Effect of Chronic Treatment of Propranolol on Lipid Metabolism in Spontaneously Hypertensive Rats (SHR)

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Abstract—The effects of propranolol on lipid metabolism were studied in spontaneously hypertensive rats (SHR). Male SHR and corresponding Wistar Kyoto rats (WKY) were used at 5 weeks of age. The SHR were given 10 mg/kg/day of dl-propranolol-HCl by gavage for 10 weeks. Body weight gain in untreated SHR and propranolol-treated SHR (SHR-P) groups were low, as compared with those of the WKY group. Total cholesterol, phospholipid and total lipid of the serum and liver in the SHR-P group were higher than in the SHR group. In the early weeks of treatment, serum triglyceride and non-esterified fatty acid levels in the SHR-P group were slightly lower than those in the SHR group. Aortic lipid levels in the SHR-P group were lower than those in the SHR group. During the later weeks of treatment, blood glucose level in the SHR-P group was higher than in the SHR group. The serum immunoreactive insulin value in the SHR-P group was slightly lower than in the SHR group. These results may suggest that propranolol inhibits hormone-sensitive lipase activity in the early weeks of treatment and influences cholesterol biosynthesis and/or catabolism.

Propranolol, a potent beta-adrenergic blocking agent, has been used widely in the treatment of angina pectoris, hypertension and various arrhythmias. Recently, many clinicians have recognized the possible adverse effect of long-term treatment with beta-blocking agents on lipid metabolism. In former studies, increases in human plasma triglycerides after administration of propranolol were reported (1-4). However, the same findings were not duplicated in studies on animal species. We previously reported the low plasma triglyceride level in normotensive Sprague Dawley rats after treatment with propranolol (5). The purpose of this paper is to describe the chronic effect of propranolol on serum, liver and aortic lipids in spontaneously hypertensive rats (SHR). SHR are a strain of Wistar Kyoto rat which had been developed by Okamoto and Aoki (6). This animal model appears to be a suitable model for human essential hypertension and is now available as a genetically pure strain (7).

Materials and Methods
Animals and drug administration: Male normotensive rats of the Wistar Kyoto (WKY) strain and male spontaneously hypertensive rats (SHR), developed by Okamoto and Aoki (6), were used. Four-week-old (80-90 g) WKY and SHR of the F38 generation were divided into three groups: a WKY group, a SHR group and a propranolol-treated SHR group (SHR-P); each group consisted of five rats. Rats were fed a stock diet (MF, Oriental Kobo Co. Ltd.), and they were kept under standard laboratory conditions. WKY and SHR groups were given distilled water, 0.2 ml/100 g/day by gavage, and the SHR-P group was given propranolol, 10 mg/kg/day by the same means. Treatment was started at 5 weeks of age and continued up to 15 weeks of age.

Measurements of heart rate and blood pressure: Heart rate and blood pressure were determined weekly prior to drug adminis-
Preparation of sample for biochemical determinations: Rats were anesthetized with pentobarbital sodium (40 mg/kg, i.p.) between 9-12 a.m., after 12 hr of fasting. Blood was drawn from the inferior vena cava by a syringe, and the liver and thoracic aorta were removed. Serum, liver and aortic lipid levels of rats in each group were examined on the third day and at two-week intervals after treatment. The lipid fraction of the liver and aorta were extracted by the Bragdon method (8). Total cholesterol (TC) in the serum, liver and aorta was determined by the modified Rosenthal method (9). Phospholipid (PL) in the serum was determined by an enzymatic spectrophotometric method (10). PL in the liver and aorta was determined by the method of Yamanishi et al. (11). Triglycerides (TG) in the serum, liver and aorta (12), free cholesterol (FC) in the

Fig. 1. Effect of age on heart rate and blood pressure in rats. The values were the means ± S.D. of 5 rats in each group. △-▲: Wistar Kyoto Rats (WKY) without treatment, ○-○: Spontaneously Hypertensive Rats (SHR) without treatment, ●-●: SHR perorally administrated of propranolol 10 mg/kg/day for 10 weeks (SHR-P). *P < 0.05, **P < 0.01 WKY vs. SHR, ■ P < 0.05, □ P < 0.01 SHR vs. SHR-P.
serum (13), and non-esterified fatty acid (NEFA) in the serum (14) were determined by an enzymatic spectrophotometric method. High density lipoprotein-cholesterol (HDL-C) and HDL-phospholipid (HDL-PL) in the serum were separated by a dextran sulfate-magnesium precipitation method (15). HDL-C in the serum was determined by the modified Rosenthal method (9) and HDL-PL in the serum was determined by an enzymatic spectrophotometric method (10). Serum glucose was measured by the o-toluidine-borate method (16), and serum insulin was measured by radioimmunoassay (17).

Results

Heart rate and blood pressure: Heart rate in both WKY and SHR groups varied; however, the rate in the SHR group was slightly higher than that in the WKY group. At the 6th week of treatment with propranolol, heart rate in the SHR-P group decreased significantly compared to that in the SHR group.

Blood pressure in the WKY group increased gradually until 9 weeks of age; however, it subsequently remained between 120 and 130 mmHg. Blood pressure in the SHR group was slightly higher than that in the WKY group, even at 5 weeks of age. Blood pressure in the SHR group increased rapidly after 7 weeks of age and reached the highest level of 170 to 180 mmHg. At the 4th week of treatment with propranolol, blood pressure in the SHR-P group was significantly lower compared to that in the SHR group (Fig. 1).

Body weight: Body weight gains in the SHR and SHR-P groups were significantly lower than in the WKY group at the 2nd week of treatment. However, there was no significant difference in the body weight gain of SHR and SHR-P groups (Fig. 2).

Variation in serum lipid levels: As shown in Figs. 3 and 4, time-dependent changes were observed in rat serum lipid levels through 10 weeks of treatment with propranolol. Serum TC level decreased with age in the SHR group and was significantly higher in the SHR-P group than in the SHR group. However, there was no significant difference between WKY and SHR groups in serum TC. Serum PL level decreased with age in the SHR group, and it was slightly higher in the SHR-P group than in the SHR group (Fig. 3). However, at the 6th week of treatment with propranolol, HDL-C and HDL-PL levels were 39.8±6.0 mg/dl and 54.3±5.0 mg/dl in the WKY group, 42.3±4.7 mg/dl and 52.6±2.8 mg/dl in the SHR group, and 41.5±3.4 mg/dl and 57.1±5.3 mg/dl in the SHR-P group, respectively; these levels were not significantly different among the three groups.

Serum TG and NEFA levels in the SHR group were low, compared to those in the

![BODY WEIGHT](image)

**Fig. 2.** Effect of age on rat body weight. Conditions were the same as for Fig. 1. **P<0.01 WKY vs. SHR.**
WKY group in the early weeks of administration. They were slightly lower in the SHR-P group than in the SHR group in the early weeks of treatment with propranolol, but there was no difference among the three groups at the 8th and 10th weeks of treatment with propranolol (Fig. 4).

At the 6th week of treatment with propranolol, serum FC level was 4.67±0.53 mg/dl in the WKY group, 4.88±1.20 mg/dl in the SHR group, and 6.26±1.24 mg/dl in the SHR-P group, respectively, and these levels were not significantly different among the three groups.

At the 6th week of treatment with propranolol, the serum atherogenic cholesterol index ($\frac{TC-HDL-C}{HDL-C}$) and the serum atherogenic phospholipid index ($\frac{PL-HDL-PL}{HDL-PL}$) (18) were 0.46±0.16 and 0.37±0.07 in the WKY group, 0.38±0.11 and 0.26±0.11 in the SHR group, and 0.62±0.15 and 0.37±0.12 in the SHR-P group. The serum atherogenic cholesterol index in the SHR-P group was significantly higher than in the...
SHR group (P<0.05); however, the other index was not significantly different among the three groups.

Variation in liver and aortic lipid levels: At the 6th week of treatment with propranolol, liver TC and TL levels were 3.47±0.58 mg/g and 43.6±4.2 mg/g in the WKY group, 3.63±0.44 mg/g and 43.2±4.8 mg/g in the SHR group, and 3.94±0.63 mg/g and 46.4±5.6 mg/g in the SHR-P group, respectively. These levels were not significantly different among the three groups.

Time-dependent changes in aortic lipid levels in the three groups through 10 weeks of treatment with propranolol are shown in Figs. 5 and 6. Aortic TC in the SHR group was significantly lower than in the WKY group in the later weeks of treatment, but there was no significant difference between SHR and SHR-P groups. Aortic PL in the SHR group was significantly lower than in the WKY group at the 8th and 10th weeks of treatment; however, there was no significant difference between SHR and SHR-P groups (Fig. 5).

Aortic TG and TL in the SHR-P group were significantly lower than those in the SHR group in the early weeks of treatment (Fig. 6).

Serum immunoreactive insulin values and blood glucose levels: Time-dependent changes in serum immunoreactive insulin values and blood glucose levels through 10 weeks of treatment with propranolol are shown in Fig. 7.

Serum immunoreactive insulin values in the SHR group was lower than in the WKY group in the later weeks of treatment, especially at the 10th week of treatment. These values in the SHR-P group were slightly lower than in the SHR group in the later weeks of treatment with propranolol.

Blood glucose level in the WKY group was significantly lower than in the SHR group at the 4th week of treatment, and it was significantly higher in the SHR-P group than in the SHR group at the 10th week of treatment with propranolol (Fig. 7).

Discussion

Recent studies have demonstrated varying effects of beta-blocking agents on blood lipids. Tanaka et al. (4) reported that administration of propranolol to patients who had previously had strokes caused a significant decrease in HDL-C and an increase in NEFA; however, plasma TG and TC were not affected. Studies by Helgeland et al. (2) and Ingeburg et al. (19) showed a significant decrease in HDL-C and TC and an increase in TG by propranolol treatment. These reports have directed attention towards the probable unfavourable effects of beta-blocking agents on lipid metabolism. However, Nilsson et al. (20) failed to replicate any such effect of
metoprolol on serum TC and TG. Thus, there are some discrepancies among the results of studies on the effects on lipid metabolism of beta-blocking drugs in man.

In general, the serum lipid levels in the SHR group were low compared to that in the WKY group. Yamori et al. (21) and Iritani et al. (22) reported that plasma cholesterol levels in the SHR group were lower in comparison to those in the WKY group. However, Sassolas et al. (23) reported that serum lipid levels in the Lyon spontaneously hypertensive strain increased with body weight gain. The present study showed that body weight gain was significantly lower in SHR and SHR-P groups than in the WKY group. These phenomena suggest that serum lipid levels might be correlated with body weight gain.

In the present study, early changes in lipids were observed despite the lack of hemodynamic changes during propranolol treatment. That is, serum TG and NEFA levels in the SHR-P group were slightly lower

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**Fig. 5.** Effect of age on total cholesterol and phospholipid in the aorta. Conditions were the same as for Fig. 1. *P<0.05, **P<0.01 WKY vs. SHR.
than those in the SHR group in the early weeks of treatment. These phenomena suggest that propranolol may have inhibited adenylate cyclase activity as well as hydrolysis of TG in adipose tissue. Previously, Yasuhara et al. (5) reported that serum NEFA and TG in normotensive rats treated with propranolol was low compared to that in untreated normotensive rats. However, there was no difference between SHR and SHR-P groups in the later weeks of treatment with propranolol. That is, the tendency for the serum NEFA level to increase suggests that propranolol may have inhibited beta-oxidation of NEFA (14) and re-esterification of NEFA to TG (24); also, this tendency for the serum TG level to increase suggests that lipoprotein catabolism (LPL activity) may have been inhibited by propranolol. Therefore, it seems likely that these levels in the SHR-P group might be higher than in the SHR group if that group were treated with propranolol after 10 weeks.

Our results also demonstrated that serum TC in the SHR-P group was significantly
higher than in the SHR group. This suggests that propranolol may have either enhanced cholesterol biosynthesis and/or inhibited cholesterol catabolism.

At the 10th week of treatment with propranolol, serum immunoreactive insulin value in the SHR-P group was slightly lower than in the SHR group, and the blood glucose level in the SHR-P group was higher than in the SHR group. Charles et al. (25) showed that fasting insulin concentrations fell by 70% during beta-adrenergic blockade, whereas blood glucose remained unchanged during beta-adrenergic blockade. Furthermore, Akerblom et al. (26) reported that the serum immunoreactive insulin values and blood glucose levels in propranolol treated rats were lower than those in Wistar rats. Birnbaum et al. (27) reported that propranolol induced elevation in basal serum glucose concentrations and decreased glucose tolerance at 2.5 and 3 hr. However, there was no noticeable effect on insulin secretion, although insulin secretion is known to be
decreased by other beta-blockers in man (28). Our results showed a propranolol-induced decrease in serum immunoreactive insulin value. This insulin decrease might inhibit incorporation of glucose into the tissue.

In conclusion, propranolol increased serum TC and decreased serum TG and NEFA levels in SHR. These results failed to correspond with previous studies reporting increases in serum TG after administration of propranolol to humans (3, 4, 19, 29, 30). These phenomena suggest that propranolol may inhibit hormone sensitive lipase activity and may influence cholesterol biosynthesis and/or catabolism. Further study will be required to clarify the mechanisms.

References


