance of triglyceride-rich lipoprotein remnants. To assess this possibility, we monitored the clearance of endogenously radiolabeled VLDL triglyceride in control and diabetic rats. Clearance was less rapid in diabetic rats compared with control animals, as has been previously demonstrated by others. However, probucol increased the efficiency of VLDL triglyceride clearance in diabetic rats such that it was not different from that in untreated control animals. Probucol also enhanced VLDL triglyceride clearance in control rats.

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Clearance of emulsion or chylomicron triglyceride is the sum of two processes, lipolysis by endothelial lipases and particle removal, whereas clearance of cholesteryl ester represents particle clearance alone. Typically, clearance is rapid, and triglyceride is cleared more quickly than is cholesteryl ester. Chylomicron triglyceride is cleared very rapidly from the plasma in normal animals; however, in some rats receiving probucol, clearance was still enhanced. In diabetic rats we confirmed the slow clearance of chylomicron triglyceride and remnants. However, when diabetic rats were given probucol in their diet, clearance from the plasma was partially or completely normalized depending on the duration of probucol treatment. Our studies with emulsions and chylomicrons indicate that 10 days of probucol therapy was insufficient to completely restore plasma clearance, although at 3 weeks there was no difference in the clearance patterns of triglyceride or cholesteryl esters between control and diabetic rats. Perhaps of more importance than plasma kinetics is the uptake of chylomicron remnants. In diabetic rats, on average the liver only cleared about half the amount of remnants typically expected for control rats. In contrast, there was increased uptake of remnants in a number of extrahepatic tissues, notably in organs more prone to atherosclerotic lesion development, such as the heart, kidney, and brain. Despite incomplete normalization of plasma clearance in diabetic rats after 10 days of probucol therapy, there were improvements in the pattern of organ uptake. There were no longer any differences in liver uptake between control and diabetic rats. Furthermore, tissues that in diabetic rats had increased uptake (such as the heart) were partly and in some cases completely normalized.

The apolipoprotein B100/E receptor is the primary route by which chylomicron remnants are cleared in vivo. Insulin stimulates the synthesis of the apolipoprotein B100/E receptor, and so in diabetic rats, downregulation of activity and consequently lowering of hepatic uptake of remnants would be expected. Increased uptake by the liver (and by other tissues that have significant apolipoprotein B100/E receptor activity, e.g., adrenal glands) in probucol-treated rats suggests that enhanced clearance of remnants may be due to an increase in apolipoprotein B100/E receptor activity. However, on the basis of the levels of mRNA for the apolipoprotein B100/E receptor after probucol treatment, Staels and colleagues concluded that synthesis of the receptor was downregulated in control rats. Alternatively, probucol may increase the interaction
between chylomicron remnants and the apolipoprotein B100/E receptor, as suggested by the exclusive uptake of emulsions containing 3.5% probucol by weight in the livers of untreated control rats. However, in addition to such a mechanism, probucol also promotes the mechanisms responsible for remnant clearance because clearance of emulsions or chylomicrons not containing probucol was also enhanced in probucol-treated rats. The plasma chylomicron and VLDL fraction of probucol-treated rats contained a greater apolipoprotein E/C ratio, which could promote binding with the apolipoprotein B100/E receptor. Increased levels of apolipoprotein CII relative to apolipoprotein CIII in chylomicrons and VLDL of probucol-treated rats may also promote remnant formation (and as a consequence, clearance) by promoting hydrolysis by lipoprotein lipase. McLean and Hagaman have shown that probucol reduces the affinity of dimyristoylphosphatidylcholine liposomes for binding apolipoprotein CIII, a protein that inhibits interaction of remnants with the apolipoprotein B100/E receptor. Whatever the biochemical mechanism for increased plasma clearance may be, it is clear that probucol promotes liver uptake of chylomicron remnants in diabetic rats.

On prolonged administration, probucol accumulates in adipose tissue. Probucol’s hydrophobicity suggested to us that the drug may be incorporated by intestinal mucosal cells into chylomicrons and thereafter metabolized within the plasma compartment as a chylomicron component. Our data show that in the lymph, probucol was specifically incorporated into chylomicrons. The percentage incorporated was low, consistent with poor uptake from the gastrointestinal tract. Chylomicron-incorporated probucol was metabolized in parallel with cholesteryl ester in normal rats. In rats, after 30 minutes the transfer of cholesteryl ester to other lipoprotein fractions is negligible, and so we conclude that probucol is metabolized with the particle per se. However, rats do not have active cholesteryl ester transfer protein activity, and it may be that probucol is transferred to other lipoprotein groups in rabbits and humans, species in which cholesteryl ester transfer protein activity is present in the plasma. Differences in cholesteryl ester transfer protein activities between species may in part determine the hypolipidemic nature of probucol.

Probucol is a potent hypolipidemic agent in diabetic rats. Probucol lowers plasma lipid levels by increasing the rate of clearance of chylomicrons and VLDL, an extension of the findings previously demonstrated for low density lipoproteins. Increased clearance of remnants appears to be primarily due to a stimulation in hepatic uptake. Greater liver uptake in probucol-treated rats primarily reflects an enhanced ability of the recipient animal to clear chylomicrons and VLDL. However, probucol that is incorporated into lipoproteins may also preferentially direct uptake of the particles by the liver.

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Effect of probucol on plasma clearance and organ uptake of chylomicrons and VLDLs in normal and diabetic rats.

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