Blockade of β-adrenoceptor in control of blood pressure in fowl

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Kamimura, K., H. Nishimura, and J. R. Bailey. Blockade of β-adrenoceptor in control of blood pressure in fowl. Am. J. Physiol. 269 (Regulatory Integrative Comp. Physiol. 38): R914–R922, 1995.—Several avian species show elevated blood pressure (BP) and spontaneous atherogenesis in the aorta and other large arteries. The BP appears to be influenced by age, sex (higher in males), environment, and diet in some species. We reported previously that mean aortic pressure and heart rate, but not plasma renin activity (PRA), of conscious female domestic fowl were markedly reduced by propranolol. In the present study, we aimed to determine further in conscious chickens whether 1) hypotension evoked by atenolol or practolol, which selectively inhibit cardiac β-receptors in mammals, is more potent than that evoked by propranolol, and 2) the renin-angiotensin (ANG) system and/or catecholamines are involved in β-adrenoceptor antagonist-induced hypotension. Mean arterial pressure (171.2 ± 3.5 mmHg) and heart rate (281 ± 4 beats/min) of chronically cannulated roosters (n = 38) were markedly reduced by acute infusion or repeated injections (14 days) of propranolol, atenolol, or practolol, but not by SQ-14,225 (ANG-converting enzyme inhibitor) or (Sar1, Thr3)ANG II (nonselective ANG receptor antagonist). None of the β-adrenoceptor blockers, however, showed cardioselectivity. The resting PRA of conscious roosters (1.27 ± 0.09 ng·min⁻¹·ml⁻¹, n = 38) was low and did not change significantly after chronic or acute treatment with β-adrenoceptor blockers except for a slight decrease induced by practolol. PRA increased after SQ-14,225. The plasma levels (pg/ml) of norepinephrine (701.9 ± 76.0), epinephrine (337.2 ± 57.1), and dopamine (206.1 ± 29.0) of conscious roosters were further increased by propranolol. Practolol also increased dopamine significantly. These results suggest that β-adrenoceptor antagonists decrease BP primarily via their actions on a cardiac mechanism rather than through suppression of renin. The differentiation of cardiac β₁- and vascular β₂-receptors may be absent in chickens.

β-adrenoceptor blockers: propranolol; atenolol; practolol; SQ-14,225; adreno sympathetic activity; cardioselective β-blockers; fowl blood pressure

MANY AVIAN SPECIES have blood pressure (BP) levels higher than most mammals and a high incidence of spontaneous vascular lesions resembling atherosclerosis in the aorta and other large arteries (7, 18, 24, 29). The mechanism and physiological implications of elevated BP and atherogenesis in birds are not understood. In turkeys and chickens, the increase in BP appears to be age dependent and higher in males than in females (29). Simpson and co-workers (27) have reported that reserpine and β adrenoceptor blocking drugs decrease BP in turkeys. Our previous studies indicate that mean aortic pressure (137.6 ± 2.0 mmHg, n = 45) and heart rate (HR; 295 ± 4 beats/min), but not plasma renin activity, of conscious female domestic fowl were markedly reduced by propranolol (18). In contrast, SQ-14,225, an angiotensin-converting enzyme inhibitor, evoked only a slight decrease in BP, whereas it significantly increases plasma renin activity. The hypotensive effect of propranolol may be ascribed either to the reduction in cardiac output or to its effect on the central nervous system, since propranolol penetrates the blood-brain barrier in mammals (9, 28). In the present study, we therefore aimed to determine further in conscious chickens whether 1) atenolol and practolol, which, in mammals, selectively inhibit cardiac β-adrenoceptors and do not (or minimally) affect the central nervous system, exert a more potent hypotensive effect than propranolol, and 2) the renin-angiotensin system or catecholamines are involved in the β-adrenoceptor antagonist-induced hypotension. Conscious chronically cannulated roosters were used since their BP appears to be higher than that of fowls; therefore, the hypotensive effects of the drugs may be more clearly shown. The cardioselectivity of β-adrenoceptor blockers was examined in anesthetized hens. Circulating catecholamines measured in a few species of birds (3, 18, 29) are higher than those reported for most mammals. Furthermore, BP is decreased by the blockade of α- and β-adrenoceptor antagonists (18, 27), adrenalectomy, or catecholamine depletion (3, 18), suggesting that the sympathetic nervous system may be involved in the BP regulatory mechanism. The study of the mechanism of β-adrenoceptor antagonist-induced hypotension will provide insights into cardiovascular regulation in birds.

METHODS

Animals and Maintenance

Male and female White Leghorn chickens (4–6 wk of age) were purchased from local breeding farms in Tupelo, MS. The chickens were kept in groups in large indoor pens and were moved into individual cages (45 cm wide × 60 cm depth × 75 cm height) 5 days before surgery. The photoperiod (12:12-h light dark cycle) and temperature (22 ± 1°C) were controlled. Chickens under 20 wk of age were fed with Start and Grow (Purina, 17% protein, 1% calcium) and thereafter a laboratory chow (Wayne 15% Egg Ration, Allied Mills) containing NaCl (0.03 ± 0.12 meq/g); tap water was allowed ad libitum. The weights (ages) of chickens at the beginning of the experiment were 60.5 g wk and 2.16 ± 0.03 kg (54–66 wk) for roosters (acute and chronic drug treatment, n = 38) and 1.36 ± 0.04 kg (19.4 ± 1.1 wk) for hens (cardioselectivity test, n = 12). Birds were maintained according to the “Guide for the Care and Use of Laboratory Animals” (DHHS Publication No. (NIH) 85-23, Revised 1985, Office of Science and Health Reports, DRR/NIH, Bethesda, MD 20205). Animal protocols were reviewed and approved by Institutional Animal Care and Use Committee.
Surgical Procedures

Acutely anesthetized birds. Female chickens were anesthetized with an aniprertonene injection of Dial-urethane mixture containing 5,5'-diallylbibutaric acid (75 mg/kg, Sigma Chemical, St. Louis, MO), urethane (600 mg/kg, Sigma), and ethyluracil (600 mg/kg, Eastman Kodak, Rochester, NY). The thigh muscles were dissected from the lateral side, and an expanded vinyl catheter (Dural Plastic and Engineering, Auburn, Australia) was inserted into the abdominal aorta through the ischiadic artery for measurement of BP and HR. The left cutaneous ulnar vein and external iliac veins were also cannulated with polyethylene tubing (PE 50, Clay Adams, Parsippany, NJ) for drug injection or infusion.

Chronic catheterization. Male chickens were anesthetized with ketamine (Ketaset, 75-100 mg/kg im, Bristol-Myers, Syracuse, NY), supplemented by a local anesthetic (2% lidocaine; Abbott Laboratory, North Chicago, IL). The expanded vinyl catheter was chronically implanted into the aorta as above. This catheter was used for measuring BP and collecting blood samples. Two expanded catheters were also implanted into the vena cava via the left and right external iliac veins for drug infusion and injection, as needed. We confirmed by autopsy that the tips of the catheters (0.75 mm OD) were floating, without occluding the aorta. The other ends of the catheters were tunneled through the subcutaneous space to a point of exteriorization. The chickens promptly recovered from anesthesia, showing no signs of distress. The catheters were flushed daily with a small amount of heparin (100 point of exteriorization. The chickens promptly recovered from anesthesia, showing no signs of distress. The catheters were flushed daily with a small amount of heparin (100 U/ml)-saline (0.9% NaCl) solution, and the tips of the catheters were tightly closed with polished stainless steel plugs (1.1 mm OD). Six of 27 chickens were recannulated on the 18th day of the experiment because of partial occlusion of the cannulas.

Drugs

DL-Propranolol HCl (Ayerst Laboratories, New York, NY), atenolol (Stuart Pharmaceuticals, ICI, Wilmington, DE), practolol (Stuart Pharmaceuticals, ICI), and SQ-14,225 (captopril, Squibb, Princeton, NJ) were gifts from the respective companies. [Sar1, Thr3]-angiotensin II and catechol-O-methyltransferase were given by Drs. Mahesh C. Khosla and Robert C. Speth, respectively, of the Cleveland Clinic Foundation, Cleveland Clinic, Cleveland, OH. 1-Norepinephrine bitartrate (Regis, Morton Grove, IL), 1-epinephrine bitartrate (Regis), 3-hydroxytyramine HCl (dopamine, Regis), normetanephrine (Sigma), metanephrine (Sigma); 3-methoxytyramine (Sigma), 125I-labeled Na (Union Carbide) S-adenosyl-L-methyl-[3H]methionine (Amersham, Arlington Heights, IL), and CAT-A-KIT (Upjohn, Kalamazoo, MI) were purchased commercially.

Measurement of BP and Blood Sampling

Prior to (10-15 min) and during BP measurement or blood sample collection, the conscious bird was taken to a room with dimmed light and was covered with a black Plexiglas box to prevent excitement, while restraint of the body was kept to a minimum. The Plexiglas box had sufficient slits and holes for maintenance of ventilation. We also measured BP without a cover under normal light. Although there was no difference in BP levels, quick movement of the bird often made basal BP levels unstable, exhibiting sharp transient peaks (~10 s). In contrast, with a more quiet and dark environment, the birds remained quiet without restraint. This procedure is particularly important for obtaining reliable circulating levels of catecholamines. The BP was measured by a strain-gauge pressure transducer (Statham P23 DC or P23 ID) and a polygraph (Grass 7C or 79D). For measurement of plasma renin activity, blood (0.4 ml) was collected from the implanted catheter into a chilled capillary tube coated with ammonium EDTA and was placed in a cooled chamber (2-4°C). The blood sample (0.8 ml) for catecholamine measurement was taken into a syringe moistened with a mixture of ethylene glycol-bis(β-aminoethyl ether)-N,N',N'-tetraacetic acid (90 mg/ml) and glutathione (60 mg/ml). The blood collected into the hemocrit tube was used for measurement of hematocrit and plasma concentrations of sodium and potassium. Before blood samples were collected, 0.3 ml of blood was withdrawn into a heparinized syringe to clear a deadspace, the blood was subsequently returned to the chickens. If the chickens showed excitement, the blood samples were not collected.

Experimental Protocol

Cardioselectivity of propranolol, atenolol, and practolol. The relative cardioselectivity of the various β blockers can be determined by comparing the degree of blockade of the cardiac and vascular responses to isoproterenol. Hence, the drugs that exhibit greater antagonism of cardiac β1-receptors and induce relatively less blockade of vascular and pulmonary β2-receptors are called "cardioselective" (12, 33). We, therefore, determined the cardioselectivity index for propranolol, atenolol, and practolol in anesthetized hens (19.4 ± 1.1 wk old, 1.36 ± 0.04 kg body wt, n = 12) by the method of Kudo et al. (12).

Briefly, after measurement of control diastolic BP (dBP) and HR (usually 15-20 min), isoproterenol (0.01, 0.02, 0.05, 0.1, 0.2, 0.5, 1.0, 2.0, 5.0, 10.0, 20.0, 50.0, and 100.0 µg/kg) was injected (0.1 ml/kg) in a cumulative fashion (application of the next dose at the stable maximum response) to determine the dose-response curves for dBP and HR. The cannula was flushed with 0.25 ml of 0.9% saline solution after each injection. After the last injection of isoproterenol, 60 min was allowed for recovery. The β-adrenergic blocking drugs were then infused (1 ml·kg⁻¹·h⁻¹) at the following doses: propranolol (n = 4), initial dose of 0.05 mg/kg followed by 0.05 mg·kg⁻¹·h⁻¹; atenolol (n = 4) or practolol (n = 4), initial dose of 1 mg/kg followed by 5 mg·kg⁻¹·h⁻¹. Fifteen minutes after initiation of the β-adrenergic blocking drug, isoproterenol, dose response studies were repeated as above.

We calculated J, the percentage of maximum changes in HR ([ΔHR/ΔHRmax] × 100) and diastolic BP ([ΔdBP/ΔdBPmax] × 100), 2) the dose ratio (median effective dose [ED50] of isoproterenol, calculated from the dose-response curve with β-adrenoceptor antagonist divided by the ED50 of isoproterenol obtained from the dose-response curve without β-adrenoceptor antagonist), and 3) a cardioselectivity index (HR dose ratio/dBP dose ratio). A larger dose ratio indicates that the antagonist drug shifted the isoproterenol dose-response curve more to the right (more potent inhibitor). Furthermore, the higher the cardioselectivity index, the more cardioselective the drug is.

Effects of acute infusion (or injection) of β-adrenoceptor antagonists SQ-14,225 and [Sar1, Thr3]-angiotensin II. The experiment began 40-48 h after the bird recovered from surgery. Following a stabilizing period of 15 min, the resting BP was measured, and a blood sample was collected (preinfusion period). The drugs were infused or injected at the following rates: 1) propranolol (n = 10), atenolol (n = 10), and practolol (n = 6), initial dose of 1.0 mg/kg followed by 1.0 mg·kg⁻¹·min⁻¹ for 15 min; 2) SQ-14,225 (n = 10), 20 mg/kg followed by a waiting period of 20 min; and 3) [Sar1, Thr3]-angiotensin II, initial dose of 50 µg/kg followed by 10 µg·kg⁻¹·min⁻¹ for 15 min. Blood samples were taken immediately after cessation of drug infusion (infusion period). The same chickens were used repeatedly for different drug applications with intervals of 2-4 days. The birds treated with...
SQ-14,225 were not used for other studies because of the relatively long-lasting effect of SQ-14,225.

Effects of chronic treatments with β-adrenoceptor antagonists. The experiment began on the fifth postsurgical day. BP measurements (3 times/wk) were conducted for 10 days (control period). Chickens were then divided into three groups by equally distributing the birds that showed higher (>190 mmHg), middle (160–190 mmHg), or lower (<160 mmHg) BP. One of the following drugs was injected (im) twice daily at 8:30 A.M. and at 4:30 P.M.: 1) propranolol (n = 9), 2 mg/kg (4 mg·kg⁻¹·day⁻¹) in the first week and 4 mg/kg (8 mg·kg⁻¹·day⁻¹) in the second week; 2) atenolol (n = 8), same as for propranolol; and 3) solvent (5%) were conducted for 10 days (control period). Chickens. The experiment began on the fifth postsurgical day. BP, HR, plasma renin activity, 1.27 ± 0.09 ng·ml⁻¹·h⁻¹; NE, 701.9 ± 76.0 pg/ml; E, 337.2 ± 57.1 pg/ml; dopamine, 299.1 ± 39.0 pg/ml; plasma Na, 153.2 ± 0.4 meq/l; plasma K, 3.86 ± 0.03 meq/l; and hematocrit, 39.4 ± 0.5%. Furthermore, we examined whether plasma E and NE levels decreased when the birds were adapted to cannulation and handling for a longer period. Plasma levels of E and NE were measured in roosters (n = 10) cannulated for 1–2 wk (E, 244.7 ± 65.5; NE, 514.0 ± 85.0), 3 wk (E, 206.5 ± 46.6; NE, 472.3 ± 90.3), and 5 wk (E, 218.2 ± 61.0; NE, 482.0 ± 99.5). The distribution of resting BP levels among male chickens used for chronic treatment (n = 27) is shown in Fig. 1.

Cardioselectivity

Cumulative log dose-response curves (% of maximum change) of isoproterenol for the increase in HR and the decrease in diastolic BP (dBP) were shifted to the right during an infusion of atenolol (Fig. 2). Similar shifts of the dose-response curves for HR and dBP were also induced by propranolol or practolol infusion. The isoproterenol dose ratios (at ED₅₀) for HR and dBP for each β-adrenoceptor antagonist and the cardioselectivity index are shown in Table 1. The isoproterenol dose ratio

![Fig. 1. Distribution of resting mean aortic blood pressure (BP) of 27 intact conscious roosters used for chronic treatment with β-adrenoceptor blockers. BP was measured by vinyl catheters implanted chronically (5–12 days) in the aorta via the ischiadic artery. The average of the BP (176.2 ± 4.5 mmHg) was reported previously (16).](http://ajpregu.physiology.org/ Downloaded from http://ajpregu.physiology.org/ on May 8, 2017)
for HR obtained with atenolol was slightly higher ($P < 0.05$) than that evoked by practolol, indicating that on a weight basis, atenolol is more potent than practolol in inhibiting chronotropic action of the heart. When we compared the dose ratios for HR and dBP for each β-adrenoceptor antagonist, however, no significant difference was noted. Accordingly, the cardioselectivity index of each antagonist was close to unity and showed no significant differences among the three drugs, indicating that none of the three β-adrenoceptor blockers used in the present study is cardioselective in fowl.

Effects of Acute Treatments with β-Adrenoceptor Antagonists SQ-14,225 and [Sar¹,Thr⁵]ANG II on BP, HR, Plasma Renin Activity, and Plasma Catecholamines

Propranolol, atenolol, and practolol decreased BP by 16.1 ± 1.5 ($P < 0.01$), 12.7 ± 2.0 ($P < 0.01$), and 11.0 ± 2.0 mmHg ($P < 0.01$), respectively, at 15 min after initiation of β-adrenergic-blocking drug infusion (Fig. 3). Propranolol appeared to be more prompt than atenolol or practolol in reducing BP. HR decreased by 109 ± 7 ($P < 0.01$), 73 ± 10 ($P < 0.01$), and 66 beats/min ($P < 0.05$), respectively, after the start of propranolol, atenolol, and practolol infusion. The reduction in HR after propranolol was significantly greater than that after atenolol ($P < 0.05$) or practolol ($P < 0.05$). SQ-14,225 and [Sar¹,Thr⁵]ANG II changed neither BP nor HR.

Table 1. Inhibition of isoproterenol effects by β-adrenoceptor antagonists

<table>
<thead>
<tr>
<th>Isoproterenol Dose Ratio</th>
<th>Cardioselectivity index</th>
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<tbody>
<tr>
<td>Heart rate</td>
<td>dBP</td>
</tr>
<tr>
<td>Propranolol</td>
<td>$5.3 ± 2.1$</td>
</tr>
<tr>
<td>Atenolol</td>
<td>$5.6 ± 0.8^*$</td>
</tr>
<tr>
<td>Practolol</td>
<td>$3.4 ± 0.3$</td>
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</table>

Values are means ± SE, n = 4 birds for each antagonist. Isoproterenol dose ratios (with/without an inhibitor) were calculated at a mean effective dose of dose heart rate (HR) or dose diastolic blood pressure (dBP) curves. HR dose ratio/dBP dose ratio was calculated for each bird, and then the mean ± SE of 4 birds was obtained. $^*$ $P < 0.05$ compared with practolol by Student's t-test.

Practolol, but neither propranolol nor atenolol, decreased plasma renin activity (Fig. 4) significantly, whereas SQ-14,225 increased it ($P < 0.01$). Propranolol significantly ($P < 0.05$) increased NE, E, and dopamine. Atenolol slightly increased NE ($P < 0.05$; Fig. 5). Practolol and SQ-14,225 did not alter NE or E, but increased dopamine ($P < 0.05$).

Effects of Chronic Treatments with β-adrenoceptor Antagonists on BP, HR, and Plasma Renin Activity

BP (mmHg) and HR (beats/min) decreased ($P < 0.01$, paired t-test) 2 h after propranolol injection (day 0) from 182.6 ± 8.7 (mean of control period BP) to 157.2 ± 7.0 and from 288 ± 13 (mean of control period HR) to 232 ± 11, respectively (Fig. 6). BP and HR further decreased ($P < 0.01$, ANOVA) and then maintained approximately the same level during the experimental period. Both BP and HR returned to control levels 2–4 days after the cessation of propranolol treatment. Atenolol decreased BP (mmHg) significantly 2 h after injection from 182.0 ± 10.0 (mean of control period BP) to 168.1 ± 12.7 ($P < 0.05$, paired t-test), whereas HR (276 ± 7 beats/min, mean of control period HR) did not decrease significantly 2 h after atenolol injection. Both BP and HR significantly decreased ($P < 0.01$, ANOVA) during repeated atenolol treatments. BP did not return to the control level for more than 10 days after termination of atenolol treatment, whereas HR returned to the control level 2 days before cessation of the treatment (Fig. 6). In glucose-treated animals, BP and HR did not change significantly throughout the experimental period. Plasma renin activity showed no significant changes during 2 wk of treatments with either propranolol or atenolol (Table 2), whereas hematocrit showed a tendency to decrease slightly in both control and drug-treated groups (Table 2).

DISCUSSION

**Elevated Blood Pressure in Chickens**

Several bird species examined show a high incidence of elevated BP and spontaneous vascular lesions resembling in part mammalian atherosclerosis in the aorta and other large arteries (7, 24, 29, 32). Although the
exact incidence and mechanisms of elevated BP have not been elucidated, BP appears to be influenced by age, sex (higher in males), environment, and diet in some species (5, 7, 11, 24, 29). The BP (mmHg) and plasma Na concentrations were lower in turkeys kept in the field (105–110) than in captivity (220 ± 10, n = 8) (19). Furthermore, exposure of roosters to social stress did not alter BP but increased the incidence and severity of atherosclerotic lesions (34). In general, highly inbred species were used for studying BP and vascular pathology; hence, it is necessary to consider that cardiovascular function of wild birds may not be the same.

We reported previously (18) that the mean aortic pressure and HR of conscious hens (White Leghorn breed, 30–35 wk old) were 138 ± 2 mmHg and 295 ± 4 beats/min, respectively. The mean aortic pressures of conscious roosters of the same strain, used in the current study, are higher (171.2 ± 3.5 mmHg), ranging from 140 to 230 mmHg, whereas HR (281 ± 4 beats/min) is similar. Since the ages of the roosters used for the present study (54–66 wk) are higher than those of the hens (30–35 wk), the difference in BP can be ascribed to either age and/or sex. Distribution of the resting BP among 27 roosters used for chronic treatment showed two apparent peaks (150 and 200 mmHg). It is not clear at present whether this finding indicates two populations of birds that have higher and lower BP or merely reflects a variation in BP due to physical, humoral (such as catecholamine/glucocorticoid levels), or environmental (such as pecking order in a group) factors. The resting BP levels of roosters in the present study are comparable to those reported in other strains of domestic fowl (29).

Our previous study (13) indicates that the HR of conscious chickens increased in response to depressor substances, including acetylcholine, histamine, arginine

Fig. 4. Plasma renin activity before and after (15 min) infusion (1 mg/kg + 1 mg•kg⁻¹•min⁻¹) of propranolol, atenolol, or practolol or after (21 min) an intravenous injection (20 mg/kg) of SQ-14,225 in conscious roosters (○). Practolol significantly decreased, whereas SQ-14,225 increased, plasma renin activity. Plasma renin activity responses were variable after propranolol and atenolol. ○, means ± SE.
vasotocin, and angiotensin (angiotensin II causes depressor action followed by a pressor effect). Atropine increased HR and significantly reduced the tachycardiac responses to angiotensin and acetylcholine. These findings suggest that fowl have a baroreflex partially mediated by the parasympathetic nervous system.

**Hypotensive Effects of β-Adrenoceptor Blockers**

In the present study, infusion of propranolol, atenolol, or practolol reduced both BP and HR of conscious roosters. Repeated injections of propranolol (4–8 mg kg\(^{-1}\) day\(^{-1}\) im for 2 days) decreased mean BP by 19 ± 1 mmHg and HR by 76 ± 6 beats/min in conscious hens (\(n = 14\)) (18) and decreased mean BP and HR of the roosters (\(n = 9\)) by 37 ± 11 mmHg and 62 ± 15 beats/min, respectively. β-Adrenoceptor blockers have been used for treatment of essential hypertension in humans, but the mechanisms of their hypotensive effect are not completely understood; a decrease in cardiac output via a cardiac β₁-adrenoceptor, suppression of renin release, and action on the central nervous system have been suggested (31). In mammals, administration of β-adrenoceptor-blocking drugs causes an immediate reduction of cardiac output, whereas BP does not decrease immediately because of the increase in total peripheral resistance (31). In contrast, acute infusion of β-adrenoceptor blockers in chickens decreased BP, HR, and cardiac output, whereas the total peripheral resistance remained unaltered (23). Therefore, the immediate hypotension following propranolol, atenolol, and practolol infusion, shown in the present study, can be ascribed to the direct action of the drugs on the heart with lack of a compensatory rise in total peripheral resistance via the baroreflex. Simpson and co-workers (27) reported that propranolol and practolol reduced systolic and dBP in turkeys and prevented β-aminopropionitrile-induced aortic ruptures.

In the present study, we compared in fowl the cardiovascular effects of propranolol with those of atenolol and practolol, which selectively inhibit cardiac β-adrenoceptors in mammals, to see, first, whether these drugs are also cardioselective in fowl and, second, whether the hypotensive effects of propranolol, atenolol, and practolol are different. The dose ratios (at ED₅₀ for dBP (represents potency of vascular β-receptor blockade) and for HR (represents potency of cardiac β-receptor blockade) are similar compared for each drug; and for all three β-adrenoceptor antagonists, the cardioselective index is not significantly different from 1.0. In contrast, cardioselectivity indexes for atenolol and propranolol measured in anesthetized rats using the same method are 9.77 and 1.20, respectively (12). These results suggest that none of these β-adrenoceptor blockers is cardioselective in fowl and that there is no distinct functional differentiation of cardiac β₁ and peripheral β₂ receptors in chickens.

In the present study, the reduction of BP and HR by propranolol appears most prompt, possibly because of the rapid absorption and distribution of this drug (9, 25). Although BP and HR appear more consistently decreased by repeated treatment with propranolol than with atenolol, BP remained low over 10 days after the atenolol treatment was discontinued, despite the fact that atenolol-induced HR reduction was restored prior to the cessation of the treatment. The mechanism of the prolonged hypotensive effect of atenolol is not clear at present, but may be attributed to the slower metabolism of atenolol (6, 9). Dissociation between atenolol effects on HR and BP suggests that mechanisms other than suppression of β-adrenoceptor-mediated chronotropic effect may be involved in atenolol-induced hypotension. In rats, propranolol penetrates the blood-brain barrier, whereas atenolol and practolol exhibit little uptake by the central nervous system (28). If this is the case in fowl, it is unlikely that the hypotensive responses to these drugs, for the most part, are due to their effects on the central nervous system, since the hypotensive effects of atenolol and practolol were clearly demonstrated.
Table 2. Plasma renin activity, plasma electrolytes, and hematocrit in fowl chronically treated with β-adrenoceptor blockers

<table>
<thead>
<tr>
<th></th>
<th>PRA (ng·ml⁻¹·heart rate⁻¹)</th>
<th>Plasma Na. (meq/l)</th>
<th>Plasma K. (meq/l)</th>
<th>Hematocrit. (%)</th>
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<tr>
<td>Control (solvent) (n = 9)</td>
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<tr>
<td>Week 1</td>
<td>1.37 ± 0.20</td>
<td>153.3 ± 0.8</td>
<td>3.90 ± 0.04</td>
<td>39.9 ± 0.4</td>
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<tr>
<td>Week 2</td>
<td>1.24 ± 0.18</td>
<td>154.8 ± 1.1</td>
<td>3.65 ± 0.05</td>
<td>37.5 ± 0.9†</td>
</tr>
<tr>
<td>Recovery</td>
<td>0.96 ± 0.09</td>
<td>154.6 ± 0.7</td>
<td>3.77 ± 0.06</td>
<td>36.7 ± 0.9*</td>
</tr>
<tr>
<td>Propranolol (n = 7)</td>
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<tr>
<td>Control</td>
<td>1.16 ± 0.29</td>
<td>152.4 ± 0.6</td>
<td>4.05 ± 0.05</td>
<td>38.8 ± 1.3</td>
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<tr>
<td>Week 1</td>
<td>1.33 ± 0.23</td>
<td>152.0 ± 0.3</td>
<td>3.85 ± 0.06</td>
<td>35.0 ± 1.6†</td>
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<td>Week 2</td>
<td>1.24 ± 0.29</td>
<td>153.9 ± 1.3</td>
<td>3.87 ± 0.09*</td>
<td>34.5 ± 1.8*</td>
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<tr>
<td>Recovery</td>
<td>1.08 ± 0.23</td>
<td>153.6 ± 0.8</td>
<td>3.96 ± 0.04</td>
<td>33.9 ± 2.1</td>
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<td>Atenolol (n = 8)</td>
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<tr>
<td>Control</td>
<td>1.22 ± 0.07</td>
<td>152.7 ± 0.9</td>
<td>3.99 ± 0.09</td>
<td>39.7 ± 1.4</td>
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<td>Week 1</td>
<td>1.47 ± 0.30</td>
<td>156.4 ± 1.2</td>
<td>3.58 ± 0.09*</td>
<td>36.0 ± 1.5†</td>
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<td>Week 2</td>
<td>1.44 ± 0.17</td>
<td>155.6 ± 0.9*</td>
<td>3.81 ± 0.10</td>
<td>34.6 ± 1.1†</td>
</tr>
<tr>
<td>Recovery</td>
<td>1.35 ± 0.12</td>
<td>153.7 ± 0.5</td>
<td>3.86 ± 0.09*</td>
<td>35.2 ± 1.2*</td>
</tr>
</tbody>
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Values are means ± SE. Control: mean of 3 measurements in control period. Weeks 1 and 2: means of 2 measurements in the 1st and 2nd experimental weeks, respectively. Recovery: mean of 3 measurements in recovery period. PRA, plasma renin activity. *P < 0.05; †P < 0.01 by paired t-test against control.

Roles of Adrenergic Nervous Mechanism in β-Adrenoceptor Antagonist-Induced Hypotension and in Elevated BP in Fowl

The resting levels of plasma NE, E, and dopamine in the roosters used in the present study are higher than those in the younger hens (n = 45) (18), measured previously by a similar radioczymatic assay method (NE, 370.3 ± 56.3; E, 106.2 ± 25.2), and higher than those reported for conscious cannulated humans (supine or standing) (1, 4), rabbits (1), or rats (21). Plasma NE and E levels tend to become slightly lower after 2-3 wk of cannulation and to stabilize, suggesting that the birds were adapted to the experimental conditions. In birds, inhibition of α- and β-adrenoceptors, treatment with ganglion or neuron blockers, or depletion of catecholamines decreases BP (17, 18, 27, and unpublished observations). This finding and the high catecholamine levels suggest that sympathetic and/or adrenomedullary activities may be high in birds. The NE overflow from adrenergic neuroterminals in response to stimuli, however, remains to be determined. In the present study, no significant correlation was shown between resting levels of BP and E or NE levels. It has been reported that adrenalectomy progressively decreases BP and cardiac output in the Pekin duck (3). Synthetic glucocorticoid prevented the reduction of BP (3), suggesting that, as in mammals, glucocorticoid plays an important role in the maintenance of vascular reactivity directly or via a permissive action to catecholamines.

We divided the birds into two groups, one with a higher (190–210 mmHg) and one with a relatively lower (140–160 mmHg) basal BP (see the 2 peaks shown in Fig. 1), and compared their responsiveness to the treat-
ment. Since the purpose of this analysis was to examine whether the basal level influences the responsiveness to β-adrenoceptor blockade, the results from propranolol and atenolol treatment were combined (Fig. 7). The group that had a higher basal BP showed a marked drop in BP immediately after the start of drug treatment, whereas the reduction of BP was only minor in the lower hens. Although many animal species respond to hypotensive treatments more clearly when their basal BP is high, it is unlikely that the difference in basal levels alone can explain the difference in responsiveness. It is possible that the involvement of the adrenergic mechanism may be greater in birds that have higher resting BP levels and thus show a greater response to β-adrenoceptor blockers.

In the present study, plasma NE and E levels were increased markedly by propranolol and NE and slightly by atenolol. Practolol also increased plasma dopamine levels. The increase in catecholamines may reflect a compensatory neural response to the reduction in BP since infusion of propranolol, atenolol, and practolol significantly decreased BP in chickens, the reduction of BP and the rise in NE showed a tendency toward an inverse relationship (r = 0.74). In humans and other mammals, it has been reported that acute treatment with β-adrenergic blocking drugs increases plasma catecholamines during activation of the adrenosympathetic system, such as during exercise (22), whereas the stimulation of HR and BP normally evoked by exercise is suppressed. Sugawara and co-workers (30) suggested, on the other hand, that the catecholamine-releasing action of β-adrenergic blockers may be partially attributed to a direct action of the drug on the adrenal medulla and possibly on the central nervous system.

**Role of Renin-Angiotensin System in β-Adrenoceptor Antagonist-Induced Hypotension and in Elevated BP in Chickens**

The plasma renin activity of the roosters in the present study is lower than that reported previously for hens (18), possibly reflecting the higher BP in roosters, and is comparable to that in humans (2) and dogs (8). In mammals, β-adrenoceptor blockers suppress plasma renin activity by inhibiting the tonic release of renin mediated by the β-adrenoceptor on juxtaglomerular cells (10). Plasma renin activity was not decreased in fowl, however, by acute infusion of propranol or atenolol but was slightly decreased by practolol. Likewise, plasma renin activity was not altered by chronic treatment with propranolol or atenolol, suggesting that the hypotensive action of the β-adrenoceptor blockers is not due to suppression of the renin-angiotensin system. The lack of suppression of resting levels of plasma renin activity by propranolol agrees with the findings reported previously for hens (18). In contrast, acute reduction of BP by sodium nitroprusside increased plasma renin activity in anesthetized fowl and was inhibited partially by simultaneous infusion of propranolol (14 and unpublished observations), indicating that the β-adrenergic mechanism may be involved in the control of renin release. It is therefore possible that, in chickens, although basal tonic release of renin may partially be regulated via the β-adrenoceptor on the renin secretory cells, stimulation of renin release due to the prompt reduction in BP induced by propranolol or atenolol may have counteracted an inhibitory effect of these β-adrenoceptor antagonists on renin release. Indeed, with practolol and atenolol, which evoked a slower reduction of BP than propranolol, there is a tendency toward an inverse relationship between changes in PRA and BP (r = 0.66). It has been reported that SQ-14,225, an ANG-converting enzyme inhibitor, prevents the age-dependent rise in BP in turkeys (26). In our previous and present studies, however, SQ-14,225 and [Sar1, Thr9]ANG II, a nonselective ANG II receptor antagonist, altered neither BP nor HR; whereas SQ-14,225 significantly increased plasma renin activity, presumably by inhibition of a negative feedback loop of ANG II on renin secretion. Relatively low resting levels of plasma renin activity and failure of BP reduction by the inhibitors for the renin-angiotensin system suggest that the renin-angiotensin system is unlikely to be involved in the maintenance of elevated BP in chickens.

In summary, we have reported that the mean arterial pressure of roosters is higher than that of hens and of most mammals. Acute infusion or repeated treatment with propranolol, atenolol, or practolol, but not SQ-14,225 or an angiotensin antagonist, decreased the BP and HR of the roosters. Neither propranolol, atenolol, nor practolol demonstrated cardioselective β-adrenoceptor inhibition. Suppression of plasma renin activity by these drugs was not clearly demonstrated, suggesting that β-adrenoceptor antagonist-induced hypotension is not due to inhibition of the renin-angiotensin system. Furthermore, high plasma levels of E and NE and the prompt hypotension caused by blockade of the adrenerg-
gic mechanisms shown in previous and present studies suggest that the activity of the sympathetic/adrenomedullary mechanism may be elevated in chickens, whereas the renin-angiotensin system is unlikely to be a primary mechanism of elevated BP.

Human hypertension and atherosclerosis are multifactorial diseases that involve a complex interplay among physical, neural, and humoral mechanisms. The antihypertensive effect of β-adrenoceptor blockade has been investigated over two decades, but the mechanism of its action has not been completely understood. The present study indicates that there appear to be no distinct β1- and β2-receptor subtypes in fowl and that the β-adrenoceptor antagonist-induced hypotension is simpler, being primarily induced via suppression of cardiac mechanisms without suppression of the renin-angiotensin system or compensation by peripheral vasoconstriction. Fowl provide a simpler and useful model with which to examine the mechanism of β-adrenoceptor antagonists-induced hypotension and the role of sympathetic/adrenomedullary mechanisms in the regulation of BP.

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