Chronic Propranolol Treatment Inhibits Sympathetic Nerve Activity and Keeps Blood Pressure from Rising in Spontaneously Hypertensive Rats

KAZUO TAKEDA, M.D., AND RUBEN D. BUÑAG, M.A., M.D.

SUMMARY When D,L-propranolol, 100 mg/kg/day, was added to the drinking water of spontaneously hypertensive rats (SHR), systolic pressures measured with the tail-cuff method fell significantly within 1 month and were almost the same as those in normotensive controls (KNR) by the end of 3 months. This antihypertensive effect was later confirmed by direct recording of phasic aortic pressures from indwelling catheters. Blood pressure was lowered selectively only in SHR and not in KNR; by contrast, body weight, fluid intake, and heart rate always decreased whether the rats were hypertensive or not. Because pressor responses to hypothalamic stimulation in SHR treated with propranolol were reduced while those to injected norepinephrine were unaltered, a peripheral inhibition of cardiovascular reactivity was considered unlikely. Supporting the interpretation that diminished pressor responsiveness was caused by concurrent reduction of sympathetic vasomotor activity, frequency of spike potentials recorded from abdominal sympathetic nerves was appreciably lessened in propranolol-treated SHR, as was the vasodepression resulting when autonomic ganglia were pharmacologically blocked with pentolinium. These findings are consistent with the conclusion that prolonged oral administration of propranolol prevents development of spontaneous hypertension in rats by reducing sympathetic vasomotor tone. (Hypertension 1: 228-235, 1980)

KEY WORDS • antihypertensive drugs • blood pressure • cardiovascular reactivity • heart rate • hypothalamic stimulation • ganglion blockade • propranolol • spontaneous hypertension • sympathetic nerves

PROPRANOLOL has been widely used as an antihypertensive drug ever since Pritchard and Gillam\(^1\) first introduced it in 1964; yet even now, its effects on hypertensive rats still remain debatable. Neither the development nor maintenance of renal hypertension is affected,\(^2,4\) but the development of DOCA-salt hypertension is inhibited,\(^4,6,7\) and once DOCA-salt hypertension becomes established, then blood pressure may be unaffected,\(^4,6,9\) lowered,\(^7\) or even elevated.\(^10\) In rats with established spontaneous hypertension, blood pressures have been variously found increased,\(^11-14\) decreased,\(^15,16\) or unaffected.\(^4,7,17-20\) A unique ability to prevent spontaneous hypertension from developing was reported by Folkow and colleagues in 1972\(^21\) and then published in full two years later by Weiss et al.\(^1\) Other studies since then have shown that the pressure elevation is either suppressed,\(^22,23\) reduced,\(^24-27\) or inexplicably unaltered.\(^28,29\) Because failure to show the antihypertensive effect could result from different treatment regimens, we added propranolol, 100 mg/kg/day, to the drinking water of 2.5-month-old Kyoto-Wistar rats (KNR), exactly as described by Weiss et al.\(^1\) After finding that blood pressures indeed became lower in treated than in untreated SHR, we conducted additional experiments to determine whether pressor responsiveness and sympathetic nerve activity had also been altered.

Methods

Two groups of age-matched female rats (19 KNR and 26 SHR), from the strain bred originally by Okamoto and Aoki,\(^30\) were purchased from Charles River Breeding Laboratories (Wilmington, MA). All rats were first treated chronically with propranolol and then used for terminal measurement of pressor responsiveness. In addition, eight untreated and eight propranolol-treated SHR were subsequently anesthetized with urethane to allow recording of sympathetic nerve activity.

Chronic Treatment with Propranolol

Beginning when the rats were 2.5 months old, D,L-propranolol hydrochloride (Inderal, Ayerst Labora-
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100 mg/kg/day, was added to the drinking water of 10 KNR and 13 SHR, while the rest served as untreated controls. Rats belonging to each subgroup were caged together. Body weight and fluid consumption were measured weekly, and values thus obtained were used to adjust propranolol doses for succeeding weeks. Drinking solutions containing ascorbic acid, 20 mg/liter, were prepared fresh every week and kept in bottles wrapped with tinfoil to protect them from light. Daily fluid consumption was determined by subtracting amounts remaining at the end of each 24-hour period from amounts initially added to the drinking bottles. Systolic pressures and heart rates were measured indirectly (before treatment, and after the first and third months of treatment) by a tail-cuff method validated for use in awake rats. These measurements were always taken at the same time in the morning, after a standard 10-minute period of preheating at 39°C, by the same technician who was unaware of rat group identities.

Terminal Measurements Made After Completion of Chronic Treatment

After 3 months of pretreatment with propranolol, rats were anesthetized with sodium amobarbital (7 mg/100 g i.p.) and a concentric electrode (NE-100 with chronic connectors, Rhodes Medical Instruments, Woodland Hills, CA) was placed in the posterior hypothalamus at stereotaxic coordinates: anteroposterior 4.6, lateral 1.0, and dorsoventral −2.5. Electrodes were fixed to the skull with stainless steel screws and dental cement. Rats were reanesthetized with amobarbital 2 weeks later, and indwelling catheters were implanted into the lower abdominal aorta (via a common iliac artery) and the left jugular vein; the free ends of both catheters were passed through the hypothalamic electrode for 5 seconds. Nerves and electrode tips were immersed in mineral oil to reduce tissue dryness. Spike potentials were amplified (Grass P15 AC amplifier) and monitored on a storage oscilloscope (Tektronix 5111); to reduce noise, spontaneous respiration was abolished by paralyzing skeletal muscles with decamethonium bromide (Syncurine, 0.2 mg/100 g i.v.) and connecting the rats to a respirator ventilated with a mixture of 50% oxygen and 50% nitrogen. Analog signals for aortic pressure and nerve activity were recorded continuously on magnetic tape. To quantitify nerve activity, original analog signals were played back from tape into an ink-writing recorder (fig. 1) and simultaneously fed into an amplitude analyzer (F. Haer and Co., Brunswick, ME) to convert individual spikes into uniform pulses and delete background noise. Because residual activity remaining after ganglion blockade with pentolinium (Ansolysen), 0.5 mg (salt)/100 g i.v., was the same as that after crushing the nerve, the low-level control of the window discriminator was routinely set to filter background noise persisting after pentolinium injection. Number of individual pulses per second were counted with a rate analyzer (F. Haer and Co.) whose output was recorded separately as a histogram, digitized by a computer interface, and printed by a programmed calculator (Monroe 1860).

After each experiment, a 2 mA direct current was passed through the hypothalamic electrode for 5 seconds to produce a small lesion and thereby facilitate histologic localization of the electrode tip. A perfusion needle was inserted into the ascending aorta via the left ventricle, and rats were killed with an overdose of pentobarbital; 10% formalin was then perfused into the brain. Excised brains were sectioned transversely at 40 µ intervals, and location of electrode tips were verified by comparison with the atlas of Pellegrino and Cushman. All lesion sites were immediately lateral to the fornix and mamillothalamic tract; in addition to the posterior hypothalamic nucleus, other structures within or adjacent to the terminal lesion included the lateral hypothalamic area, prefrontal nuclei, zona incerta, and median forebrain bundle.

Statistics

Data are expressed as averages ± SEM. Baseline data from four subgroups were compared by an analysis of variance, and for F ratios significant at 5%, differences between pairs of means were examined with Duncan’s multiple range test. Because baselines
Results

Effects of Chronic Treatment with Propranolol

Before propranolol administration began, 2.5-month-old SHR rats had significantly higher systolic pressures than KNR of the same age, but heart rates were almost equal. Propranolol invariably reduced heart rates, but lowered systolic pressures selectively only in SHR and not in KNR (table 1). Heart rates were consistently slower in all treated rats throughout the 3-month treatment period. Differences between pretreatment averages and those for any month of treatment within the same treated subgroup (i.e., treated KNR and SHR in table 1A) were all significantly higher than the corresponding R values at the 1% level; those for corresponding comparisons among untreated controls were not statistically significant. By contrast, systolic pressures during the third month of treatment were generally higher in all subgroups except propranolol-treated SHR (table 1B), in whom differences between average pressures before treatment and those during the first, second, or third months of treatment were consistently higher than the corresponding R values at 1%. During the third month, the average pressure in propranolol-treated SHR was not only much lower than that in untreated SHR, but also almost identical with those for both KNR subgroups (table 1B).

Fluid intake diminished markedly as soon as solutions containing propranolol were substituted for regular drinking water. Averages for fluid intake (ml/day ± SEM) during the first month of treatment were: 37 ± 2 in untreated KNR, 18 ± 2 in propranolol-treated KNR, 34 ± 2 in untreated SHR, and 14 ± 1 in propranolol-treated SHR; corresponding values for the third month of treatment were 74 ± 1, 25 ± 1, 68 ± 2, and 24 ± 2, respectively. All F ratios during treatment were significant at 1%, as were comparisons between untreated and treated rats (e.g., untreated versus treated KNR during the first month, or untreated versus treated SHR during the third month), by the multiple range test. On the other hand, none of the differences between KNR and SHR subgroups (e.g., untreated KNR versus untreated SHR, or treated KNR versus treated SHR) for any month were significant. Thus, addition of propranolol to drinking water clearly reduced fluid intake in both KNR and SHR.

Normal weight gain was also appreciably retarded by propranolol treatment in both KNR and SHR. Average body weights (g ± SEM) before treatment were: 113 ± 4 in untreated KNR, 121 ± 3 in propranolol-treated KNR, 119 ± 2 in untreated SHR, and 113 ± 3 in treated SHR (F ratio of 1.79 less than F_{4,11} = 2.83, which indicates that there were no significant differences initially). Loss in body weight was noticeable even during the first month and was thereafter maintained throughout the duration of treatment; corresponding averages at the end of 3 months were 214 ± 7, 175 ± 4, 206 ± 4, and 165 ± 4 respectively (F ratio of 31.55 significant at 1%). Inhibition of weight gain was similar in magnitude in

Figure 1. Neural and cardiovascular baselines in spontaneously hypertensive rats anesthetized with urethane: untreated control in A, and propranolol-treated in B. Tracings from top to bottom: phasic aortic pressure (mm Hg), heart rate (/min), original analog signal, and integrated (spikes/sec) nerve activity. Bottom photographs show analog signals for sympathetic nerve activity at a faster speed as seen on the oscilloscope.
both KNR and SHR; none of the differences were larger than the corresponding R values obtained with the multiple range test even at the 5% level.

Pressor Responsiveness in Awake Propranolol-treated Rats

To explore the possibility that the antihypertensive activity of propranolol may involve a reduced pressor responsiveness, after 3 months of pretreatment, an indwelling hypothalamic electrode and vascular catheters were implanted chronically. Initial baselines for systolic pressure and heart rate recorded from the aortic catheter confirmed the differences noted previously with the tail-cuff method. Averages for aortic systolic pressure (mm Hg ± SEM) and heart rate (/min ± SEM) respectively were: 128 ± 4 and 397 ± 19 in untreated KNR, 132 ± 5 and 341 ± 26 in treated KNR, 177 ± 5 and 444 ± 8 for untreated SHR, and 133 ± 10 and 339 ± 21 for treated SHR. Corresponding F ratios of 9.53 for pressure and 7.94 for heart rate (exceeding F.OT (3, 29) = 4.51) are significant at 1%. Average pressures in untreated SHR were higher than those in the other three subgroups (all differences obtained with the multiple range test significant at 1%); however, for heart rate, because of large variations, only the difference between untreated and treated SHR is significant at 1%, while that between untreated and treated KNR is significant at 5%. These results also indicate, therefore, that while propranolol slowed heart rate in all the rats, it lowered blood pressure only in hypertensive ones.

Pressor responses were elicited consistently with either hypothalamic stimulation or injected norepinephrine (table 2). Magnitude of pressor responses to injected norepinephrine was unaffected, but for both KNR and SHR, reflex bradycardia was usually

### Table 1. Effects of Chronic Propranolol Treatment on Systolic Pressure and Heart Rate in Awake Normotensive (KNR) and Hypertensive (SHR) Rats*

<table>
<thead>
<tr>
<th>Rat groups</th>
<th>Time of measurement (month)</th>
<th>F ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>1</td>
</tr>
<tr>
<td>Heart rate (/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untreated KNR</td>
<td>475 ± 11</td>
<td>456 ± 12</td>
</tr>
<tr>
<td>Treated KNR</td>
<td>469 ± 8</td>
<td>416 ± 9</td>
</tr>
<tr>
<td>Untreated SHR</td>
<td>487 ± 7</td>
<td>465 ± 10</td>
</tr>
<tr>
<td>Treated SHR</td>
<td>479 ± 9</td>
<td>417 ± 8</td>
</tr>
<tr>
<td>Systolic pressure (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untreated KNR</td>
<td>132 ± 3</td>
<td>136 ± 3</td>
</tr>
<tr>
<td>Treated KNR</td>
<td>130 ± 4</td>
<td>130 ± 4</td>
</tr>
<tr>
<td>Untreated SHR</td>
<td>167 ± 4</td>
<td>166 ± 5</td>
</tr>
<tr>
<td>Treated SHR</td>
<td>166 ± 3</td>
<td>148 ± 6</td>
</tr>
</tbody>
</table>

*Number of rats were: 9 KNR untreated, 9 KNR treated, 13 SHR untreated, 13 SHR treated. With f1 = 3 and f2 = 132-38, an F ratio of 2.85 is significant at 5% and of 4.34 at 1%.

### Table 2. Responses to Sympathomimetic Stimuli in Awake Normotensive (KNR) and Hypertensive (SHR) Rats*

<table>
<thead>
<tr>
<th>Stimulus strength</th>
<th>Variable</th>
<th>Untreated KNR</th>
<th>Treated KNR</th>
<th>Untreated SHR</th>
<th>Treated SHR</th>
<th>F ratio</th>
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<tbody>
<tr>
<td>Injected norepinephrine</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>BP</td>
<td>17 ± 2</td>
<td>17 ± 3</td>
<td>23 ± 2</td>
<td>21 ± 3</td>
<td>0.33</td>
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<tr>
<td></td>
<td>HR</td>
<td>-82 ± 11</td>
<td>-30 ± 11</td>
<td>-56 ± 10</td>
<td>-27 ± 4</td>
<td>5.63</td>
</tr>
<tr>
<td>100</td>
<td>BP</td>
<td>29 ± 3</td>
<td>26 ± 3</td>
<td>36 ± 2</td>
<td>30 ± 4</td>
<td>1.06</td>
</tr>
<tr>
<td></td>
<td>HR</td>
<td>-112 ± 16</td>
<td>-48 ± 17</td>
<td>-56 ± 9</td>
<td>-63 ± 19</td>
<td>6.93</td>
</tr>
<tr>
<td>Hypothalamic stimulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>BP</td>
<td>0.7 ± 4</td>
<td>0</td>
<td>15 ± 4</td>
<td>3 ± 1</td>
<td>5.12</td>
</tr>
<tr>
<td></td>
<td>HR</td>
<td>-0.5 ± 1</td>
<td>0</td>
<td>-7 ± 5</td>
<td>-2 ± 7</td>
<td>0.14</td>
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<tr>
<td>40</td>
<td>BP</td>
<td>23 ± 2</td>
<td>16 ± 4</td>
<td>41 ± 4</td>
<td>27 ± 2</td>
<td>3.56</td>
</tr>
<tr>
<td></td>
<td>HR</td>
<td>2 ± 2</td>
<td>-33 ± 18</td>
<td>-36 ± 11</td>
<td>-21 ± 18</td>
<td>2.98</td>
</tr>
</tbody>
</table>

*Average ± SEM changes from baselines for mean aortic pressure (mm Hg) and heart rate (/min) of: 112 ± 2 and 307 ± 19 in untreated KNR; 115 ± 5 and 341 ± 26 in propranolol-treated KNR; 151 ± 4 and 448 ± 8 in untreated SHR; and 177 ± 9 and 339 ± 21 in propranolol-treated SHR. Stimulus strength expressed in ng/100 g for norepinephrine and μA for hypothalamic stimulation. F ratios obtained by covariance analysis; with f1 = 3 and f2 = 18, F ratios of 3.16 are significant at 5% and of 5.09 at 1%.
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lessened in propranolol-treated subgroups (fig. 2). With covariance analysis, F ratios obtained for bradycardia induced by both test doses of norepinephrine were larger than F_{.00} (3,18) = 5.09 and, therefore, are significant at 1%; those for corresponding pressor responses being smaller than F_{.00} (3,18) = 3.16, are not statistically significant (table 2A). All differences obtained from the multiple range test between untreated and treated subgroups for norepinephrine-induced bradycardia were significant at 1%; this means that norepinephrine always produced considerably less reflex bradycardia in rats pretreated with propranolol.

On the other hand, responses to hypothalamic stimulation were affected almost oppositely: heart rate changes were equivocal, while pressor responses tended to be weaker in propranolol-treated than in untreated subgroups (table 2B). Using the same values for significance as those for norepinephrine, we found that while F ratios for changes in heart rate were not significant, those for corresponding pressor responses to either current strength were significant at 5%. As in previous studies, KNR did not respond like SHR, and consequently, effects of propranolol treatment in KNR were not prominent. Among SHR, differences obtained with the multiple range test between untreated and treated subgroups were significant at 5% for both current strengths. These results show that, in SHR, pretreatment with propranolol reduced pressor responsiveness to hypothalamic stimulation without affecting that to norepinephrine.

Sympathetic Tone in Propranolol-treated Hypertensives

Because centrally-induced sympathetic hyperactivity contributes to the blood pressure elevation in SHR, it was considered possible that pretreatment with propranolol had caused a reduction in sympathetic vasomotor tone. To explore this possibility, after completing tests for pressor responsiveness, eight untreated and eight propranolol-treated SHR were anesthetized with urethane, and spike potentials were recorded from their abdominal sympathetic nerves. Average baselines not only for mean aortic pressure and heart rate, but also for frequency of sympathetic nerve firing, were significantly lower in SHR that had been pretreated with propranolol than in those that had not (figs. 1 and 3). This reduction in sympathetic tone was further substantiated by the magnitude of vasodepression that resulted when the ganglioplegic drug, pentolinium, was routinely injected at the end of each experiment. After ganglion blockade, mean aortic pressure was almost the same in both subgroups (62 ± 3 in untreated and 58 ± 4 in treated rats) because the fall of -67 ± 4 in untreated rats was significantly larger (p < 0.025) than that of -41 ± 8 in treated ones. Hence, both the lower frequency of sympathetic neural firing and the smaller blood pres-

![Figure 2](http://hyper.ahajournals.org/)

**Figure 2.** Cardiovascular responses to injected norepinephrine in two awake, spontaneously hypertensive rats: untreated control in A, and propranolol-treated in B. Tracings from top to bottom: phasic aortic pressure (mm Hg), heart rate (bpm), and mean aortic pressure (mm Hg). Arrows in each panel indicate injections of norepinephrine, 100 ng/100 g i.v.
suggested by the different growth patterns recently obtained at two commercial suppliers for the Ōkamoto-Aoki strain; whereas KNR are heavier than SHR of the same age and sex at Taconic Farms (Germantown, NY), the opposite holds true for similar rats bred at Charles River Breeding Laboratories (Wilmington, MA). Furthermore, when two groups of SHR from different sources were compared, reduced levels of vascular cyclic AMP were found in one group but not in the other.42

Our results, like those of most previous studies, suggest that the antihypertensive activity of propranolol is unrelated to the bradycardia invariably produced by blocking myocardial β1-adrenergic receptors. Possibly because baselines for heart rate fell even among KNR whose blood pressures were unaltered (table 1), reflex bradycardia elicited by injected norepinephrine was always attenuated (table 2A). A sex difference in autonomic regulation of heart rate exists among normotensive rats such that sympathetic tone predominates in females and parasympathetic tone in males;43 thus, attenuation of norepinephrine-induced reflex bradycardia in the females studied here probably signifies abolition by propranolol of a β-adrenergic mechanism for myocardial chronotropic regulation.

Whereas neither fluid intake nor body weight was measured in the original studies of Weiss et al.,19 others have nonetheless reported substantial reductions like those seen here after chronic treatment of SHR with large oral doses of propranolol. Weight loss must be due, at least in part, to diminished fluid intake resulting from the bitter taste imparted to drinking water by propranolol, but other factors may also be involved. For instance, decreased fluid intake could result from inhibition of renin release from kidneys, which would reduce dipsogenic stimulation of the brain by angiotensin.44 Averages for daily fluid consumption (ml) found among 12-week-old females by Pfeffer et al.29 were: 30 ± 2 in untreated KNR, 13 ± 1 in propranolol-treated KNR, 27 ± 1 in untreated SHR, and 15 ± 1 in propranolol-treated SHR. But despite these reductions in fluid intake (which resembled those that occurred in our experiments), they did not induce an antihypertensive effect. Differences in average body weight between untreated and propranolol-treated SHR of 140 versus 180 g were obtained after 1 month by Yamori,45 and of 299 versus 344 g after 6 months by Ablad et al.35 An average weight loss of about 40 g regardless of the duration of treatment seems common to all propranolol-treated SHR (including ours), yet development of hypertension was inhibited in our studies and in those by Ablad et al.35 but not in those by Yamori.45 Furthermore, an antihypertensive effect unaccompanied by loss of body weight occurred when the same dose of propranolol (i.e., 100 mg/kg/day) was given by gavage instead of by addition to drinking water.35 Thus, these various studies collectively indicate that reductions in body weight or fluid intake do not account for the antihypertensive effect of propranolol.
On finding that D,L-propranolol decreased both mean arterial pressure and splanchic nerve activity in normotensive rabbits, Lewis and Haeusler suggested that blood pressure fell because sympathetic nerve activity was reduced. In accord with this interpretation, we found pressor responses to hypothalamic stimulation smaller among propranolol-treated than among untreated SHR (table 2B). A generalized reduction in cardiovascular reactivity was unlikely inasmuch as pressor responses to exogenous norepinephrine were not appreciably altered (table 2A). Similarly, Ljung et al. showed that portal veins from propranolol-treated SHR have reduced responses to sympathetic nerve stimulation but not to norepinephrine. We later found that frequency of sympathetic neural firing was less in propranolol-treated (averaging 28 ± 3 spikes/sec as shown in figure 3, and being almost the same as the average of 26 ± 3 found previously in KNR under similar conditions; see reference 35), than in untreated SHR, as was the vasodepression ensuing when autonomic ganglia were pharmacologically blocked with pentolinium. While none of these findings are individually conclusive, as a whole they imply that by inhibiting the sympathetic hyperactivity that would otherwise exist, propranolol prevents blood pressure from rising in SHR. A similar mechanism was proposed by Ablad et al. when they found adrenal tyrosine hydroxylase activity and dopamine content markedly reduced in SHR that had been treated with propranolol for 6 months. The resulting decrease in adrenomedullary catecholamines could diminish the secondary phase of the hypothalamic pressor response in rats anesthetized with urethane, but was probably not seen here because only primary pressor responses were recorded.

In spite of the well-known effects of \( \beta \)-adrenergic antagonists in suppressing sympathetic stimulation of renin release, the possible contribution of this to the antihypertensive effect of propranolol in SHR is questionable. In addition to blocking \( \beta \)-adrenergic receptors in the kidneys, the reduction in sympathetic nerve activity caused by propranolol could conceivably also diminish neural stimulation of renin release. However, plasma renin levels in SHR, which are either lower than or equal to those in normotensive rats, are usually unaffected by propranolol treatment. During prolonged treatment with atenolol (another \( \beta \)-adrenergic blocking drug), differences in plasma renin concentration between SHR and KNR appeared accentuated at the beginning, but these differences disappeared as treatment progressed, even though the antihypertensive effect persisted. Where or how propranolol diminishes sympathetic tone cannot be determined from our results. Since reduced sympathetic activity was found in splanchic nerves that are postganglonic, the site of action could be anywhere between the brain centers and peripheral nerves. Adrenergic neuron blockade resulting from inhibition of presynaptic \( \beta \)-adrenergic receptors could reduce release of endogenous norepinephrine from peripheral sympathetic nerves and thereby explain diminished pressor responsiveness to hypothalamic stimulation. On the other hand, it can be argued that because propranolol is highly lipid-soluble, it crosses the blood-brain barrier readily and becomes concentrated in many brain areas, including the hypothalamus. Pressor responses to electrical stimulation of the posterior hypothalamus have been attributed to \( \beta \)-adrenergic receptors in the posterior hypothalamus because they are enhanced by isoproterenol and inhibited by propranolol. If presynaptic \( \beta \)-adrenergic receptors also exist in the brain, propranolol could act on them to reduce release of endogenous norepinephrine, inhibit sympathetic vasomotor tone, and thus lower blood pressure. Cerebroventricular injections of propranolol have also been shown to lower sympathetic nerve activity in cats, as well as mean aortic pressure in SHR. All these, together with the evidence for sympathetic hyperactivity as an important pressor mechanism in spontaneous hypertension, indicate that a plausible mechanism could be that propranolol acts on the posterior hypothalamus to reduce sympathetic vasomotor activity and thereby prevent development of spontaneous hypertension.

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