Probucol Suppresses the Development of Chronic Renal Failure in Dahl Salt-Sensitive Rats: An Animal Model of Spontaneous Focal and Segmental Glomerulosclerosis

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Dear Sir,

Studies in experimental models have suggested that hyperlipidemia may play a role in the development of focal and segmental glomerulosclerosis (FSGS) [1]. We reported that the development of FSGS was able to be suppressed by a lipid-lowering agent, probucol, in aminonucleoside-nephrotic rats (PAN) [2]. This suggests that secondary hyperlipidemia could exacerbate the primary renal lesion. Recently, we found that male Dahl salt-sensitive rats (DS), even when fed a standard rat chow (0.3% NaCl), spontaneously developed FSGS, and the kidney function became worse with age [3]. Therefore, the present study was conducted to examine whether probucol can suppress the development of kidney injury in DS.

Male DS aged 15-18 weeks were fed ad libitum either standard rat chow (containing 0.3% NaCl) or the same chow containing 1% probucol (w/w) for 10-11 weeks. Male Sprague-Dawley rats (SD) of the same age were used as the controls. The mean blood pressure was measured by the tail cuff method [3]. The kidney sections were stained with periodic acid-Schiff to examine the degree of FSGS according to the classification, grade 1 to grade 4 (mild-severe), as described previously [2]. The plasma concentrations of triglyceride (TG), cholesterol, high-density lipoprotein (HDL)-cholesterol, apoprotein B, albumin, urea nitrogen and creatinine were measured by the same methods as described previously [2, 3]. The TG secretion rate (TGSR) was determined by the Triton WR1339 method [3]. The results are summarized in table 1. The mean blood pressure was not significantly decreased by the treatment with probucol, with only the significant reduction being observed for HDL-cholesterol. Probucol did not suppress the elevation of TGSR in the DS (0.29 ± 0.03 vs. 0.32 ± 0.08 mg/min/100 g b.w.). In accordance with this lack of a hypolipidemic effect, the urinary protein excretion and plasma albumin concentration were not affected by the probucol treatment. The severity...
of FSGS was not significantly altered by probucol: 78% of the animals were classified as grade 3 and 12% as increased in the DS fed the standard rat chow. The 26- to 29-week-old DS showed a high incidence of severe FSGS and tubulointerstitial lesions, which were classified as grade 3 (80%) and grade 4 (20%). The DS exhibited massive proteinuria, hypoalbuminemia and marked hyperlipidemia. The elevation in plasma lipids was mainly associated with very low-density lipoprotein (VLDL, d < 1.006) and low-density lipoprotein (LDL, 1.006 < d < 1.063) (data not shown), TGSR was increased twofold in the DS (0.32 ± 0.08 vs. 0.16 ± 0.05 mg/min/100 g b.w.).

grade 4. To our surprise, however, it was found that probucol prevented the development of renal failure in the DS. The plasma urea nitrogen and creatinine levels were not increased at 15-18 weeks of age (26 ± 11 and 0.6 ± 0.1 mg/dl, respectively) but these concentrations subsequently increased substantially with age. Probucol suppressed increases in plasma urea nitrogen and creatinine levels at the age of 26-29 weeks. We previously demonstrated [4] that probucol significantly lowered the plasma lipid concentration and protein excretion in the urine, and that there is good correlation between the hypolipidemic effect and reduced proteinuria in PAN. If this correlation also exists in DS, it is not surprising that probucol failed to ameliorate the nephrotic state, because probucol did not reduce the plasma lipid levels in DS. Our kinetic studies demonstrated that the hyperlipidemia in PAN is mainly associated with impaired VLDL catabolism [5], whereas overproduction and a catabolic defect of VLDL were both involved in the mechanisms of the hyperlipidemia in DS [3]. Recently, we reported that probucol significantly stimulates removal of TG-rich lipoproteins from the liver [6], and Yoshino et al. [7] demonstrated that probucol does not suppress the secretion of VLDL from the liver. These findings could explain why the hypolipidemic effect of probucol is less apparent in DS than in PAN.

Kaplan et al. [8] reported that cholesterol feeding caused renal vasoconstriction in rats, which resulted in significant reduction in the single nephron afferent plasma flow and the glomerular filtration rate. In addition, they found that probucol completely normalized these hemodynamic abnormalities in these cholesterol-fed rats. Probucol has a powerful antioxidant property besides its hypolipidemic effect; thus, this agent can suppress the oxidative modification of LDL [9]. Oxidized LDL can bind to mesangial cells, where it stimulates eicosanoid production [10]. Therefore, probucol may prevent eicosanoid-mediated vasoconstriction by suppressing LDL oxidation. A micropuncture study revealed that the glomerular capillary pressure is significantly higher and the glomerular filtration rate is lower in hypertensive DS [11], and Tolins et al. [12] reported that cholesterol feeding further increased renal vascular resistance in hypertensive DS rats. We speculated, therefore, that probucol’s prevention of renal failure may be due to its antioxidant property, which leads to inhibition of eicosanoid production by oxidized LDL in the kidney. Further studies are needed to elucidate this possibility.

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Dahl Rats and Probucol