Treatment of Hyperlipidemia with Probucol Reduces Proteinuria in Puromycin Aminonucleoside-Induced Nephrotic Rats

T. Tsutomu Hirano
J.C.L. John C.L. Mamo
K. Kayoko Ohnami
T. Tetsuzo Sugisaki

First Department of Internal Medicine and Department of Nephrology, Showa University School of Medicine, Tokyo, Japan; Department of Physiology, University of Western Australia, Nedlands, Australia

Dear Sir,

Recently, it has been suggested that secondary hyperlipidemia resulting from nephrotic syndrome can exacerbate the primary renal disorder [1–3]. Diamond and Kar-novsky [2] demonstrated that dietary cholesterol supplementation increased urinary protein excretion in puromycin aminonucleoside (PA)-induced nephrotic rats (PAN), concomitant with increased plasma cholesterol levels. PAN itself shows severe hyperlipidemia in the presence of remarkable proteinuria [4, 5]. This led us to speculate that treatment of hyperlipidemia with a hypo-lipidemic agent may attenuate PAN-induced proteinuria by inhibiting the vicious cycle. To investigate this we have studied the effects of Probucol, a potent cholesterol-lowering drug [6], on the rate of urinary protein excretion in PAN.

PA (100 mg/kg body weight) was injected intraperitoneally into male Wistar rats (150–160 g) and thereafter the animals were maintained on standard rat chow, or chow pellets containing 1% Probucol (kindly provided by Ootsuka Pharmaceutical, Osaka, Japan). Food and water were available ad libitum. Consumption of chow and body weight gain were identical for Probucol-treated and nontreated PAN (table 1). Ten days after PA injection, food was removed for a 24-hour period and total urine was collected. Blood samples were taken from un-anesthetized rats at the end of the 24-hour period from the tail vein. Plasma triglyceride, total cholesterol, phos-photid and apoprotein B (measured by an electromunoassay) were significantly increased in nephrotic rats, which were about 4–5 times higher than that in normal fasted rats (data not shown). Nephrotic rats receiving Probucol incorporated into their diet had plasma lipids and apoprotein B concentrations which were 50–65% lower than those in the nontreated nephrotic group (table 1). Urinary protein excretion was also significantly reduced in the Probucol-treated nephrotic rats compared to the nontreated nephrotic group (table 1). The mechanism by which Probucol reduced proteinuria is not understood. It may be a direct effect on glomerular filtration, or alternatively, be secondary to a lower concentration of plasma lipoproteins. The latter of these alternatives is supported by the fact that significant positive correlations existed between the severity of the proteinuria and plasma triglyceride, cholesterol...
and apoprotein B levels (fig. 1). Kasiske et al. [3] reported that hypo-lipidemic agents, mevinolin or clofibric acid, reduced proteinuria in obese Zucker rats. Our finding is comparable to their observation and supports the hypothesis

Table 1. Effects of Probucol treatment on PAN rats

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Body weight, g</th>
<th>Chow g/day intake</th>
<th>Plasma concentrations, mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nontreated, (n = 8)</td>
<td>188 ± 18</td>
<td>14 ± 6</td>
<td>165 ± 30</td>
</tr>
<tr>
<td>1% Probucol, (n = 9)</td>
<td>168 ± 30</td>
<td>17 ± 6</td>
<td>77 ± 30</td>
</tr>
</tbody>
</table>

1.0 ± 2 6 ± 3**
233 ± 122*

TG = Triglyceride; Cho = total cholesterol; PL = phospholipid; Apo B = apoprotein B. Data represent the mean ± SD. *p < 0.05, **p < 0.01.

Effect of Probucol on Proteinuria

Fig. 1. The relationship between proteinuria and plasma lipid and apoprotein B concentrations. 0=Nephrotic rats; •=nephrotic rats treated with Probucol.
that secondary hyperlipidemia resulting from nephrosis may exacerbate the primary renal disorder.