Sympathetic Responses to Stress and Rilmenidine in 2K1C Rabbits
Evidence of Enhanced Nonvascular Effector Mechanism
Geoffrey A. Head, Sandra L. Burke

Abstract—We determined whether the sympathetic excitatory responses to environmental stressors and the sympathoinhibitory responses to rilmenidine are altered by renovascular hypertension. Rabbits were made hypertensive with a clip on the right renal artery, and a left renal nerve recording electrode was implanted. After 3 or 6 weeks, the animals were given air-jet stress and loud noise stress before and after intravenous rilmenidine. Three and 6 weeks after renal clipping, mean arterial pressure was 28% and 36% greater than preclip values. Air-jet stress elicited a marked increase in renal sympathetic nerve activity, mean arterial pressure, and heart rate. Renal sympathetic nerve activity responses were much greater in hypertensive rabbits, but the pressor responses were similar to those observed in normotensive animals. Acute administration of rilmenidine decreased blood pressure more in hypertensive animals but with a much lesser inhibition of sympathetic activity. Rilmenidine markedly reduced increased sympathetic activity during air-jet stress in 3-week clipped rabbits but to a lesser extent in the other groups. These studies show that while sympathetic responses to stress were markedly enhanced in renal clip hypertensive rabbits, they did not result in greater pressor responses, thus suggesting that vascular neuroeffector mechanisms were not altered. By contrast, the increased effects of rilmenidine suggest a much greater contribution to the hypertension by the sympathetic nervous system, but one that is caused by an enhanced “nonvascular” neuroeffector mechanism. As such, sympathoinhibitory agents such as rilmenidine are very suitable and very effective agents for the treatment of renovascular hypertension. (Hypertension. 2004;43:1-7.)

Key Words: renal nerves ■ hypertension ■ stress ■ sympathetic nervous system ■ rabbits ■ blood pressure ■ heart rate

There has been a long-standing interest in the role of the sympathetic nervous system in hypertension, but more so in view of increasing evidence that it can contribute to the long-term setting of blood pressure.1 In renovascular hypertension, there is much evidence for a greater dependence of the hypertension on the sympathetic nervous system.2 A greater depressor response to ganglion blockade has been observed in renal wrap hypertensive rats.3 Studies in the rabbit by Cox and Bishop showed that during angiotensin (Ang) infusion, the hypertension was initially caused by Ang-mediated vasoconstriction that subsided and was replaced by a greater neurogenic component.4

One of the major difficulties in determining the contribution of the sympathetic nervous system in hypertension has been in making direct comparisons of microvolt values between different groups. Recently, we developed a novel method for comparing sympathetic activity between groups of animals5 and found that renal sympathetic nerve activity (RSNA) is not increased but initially decreased or unchanged in 2-kidney 1-clip (2K1C) hypertensive rabbits.6 Studies in renal wrap7 and chronic Ang-induced hypertension8 support these findings. Studies in humans using noradrenaline spillover have been inconclusive.9–11 Importantly, examining the same patient with or without renal hypertension did not show any difference in total noradrenaline spillover.9,11 Reports of noradrenaline turnover in 2K1C rabbits have found no change in turnover from a range of tissues suggesting that there is not a generalized change in sympathetic activity in this model.12 Thus there is a paradox. How can the contribution of the sympathetic nervous system increase if the level of activity stays the same? One possibility is enhanced pressor responses according to the vascular amplifier hypothesis,13 which is evident in Ang-dependent hypertension.4 Our method of quantifying RSNA between groups allows us the opportunity to determine whether there are exaggerated pressor responses to acute sympathetic stimuli (stress) that may provide evidence for the vascular amplifier hypothesis. We also wished to examine acute inhibition of the sympathetic nervous system with rilmenidine, which is a second-generation centrally acting antihypertensive agent. In conscious normotensive rabbits, rilmenidine lowers resting RSNA and suppresses the reflex response to lowering blood pressure,14 but its acute

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From Neuropharmacology Laboratory, Baker Heart Research Institute, Melbourne, Victoria, Australia.
Correspondence to Associate Prof Geoffrey A. Head, Baker Heart Research Institute, Commercial Road Prahran, P.O. Box 6492, St. Kilda Road Central, Melbourne, Victoria, 8008, Australia. E-mail geoff.head@baker.edu.au
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In the present study we examined the pressor and sympathoexcitatory responses to acute stress and the depressor and sympatho-inhibitory responses to rilmenidine in conscious rabbits. The vascular amplifier hypothesis would suggest enhanced depressor responses to sympathetic withdrawal as well.

In the present study we examined the pressor and sympathoexcitatory responses to acute stress and the depressor and sympatho-inhibitory responses to rilmenidine in conscious normotensive and 2K1C hypertensive rabbits. 2K1C hypertension in the rabbit is very stable, so we examined them at 3 weeks, corresponding to the period when circulating renin levels are high, and at 6 weeks when structural and adaptive changes have occurred. We chose a modest level of stress because it may be exaggerated in the hypertensive animals.

**Methods**

Experiments were conducted in conscious rabbits of either sex, weighing 2.2 to 3.1 kg, bred and housed at the Baker Heart Research Institute in accordance with the Australian Code of Practice for Scientific Use of Animals. In an initial operation performed under halothane anesthesia (intravenous 3 mg/kg carprofen for analgesia before and 24 hours after surgery and intravenous 10 mg/kg propofol for induction), animals were implanted with a silver clip on the right renal artery or underwent a sham implantation. Two or 5 weeks later, a recording electrode was implanted on the left renal sympathetic nerve.

**Experimental Procedures**

On the day of the experiment, arterial blood pressure was measured from the central ear artery and RSNA between 50 Hz and 2 kHz was rectified, integrated, and background noise subtracted. Mean arterial pressure (MAP), heart rate (HR), and RSNA were digitized and averaged over 2 seconds. RSNA was successfully recorded from 89% of electrodes implanted, and in each rabbit it was normalized relative to the maximum 2 seconds of RSNA evoked by the nasopharyngeal response. Rabbits were subjected to noise stress (white noise at 85 to 90 dB) and air-jet stress (15 L/min) for 10 minutes. MAP was measured weekly before and after implantation of the renal clip to determine which rabbits were hypertensive (at least 15% increase in MAP in 49% of animals). Sixteen hypertensive and 10 sham rabbits received the renal electrode after 2 weeks or after at least 5 weeks of hypertension.

**Experimental Protocol**

The first experiment was conducted at least 6 days after implantation of the renal electrode. After an initial 30-minute control period, each animal was subjected to 10 minutes of noise or air-jet stress in randomized order. A 20-minute recovery period followed and the procedure was repeated with the other stress. After a further 20 minutes of recovery, the rabbit received an intravenous injection of rilmenidine dihydrogen-phosphate (273 μg/kg bolus + maintenance infusion of 1.5 μg/kg per minute) or saline vehicle. This dose

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**Table 1. Basal Values for First and Second Experiments and for Saline and Rilmenidine Experiments**

<table>
<thead>
<tr>
<th>Group</th>
<th>Exp 1 MAP (mm Hg)</th>
<th>Exp 2 MAP (mm Hg)</th>
<th>P1 Before Saline</th>
<th>P2 Before Rilmen</th>
<th>P2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham</td>
<td>77.3±0.9</td>
<td>76.2±0.6</td>
<td>NS</td>
<td>75.2±1.1</td>
<td>78.5±1.2</td>
</tr>
<tr>
<td>3-wk 2K1C</td>
<td>100.3±1.6</td>
<td>99.1±2.0</td>
<td>NS</td>
<td>98.2±2.5</td>
<td>101.2±1.8</td>
</tr>
<tr>
<td>6-wk 2K1C</td>
<td>105.3±2.2</td>
<td>111.2±1.8</td>
<td>*</td>
<td>105.7±2.4</td>
<td>108.6±1.9</td>
</tr>
<tr>
<td>RSNA (nu)</td>
<td>7.1±0.4</td>
<td>9.2±0.5</td>
<td>**</td>
<td>8.4±0.8</td>
<td>7.7±0.8</td>
</tr>
<tr>
<td>Sham</td>
<td>5.1±0.6</td>
<td>3.7±0.3</td>
<td>NS</td>
<td>5.0±1.0</td>
<td>4.1±0.6</td>
</tr>
<tr>
<td>3-wk 2K1C</td>
<td>4.3±0.7</td>
<td>3.5±0.3</td>
<td>NS</td>
<td>2.5±0.7</td>
<td>5.1±0.9</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>159±4</td>
<td>165±4</td>
<td>NS</td>
<td>158±4</td>
<td>166±3</td>
</tr>
<tr>
<td>Sham</td>
<td>201±7</td>
<td>184±3</td>
<td>*</td>
<td>186±5</td>
<td>201±5</td>
</tr>
<tr>
<td>3-wk 2K1C</td>
<td>180±3</td>
<td>188±3</td>
<td>NS</td>
<td>184±3</td>
<td>182±5</td>
</tr>
</tbody>
</table>

Values are 5-minute averages and SEM using combination of between-animal and within-animal variance.

NS indicates nonsignificant for comparisons P1 experiment 1 compared to experiment 2, P2 pre-saline control compared to pre-rilmenidine control; MAP, mean arterial pressure (mm Hg); RSNA, renal sympathetic nerve activity (normalized units); HR, heart rate (beats per minute).

*P<0.05; **P<0.01.
produces 90% of the maximum blood pressure response.\textsuperscript{15} Forty minutes after the bolus injection, the stressors were repeated. A second experiment was performed at least 2 days later with the other treatment (rilmenidine or saline), and their order was randomized. The animals were euthanized and both kidneys and the left ventricle were removed and weighed.

**Data Analysis**

Values were expressed as mean±SEM or mean difference±SED. Treatment effects were analyzed by split-plot repeated measure analysis of variance that allowed for within-animal and between-animal (group) contrasts\textsuperscript{6} and adjusted by the Bonferroni method. The repeated nature of the data was adjusted by the Greenhouse-Geisser method.

**Results**

**Development of 2K1C Hypertension**

Experiments were conducted at 3 weeks and 6 weeks after clipping or sham clipping during which the animals received vehicle or rilmenidine treatment on 2 separate days in random order. MAP was 28%±1% higher in 3-week clipped and 36%±2% higher in 6-week clipped rabbits compared with sham operated animals (F\textsubscript{1,46}=33; \textit{P}<0.001) (Figure 1, Table 1). The slightly greater hypertension in the 6-week group was not statistically significant (F\textsubscript{1,46}=1.2; \textit{P}=0.25). HR was also 21%±2% higher in the 3-week and 12%±1% higher in the 6-week clipped groups compared with sham clipped rabbits (F\textsubscript{1,46}=7.9; \textit{P}=0.005) (Figure 1, Table 1). Conversely, basal RSNA values were highest in the sham operated rabbits (F\textsubscript{1,46}=13.1; \textit{P}<0.001) (Figure 1, Table 1).

**Rilmenidine in Sham and 2K1C Rabbits**

Rilmenidine lowered MAP, HR, and RSNA in normotensive and hypertensive animals. The maximum response was observed at 15 minutes (eg, 67±1 mm Hg for sham) and remained at this level for at least 60 minutes (68±1 mm Hg). The hypotensive responses were greater in the hypertensive animals (Figure 1) (F\textsubscript{3,120} between groups=3.4; \textit{P}=0.03) but the inhibition of RSNA was less (Figure 1) (F\textsubscript{2,120} between groups=3.4; \textit{P}=0.05). The bradycardia to acute rilmenidine was similar in the 3 groups of animals (Figure 1). Saline-treated rabbits had pretreatment values similar to those observed in sham operated rabbits (Table 1). Saline injection did not affect MAP, HR, and RSNA levels in any of the groups (changes <4%) (Figure 1).

**Stress in Sham and 2K1C Rabbits**

Air-jet produced an abrupt and sustained increase in MAP, HR, and RSNA in normotensive and both groups of hypertensive rabbits. Although there was no difference in the pressor responses between groups, the sympathetic responses were similarly enhanced in the hypertensive animals, but only during the sustained part of the response (Figure 2). Air-jet stress produced tachycardia that was greatest in the 3-week group (F\textsubscript{1,46}=6.2; \textit{P}=0.01) (Figure 2), but the response in the 6-week hypertensive animals was similar to sham. There were no significant differences in any parameter in the initial response between the sham and hypertensive animals (Figure 2).

Noise stress produced smaller pressor and sympathoexcitatory responses than did air-jet stress. The initial and sustained sympathetic responses at 3 weeks of hypertension were similar to those observed in sham animals, but a small hypotensive response was observed (Figure 3). In these rabbits, the onset of noise stress evoked a greater tachycardia than in the other groups, but this was not sustained (Figure 3). The hypotension was more marked at 6 weeks of hypertension and was accompanied by an exaggerated initial and sustained sympathoexcitatory response and an attenuated tachycardia (Figure 3).

**Rilmenidine and Responses to Stress**

After rilmenidine treatment, air-jet and noise stress were repeated. Rilmenidine suppressed the RSNA, HR, and MAP
responses to air-jet stress in both hypertensive groups with the greatest effect in the 3-week clipped rabbits (Figure 4). There were relatively few differences in the responses to air-jet stress between groups after rilmenidine treatment, both during the first minute of the response and as the air-jet was sustained. The tachycardia to air-jet stress was less at 6 weeks of hypertension compared with sham (F1,50/11005 6.0; P/11005 0.01) whereas RSNA was greater (F 1,50/11005 10.6; P/11005 0.001) (Figure 4).

The responses to noise stress were virtually abolished by rilmenidine, with only the RSNA response in the 6-week group being greater than the response observed in sham animals (Figure 5). Responses to air-jet and noise stress were similar before and after saline administration in each group. The sympathoexcitatory response to air-jet stress in the sham group was 4.0±0.8 nu before and 3.2±0.8 nu after saline. The noise stress response was 1.9±0.6 nu before and 1.8±0.6 nu after saline.

**Neuroeffector Indices**

For each of the stimuli examined (air-jet stress, noise stress, and rilmenidine), the ratio of the change in blood pressure per unit change in RSNA was calculated as an index of the neuroeffector gain in the 3 groups of rabbits. The neuroeffector index for air-jet stress and noise stress was generally not different in the normotensive and hypertensive groups, although there was a significant reduction in the ratio at 3 weeks’ hypertension with air-jet stress (Figure 6). By contrast, the ratio was markedly increased after rilmenidine at 3 and 6 weeks of hypertension (Figure 6). Analysis of the time course of the index during the 10 minutes showed no significant changes with time (F4,32/11021 2.2; P/11022 0.1).

**Organ Weights**

The left ventricle of 6-week 2K1C rabbits was 21% heavier than that of sham rabbits, but sham and 3-week clipped rabbits were not different (Table 2). The clipped kidney was lighter than the nonclipped kidney in both hypertensive groups (24% and 31%, respectively).

**Discussion**

The main findings of the present study were that resting RSNA was lower in conscious 2K1C hypertensive rabbits and that the renal sympathetic responses to environmental stress were amplified in the hypertensive animals compared with normotensive animals. However, there was no increase in the pressor responses to either stress. Calculation of the ratio of pressor response per unit nerve activity showed that there was no real change in this index of “neuroeffector gain,” which does not support the idea of a vascular amplifier present in this form of hypertension. We did observe an increase in the depressor effect of rilmenidine at 3 and 6 weeks of hypertension, but this was produced by a lesser reduction in RSNA than was observed in normotensive animals. Assuming that RSNA changes reflect the pattern that occurs in other vascular beds, then it would appear that the
renal wrapping in rabbits,16 and there is evidence of decreased change in directly recorded basal RSNA 3 to 5 weeks after of Ang-dependent hypertension. Bell et al could find no comes from three other research groups using different forms ryngeal reflex. Further evidence for a lack of increased RSNA and when the electrodes were calibrated using the nasopha-ryngeal stimulation remains stable over the life of an elec-
trode, and when used as a “calibrating factor” can eliminate differences between animals caused by electrode recording properties.5 In the present study, we observed the reduced RSNA in hypertensive rabbits in the raw microvolt values and when the electrodes were calibrated using the nasopha-
ryngeal reflex. Further evidence for a lack of increased RSNA comes from three other research groups using different forms of Ang-dependent hypertension. Bell et al could find no change in directly recorded basal RSNA 3 to 5 weeks after renal wrapping in rabbits,16 and there is evidence of decreased RSNA in dogs17 and rabbits with Ang-induced hypertension.5 Thus there is general agreement that RSNA is not elevated in nerve activity but rather by a change in a specific neuroef-
factor mechanism.

Our findings are based on being able to compare the level of sympathetic nerve activity in different groups of animals. Until recently, there has been no validated way of doing this because of the individual recording properties of implanted electrodes making comparisons virtually meaningless. However, we have shown that the relationship between resting RSNA and the maximum RSNA recorded during nasopha-
ryngeal stimulation remains stable over the life of an electro-
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An important question is whether RSNA reflects the activity from other beds. Using a biochemical marker, Tanaka et al have shown that noradrenaline turnover in the aorta, mesentry, and heart are the same in 2K1C rabbits compared with normotensive controls.12 Furthermore, the hypotension to ganglionic blockade is much greater in renovascular hypertension, suggesting that the effect we are seeing with rilmenidine reflects an effect on most if not all sympathetic beds. Results from a “within-patient” study, before and 12 months after reversal of renovascular hypertension, showed no change in total noradrenaline spillover, suggesting that the hypertension did not elevate global sympathetic activity.11 Thus our assumption that RSNA reflects sympathetic activity in other beds is reasonable, but we cannot be certain about this without direct recordings. Nevertheless, our studies and others do not support the view that the activity of the sympathetic nervous system in general is enhanced in renovascular hypertension.

It may appear to be a paradox that we observed a greater response to the sympatho-inhibitory agent rilmenidine with respect to the decrease in blood pressure in the hypertensive animals, but our findings are consistent with other studies. A greater depressor response in renovascular hypertension has been observed with clonidine and ganglionic blockade in rats and rabbits.4,18 Also, studies in human renovascular hyp-
tension have shown a greater response to clonidine.2 These findings suggest an important contribution of the sympathetic nervous system to renovascular hypertension in the early and late phases of its development. However, this increase was not reflected in the pressor responses to noise or air-jet stress, which, if anything, showed a tendency to decrease while the nerve responses were greater in the hypertensive animals. Thus the vascular responses are not enhanced in hypertension and the perceived increased role of the sympathetic nervous system is probably not related to vasoconstriction per se. Thus our studies do not provide support for the vascular amplifier hypothesis in this form of hypertension.

Because rilmenidine acts by reducing sympathetic vaso-
constriction, it is surprising that its effects are amplified and those to stress are not. The enhanced ability of rilmenidine to influence blood pressure may be related to lower renin levels caused by the withdrawal of RSNA.19 The enhanced response would be caused by an increase in the renin neuroeffector gain, because basal RSNA is lower. In human renovascular hypertension, Morgan suggested that the greater response to clonidine may involve reducing plasma renin levels.20 In support, we have observed a 3-fold greater release of renin in response to an increase in RSNA in 2K1C rabbits compared with sham.21 Thus, the effect of rilmenidine in reducing RSNA would be expected to produce a markedly greater reduction in renin and, hence, blood pressure under these conditions. This would completely explain the present findings.

The pattern of responses to stress in the sham and 2K1C rabbits was similar to that previously observed in normoten-
sive animals, that is, an abrupt initial increase in RSNA, HR and MAP followed by sustained elevation if the stress is continued.22 However, in hypertensive animals the HR and RSNA responses to air-jet were augmented at 3 weeks with the greater RSNA response still present at 6 weeks. Increased tachycardia is unlikely to be caused by diminished barore-
flexes because this persists to 6 weeks.6 The enhanced tachycardia might be caused by the higher levels of circulating angiotensin, which would be expected to facilitate the cardiac sympathetic response and attenuate the effect of cardiac vagal tone. Exaggerated cardiovascular responses to alerting stimuli have been described in hypertensives and increased responsiveness of RSNA to stress has been demonstrated in SHR compared with WKY rats.23 While the RSNA response to noise stress was enhanced at 6 weeks, the pressor responses became depressor responses, and the tachycardia was less in the 6-week hypertensive rabbits. It would appear that there is an underlying hypotensive response perhaps related to the alerting and fearful response associated with
noise stress,24 which may be more evident in the hypertensive animals.

An important finding of the current study was that the centrally acting agent rilmenidine was most effective in reducing the sympatho-excitatory responses to air-jet or to noise stress in the hypertensive groups. Indeed, the maximum RSNA response to either stress after rilmenidine treatment did not exceed the resting pre-rilmenidine level. Although we had previously observed the effects of rilmenidine in reducing the sympathetic responses to stress in conscious normotensive rabbits,22 this is the first evidence that these findings were applicable under conditions of chronic renovascular hypertension. Previous studies showed no effect of rilmenidine in the cardiovascular responses to mental stress in normotensive and hypertensive humans.25,26 However, administration of another centrally acting antihypertensive agent, clonidine, reduced the autonomic response to air-jet stress as indicated by changes in medium frequency oscillations27 and abolished the increased RSNA response to air-jet stress in hypertensive conscious rats.28 Both of these studies are consistent with our observations that rilmenidine attenuates the sympathetic-activation to air-jet stress. Rilmenidine administered centrally has also been shown to inhibit the maximum RSNA evoked by unloading the baroreceptors in rabbits.14 Thus, under rilmenidine, the kidneys have, overall, much lower sympathetic drive and are better protected from stress-induced neurally mediated vasoconstriction.

In conclusion, the present study showed that in renal clip hypertensive rabbits, the increase in sympathetic activity to acute environmental stressors was markedly enhanced; surprisingly, this did not result in a greater pressor response. However, the greater responses to rilmenidine, a centrally acting antihypertensive drug, suggest an increased role of the sympathetic nervous system in 2K1C renovascular hypertension. This has occurred with a lesser reduction in RSNA. Taken together, these findings suggest that hypertension has selectively altered the way rilmenidine achieves hypotension, presumably through inhibiting the sympathetic nervous system. Because this change does not appear to involve the sympathetic vasoconstrictor neuroeffector mechanism, it may involve the neural release of renin and would appear to be achieved by a marked increase in the gain of this "neuroeffector mechanism." If so, such a change would be an important mechanism contributing to renovascular hypertension.

Perspectives

The present study suggests that a major mechanism by which the sympathetic nervous system contributes to the maintenance of hypertension may be through alteration of the sympathetic neuroeffector mechanism possibly involving the neural release of renin. This mechanism in the long-term would mean a greater participation of the central nervous system in the maintenance of hypertension and therefore restore the ability of the central nervous system to regulate short-term to medium-term blood pressure levels, which is essential for coping with acute cardiovascular requirements. Thus treatment with a sympatholytic agent may be most beneficial because it takes advantage of these changes in gain and reduces blood pressure and its variability close to normal levels. Perhaps the most exciting aspect of these findings is the possibility that this mechanism may play a role in other forms of hypertension and even in the normotensive state. Chronic treatment of normotensive rabbits with low doses of angiotensin-converting enzyme inhibitor results in low levels of blood pressure, but only after 6 weeks.29 This effect could not be explained by accumulation of drug or increased angiotensin-converting enzyme inhibition at 6 weeks. Thus, blood pressure can be set at low, normal, or high levels, depending on the state of the renin angiotensin system. It is important to determine whether this hypotensive state also involves a reduction in the gain of the nonvascular neuroeffector mechanism. If this were the case, then it would mean that this mechanism enables the sympathetic nervous system to contribute to setting blood pressure in the long-term.

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