Pressor Response to 1-Sar-8-Ala-Angiotensin II (Saralasin) in Hypertensive Subjects

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SUMMARY An angiotensin II (AII) analogue (1-Sar-8-Ala-angiotensin II) (saralasin) was infused into 418 untreated hypertensive subjects during a 1-day evaluation while blood pressure was recorded every 2 minutes by Arteriosonde. At 5 μg/kg per min, saralasin produced a change in mean blood pressure which correlated significantly (r = -0.54, P < 0.001) with the stimulated plasma renin activity (PRA) after intravenous furosemide and ambulation for 2 hours. Saralasin caused a rise in mean blood pressure of at least 7.0 mm Hg in 97 hypertensive subjects, who also had a low stimulated PRA (1.3 ± SEM, 0.1 ng/ml per hour; normal range, 1.7-8.5). On a low sodium diet, the pressor response of hypertensive subjects to saralasin continued and was an even better indicator of a low stimulated PRA. Infusion of saralasin at 10 μg/kg per min into normal subjects on an unrestricted diet, a low sodium diet, and a high sodium diet produced, respectively, no change, a fall (P < 0.05), and a rise (P < 0.005) in blood pressure. The same saralasin dose in six hypertensive subjects who showed a pressor response to the analogue in the 1-day study also produced a rise in blood pressure when given on a low sodium diet, and this rise was more than twice that seen in normal subjects on a high sodium diet. Hypertensive subjects who showed the pressor response had a significantly greater (P < 0.01) pressor sensitivity to AII than did hypertensive nonresponders to saralasin and normal subjects on an uncontrolled diet. The affinity of the vascular receptors for the analogue was greater in the hypertensive group that showed the pressor response to saralasin. In summary, the pressor response to saralasin, as defined above, occurred in 23% of a large unselected group of hypertensive subjects and was associated with salt loading, a low stimulated PRA, and increased pressor sensitivity to AII.

Methods

HYPERTENSIVE SUBJECTS

A total of 418 hypertensive patients, all of whom had taken no antihypertensive medication for at least 3 weeks, were referred for a 1-day hypertensive evaluation. These studies were approved by the Committee for the Protection of Human Subjects of the Upstate Medical Center. Prior to study, fully informed consent was obtained from each patient. The procedure used has been described in detail.

DURING the course of infusing a highly specific, competitive analogue of angiotensin II (1-Sar-8-Ala-angiotensin II) (saralasin) into a large group of untreated hypertensive subjects, a sustained rise in blood pressure (agonistic response) was noted in approximately 23%. In this article, an attempt is made to characterize these subjects. Their response to saralasin while on a low sodium diet is compared with blood pressure responses to saralasin infusion in normal subjects on various sodium intakes. It appears that the mild pressor response to saralasin will be useful in the rapid recognition of a sizable group of hypertensive patients, many of whom have a low stimulated peripheral plasma renin activity (PRA).

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range, 2.9-14.8 ng/ml per hour. The same afternoon, patients were recumbent for 1 1/2 hours and blood pressure was recorded automatically. Saralasin was then infused with a Harvard pump at 0.1, 1.0, and 10.0 μg/kg per min, each for 1 hour.

Blood pressure responses to saralasin, angiotensin II (A II), and both peptides given together were studied in another group of randomly selected hypertensive subjects. These subjects had no evidence of a renal lesion on intravenous pyelogram or renal flow study and had normal plasma aldosterone levels after infusion of 2 liters of normal saline. They had been off all antihypertensive medication for 3 weeks and were on an uncontrolled diet. To produce a situation comparable to that obtaining for the other hypertensive subjects, furosemide (40 mg) was given intravenously 4 hours before these studies. Responses to saralasin (5 μg/kg per min) were then determined. Sensitivity to exogenously infused A II was determined as follows, starting 1 1/2 hours after the end of the saralasin infusion: After stabilization of blood pressure over about 30 minutes, A II amide solution (Hypertensin, 1 μg/ml in 5% dextrose solution) was infused intravenously by Harvard infusion pump. The rate of infusion was gradually increased by 2 ng/kg per min, at intervals of about 10 minutes, until repeated measurements of blood pressure by Arteriosonde (at least five at each infusion rate) showed an increase of 20 mm Hg in diastolic blood pressure. When necessary, this dose of A II was calculated by interpolation according to the method of Hocken et al. Blood pressure then was allowed to return to a steady state for at least 30 minutes and the effect of saralasin on the pressor response to A II was determined. Saralasin was infused by a Harvard pump at a rate twice as rapid as the rate of A II required to raise the diastolic blood pressure 20 mm Hg. After 30 minutes of saralasin infusion at this rate, A II was infused in the same arm by a second Harvard pump in the same stepwise manner of increasing rates, described above. The A II infusions were repeated at more rapid saralasin infusion rates (3 times, 4 times, 5 times, etc.) until the rise in diastolic blood pressure caused by A II was reduced by at least 50%. This blocking action of saralasin on the pressor effect of A II was found to be linear with increasing rates of saralasin infusion. If, then, a saralasin infusion rate of 30 ng/kg per min reduced the angiotensin-induced rise in diastolic blood pressure to 15 mm Hg and a saralasin infusion rate of 40 ng/kg per min reduced the rise to 5 mm Hg, then the amount of saralasin required to reduce by 50% the rise in diastolic blood pressure induced by A II would be estimated to be 35 ng/kg per min.

NORMAL SUBJECTS

Eighteen normal subjects on no medication have been studied by the 1-day hypertensive protocol. Their ages ranged from 19 to 54 years, and five were women. Five other normal subjects were fed a diet of 10 mEq of Na and 80 mEq of K per day from the Clinical Research Center kitchen. Measurements of Na, K, and creatinine were made on a 24-hour urine specimen collected on the 3rd day of the diet. On the 4th day, subjects were recumbent for 1 1/2 hours and blood pressure was recorded every 2 minutes with an Arteriosonde. Saralasin was then given at 0.1, 1.0, and 10.0 μg/kg per min, each for 1 hour. At a later date, the same five normal subjects were fed a high sodium diet (102 mEq of Na added per day to regular diet) for 4 days. A 24-hour urine sample was collected on day 4 for Na, K, and creatinine determinations. On day 5 of the high sodium diet, saralasin was again infused as had been done for the subjects receiving 10 mEq of Na. A similar saralasin infusion was given to six different normal subjects on an uncontrolled diet. In six normal subjects on an uncontrolled diet, combined responses to saralasin and A II were determined as described above for the hypertensive subjects.

Results

BLOOD PRESSURE RESPONSE TO SARALASIN IN HYPERTENSIVE SUBJECTS

Figures 1 and 2 are examples of blood pressure records of hypertensive subjects showing an increase and no change, respectively, during saralasin infusion. In Figure 1 note the gradual rise in blood pressure during saralasin infusion, which reversed after administration of the analogue had been stopped. Of the first 418 hypertensive subjects evaluated during the 1-day study, 97 showed a rise in mean blood pressure (diastolic plus 1/3 pulse pressure) above baseline of at least 7 mm Hg (i.e., greater than that seen in any of 16 normal subjects) at a saralasin infusion rate of 5.0 μg/kg per min. The average changes in mean blood pressure seen during infusion of saralasin at 0.05, 0.5, 5.0, and occasionally 10.0 μg/kg per min in these hypertensive subjects with agonistic responses to saralasin and in 16 normal subjects are shown in Figure 3. In many hypertensive subjects an immediate rise in blood pressure (first 1-5 minutes) was noted but this change almost always was transient, and for this reason has not been included in the results. The average saralasin-induced rise in mean blood pressure from control for all the hypertensive subjects with agonistic responses was progressive at the three infusion rates, being, respectively, 7.1

![Figure 1](attachment:arteriosonde_blood_pressure_record.png)
PRESSOR RESPONSE TO SARALASIN IN HYPERTENSION

PRESSOR RESPONSE TO SARALASIN IN HYPERTENSION

Most of these hypertensive subjects showed a progressive rise in blood pressure with the first three increasing rates of saralasin infusion but few showed a further rise in blood pressure when saralasin was infused at 10 µg/kg per min.

RELATION OF SARALASIN-INDUCED BLOOD PRESSURE RESPONSE AND PRA

The measurements of peripheral PRA (after furosemide and ambulation for 2 hours) in the 97 hypertensive subjects who showed the pressor response to saralasin, as defined above, are shown in Figure 4 (left column). On the right of the same figure are results of measurement of PRA in 22 normal subjects, obtained under identical conditions. The respective means (±SE) were 1.3 ± 0.1 and 5.0 ± 0.4 ng/ml per hour (P < 0.001).

The peripheral PRA levels in 22 hypertensive subjects after 2 hours of ambulation on the 4th day of a diet of 10 mEq of Na and 80 mEq of K are shown in Figure 5. All received a saralasin infusion at 5 or 10 µg/kg per min on the same day. All had a normal intravenous pyelogram or isotopic renal flow study and normal values for creatinine clearance and 24-hour urinary excretion of vanillylmandelic acid, metanephrines, and 17-hydroxysteroids. Twelve of these subjects showed a rise in blood pressure during saralasin infusion and their peripheral PRA levels while upright are shown on the left of Figure 5. The remainder of the hypertensive subjects showed no change or a fall in blood pressure during saralasin infusion and their stimulated peripheral PRA values are shown on the right of Figure 5. Normal subjects on a similar low Na diet showed a slight blood pressure fall during saralasin infusion, as is illustrated later (see Fig. 8). Sixteen of these 22 hypertensive subjects were also studied in the 1-day test. Eight out of nine who showed an agonistic response in the 1-day study also showed an agonistic response and had a low stimulated peripheral PRA level on the 4th day of a diet of 10 mEq of Na. In the ninth subject, a black woman

Figure 2 Blood pressure recording showing no response to an infusion of saralasin in a hypertensive subject with normal plasma renin activity.

Figure 3 Changes in mean blood pressures from control levels (vertical axis) during infusion of saralasin at various rates as indicated on the horizontal axis. The black dots are the blood pressure changes of the 97 out of 418 hypertensive subjects whose mean blood pressure rose by 7.0 mm Hg or more at the saralasin infusion rate of 5.0 µg/kg per min. The open circles are the blood pressure responses in 16 normal subjects who went through the same 1-day hypertensive evaluation.

Figure 4 Stimulated plasma renin activity (PRA) in the 97 hypertensive subjects who showed the agonistic response to saralasin (left) and in 22 normal subjects (right), after furosemide and 2 hours of ambulation. Horizontal lines depict mean PRA in the agonistic responders (1.3 ng/ml per hour) and in the normal subjects (5.0 ng/ml per hour).
on steroid replacement therapy for hypopituitarism, there was a change from a pressor response to saralasin in the 1-day study, to a fall in blood pressure during saralasin infusion on the low sodium diet, associated with a normal stimulated peripheral PRA.

The PRA measurements for the 22 hypertensive subjects showed a close correlation \( r = +0.84, P < 0.001 \) between the results obtained after standing for 2 hours and those obtained after an additional 40 minutes of recumbency. Because of this good correlation it appeared to be valid to relate stimulated PRA results to saralasin response.

For all 418 hypertensive subjects who completed the 1-day study, the change in mean blood pressure from control, induced by saralasin infused at the rate of 5.0 \( \mu \)g/kg per min, is plotted against the values for stimulated peripheral PRA in Figure 6. There was a significant linear correlation \( r = -0.54, P < 0.001 \) between the stimulated PRA levels and the saralasin-induced change in mean blood pressure in these hypertensive subjects. The same data showed a significant linear correlation \( r = -0.58, P < 0.001 \) when expressed as log (stimulated PRA) vs. saralasin-induced change in mean blood pressure. In Figure 7, the same relationship is shown for 18 normal subjects and the agonistic responders to saralasin. Of the agonistic responders 82% had a subnormal PRA (less than 1.7 ng/ml per hour) while 53% of hypertensive subjects with a PRA of less than 1.7 ng/ml per hour showed an agonistic response. In these agonistic respond-
ers alone, there was no correlation ($r = 0.02$) between the stimulated peripheral PRA and the saralasin-induced change in mean blood pressure. This same correlation, however, was significant for the normal subjects ($r = -0.64$, $P < 0.05$).

**RELATION OF SARALASIN-INDUCED BLOOD PRESSURE RESPONSE AND SODIUM INTAKE**

In Figure 8 is shown the change in mean blood pressure from control during three rates of infusion of saralasin, each for 1 hour, in four groups of subjects. These included (group a) five normal subjects on the 4th day of a diet of 10 mEq of Na; (group b) the same subjects after 4 days on a high sodium diet (102 mEq of Na added per day to regular diet); (group c) six different normal subjects on an uncontrolled diet; and (group d) the seven hypertensive subjects who had a pressor response to saralasin in the 1-day study, who were restudied while receiving 10 mEq of Na, and all of whom showed a similar rise in blood pressure during saralasin infusion on the 4th day of this diet. In 21 observations at the end of each infusion rate in the seven hypertensive subjects (group d) there was a significant correlation ($r = +0.71$, $P < 0.001$) between the change in mean blood pressure ($y$) and the log dose of saralasin given ($x$), as expressed by the equation: $y = 5 (\log x) + 6.75$. Calculation showed that the mean values of recumbent PRA in the normal subjects on the high sodium diet (group b) and the agonistic responders to saralasin on the low sodium diet (group d) were almost identical ($1.0 \pm 0.1$ and $1.1 \pm 0.3$ ng/ml per hour, respectively).

The effects of an infusion of 2 liters of 0.9% NaCl over 4 hours were studied in 18 hypertensive and three normal subjects. There was no significant change in serum sodium concentration or blood pressure after the infusion of the saline. However, after the NaCl infusion, saralasin induced a rise in mean blood pressure in every instance except one, and this rise in blood pressure was greater after than before the saline infusion in 60 of 63 observations (Fig. 9); the three exceptions all occurred in the same subject. Except in one subject, the rise in blood pressure after saline at the saralasin infusion rate of 0.05 $\mu$g/kg per min was greater than any change in blood pressure before saline at the saralasin infusion rate of 5.0 $\mu$g/kg per min.

Table 1 shows a comparison of four hypertensive groups, including in the first column all 418 hypertensive subjects, in the second column all agonistic responders to saralasin, in the third column all nonresponders to saralasin arbitrarily defined as those hypertensive subjects with a change in mean blood pressure of between ±7.0 mm Hg during the 1-day study at the saralasin infusion rate of 5.0 $\mu$g/kg per min, and in the last column, all nonresponders to saralasin with a PRA less than 1.7 ng/ml per hour. Although in the total group there were more men than women, 52% of the agonistic responders to saralasin were women. The agonistic responders to saralasin and the nonresponders to saralasin with a low PRA were slightly but significantly older than the group as a whole ($P < 0.001$). Renal function was similar in the different groups. The mean blood pressure on admission (initial blood pressure) was significantly greater ($P < 0.001$) for the agonistic responders to saralasin compared to all the hypertensive subjects. After furosemide, however, the recumbent blood pressures of the four groups were similar. For the agonistic responders to saralasin, the rise in mean blood pressure at the saralasin infusion rate of 5.0 $\mu$g/kg per min ($+11.6$ mm Hg) was just one-half the fall in mean blood pressure ($-24.0$ mm Hg) after furosemide. The mean PRA of the agonistic responders to saralasin was significantly lower than that of the entire hypertensive group ($P < 0.001$) and lower than that of the nonresponders to saralasin ($P < 0.001$).

**Figure 8** Changes in mean blood pressure from control during infusion of saralasin at 0.1, 1.0, and 10.0 $\mu$g/kg per min, each for 1 hour. The groups include, from the top down, six hypertensive subjects with agonistic responses to saralasin on the 4th day of a diet of 10 mEq Na, five normal subjects after 4 days of a high sodium diet (102 mEq Na added per day), six different normal subjects on an ad libitum diet, and the same five normal subjects as were studied on the high sodium diet, now after 3 days on a diet of 10 mEq Na.

**Figure 9** Changes in mean blood pressure from control during the three rates of infusion of saralasin, plotted on the horizontal axis. The black dots show changes before infusion and the open circles after infusion of 2 liters of normal saline over 4 hours. Each subject is represented in the same position from left to right at each of the three infusion rates. The circles represent hypertensive subjects and the squares normal subjects. Note in every case but three that after saline, saralasin induced a greater rise in blood pressure.
Table 1  Data on Various Groups of Hypertensive Subjects

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Agonistic responders</th>
<th>Nonresponders to saralasin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>418</td>
<td>97</td>
<td>279</td>
</tr>
<tr>
<td>Male</td>
<td>257</td>
<td>47</td>
<td>181</td>
</tr>
<tr>
<td>Female</td>
<td>161</td>
<td>50</td>
<td>98</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>41.1 ± 0.6</td>
<td>47.0 ± 1.1</td>
<td>39.3 ± 0.8</td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>16.4 ± 0.2</td>
<td>16.2 ± 0.5</td>
<td>16.4 ± 0.3</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>0.95 ± 0.2</td>
<td>0.91 ± 0.02</td>
<td>0.97 ± 0.02</td>
</tr>
<tr>
<td>Initial blood pressure (mm Hg)</td>
<td>161/104 ± 1.3/0.8</td>
<td>167/109 ± 2.5/1.4</td>
<td>155/100 ± 1.4/0.8</td>
</tr>
<tr>
<td>Blood pressure after furosemide (mm Hg)</td>
<td>134/88 ± 1.0/0.6</td>
<td>136/89 ± 2.1/1.3</td>
<td>131/87 ± 1.1/0.7</td>
</tr>
<tr>
<td>Saralasin (0.05 μg/kg/min)</td>
<td>137/90 ± 1.1/0.7</td>
<td>145/94 ± 2.6/1.6</td>
<td>133/88 ± 1.3/0.8</td>
</tr>
<tr>
<td>Saralasin (0.5 μg/kg/min)</td>
<td>137/90 ± 1.2/0.8</td>
<td>147/86 ± 2.3/1.3</td>
<td>133/88 ± 1.3/0.9</td>
</tr>
<tr>
<td>Saralasin (5.0 μg/kg/min)</td>
<td>138/90 ± 1.1/0.7</td>
<td>151/99 ± 2.5/1.3</td>
<td>133/87 ± 1.1/0.7</td>
</tr>
<tr>
<td>PRA (ng/ml/hr)</td>
<td>3.6 ± 0.1</td>
<td>1.3 ± 0.1</td>
<td>3.9 ± 0.2</td>
</tr>
<tr>
<td>Urine Na post-furosemide (mEq/3 hr)</td>
<td>148.5 ± 2.5</td>
<td>144.8 ± 5.0</td>
<td>151.9 ± 3.0</td>
</tr>
</tbody>
</table>

Data are presented as mean ± sem; n = number of subjects; NS = not significant.

Table 2  Studies of Angiotensin II (A II) Vascular Sensitivity and Saralasin Vascular Affinity in Hypertensive Subjects with Agonistic Response and Nonresponse of Blood Pressure during Infusion of Saralasin

<table>
<thead>
<tr>
<th>(a) Saralasin response (mm Hg)</th>
<th>(b) A II infusion rate (ng/kg/min)</th>
<th>(c) Saralasin infusion rate (ng/kg/min)</th>
<th>(c)/(b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonresponders (n = 7)</td>
<td>-1.0 ± 1.0</td>
<td>10.9 ± 1.3</td>
<td>43.4 ± 10.1</td>
</tr>
<tr>
<td>Agonistic responders (n = 7)</td>
<td>+8.4 ± 0.4</td>
<td>4.6 ± 0.4</td>
<td>15.4 ± 1.0</td>
</tr>
<tr>
<td>P: (1) vs. (2)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Data are presented as mean ± sem; n = number of subjects; NS = not significant.

Discussion

Previous work in man3,4 and animals5 indicates that saralasin is a highly specific, competitive antagonist of the pressor action of A II. In vascular systems which have increased pressor sensitivity to A II, however, saralasin recently has been shown to have an A II-like action (partial agonist), both in animals6 and in man.7

The present study provides further evidence that saralasin acts like A II in man under conditions known to cause increased pressor sensitivity to A II, i.e., normal subjects on a high sodium diet and hypertensive subjects after the infusion of saline.8 It also shows that A II is important in helping to maintain an adequate blood pressure in normal subjects on a low sodium diet, a finding consistent with previous results of studies in animals9 and hypertensive subjects.10

As shown in Figures 3 and 6, the abnormal pressor response to saralasin identifies a new, sizable group of hypertensive subjects, of whom 82% have a low stimulated peripheral PRA after administration of furosemide and standing for 2 hours. In addition, eight out of nine of these hypertensive subjects with agonistic responses to saralasin had a low stimulated peripheral PRA on the 4th day of a diet of 10 mEq of Na. However, approximately
48% of the low renin hypertensive subjects (after furosemide) did not have the agonistic response and this hypertensive group will require further study. On the 4th day of a diet of 10 mEq of Na, as shown in Figure 5, the blood pressure response to saralasin was an even better, although less rapid, indicator of the level of the stimulated peripheral PRA. This agonistic response should be a useful means of rapidly identifying a hypertensive group, most of whom have a low stimulated PRA. The rise in blood pressure to saralasin generally has been a gradual one and for the group as a whole, as shown in Table 1, was approximately one-half the preceding fall in blood pressure induced by furosemide in the same subjects.

The original description of the partial agonistic response to saralasin in vitro showed an association with vascular systems which had an increased sensitivity in vitro to A II. This relationship also holds true for the hypertensive subjects with agonistic responses to saralasin, as shown in Table 2. The present data show a good association between the agonistic response to saralasin and a low stimulated peripheral PRA. Although “agonistic hypertensive subjects” with greater pressor responses to saralasin had a lower stimulated PRA than those with smaller responses, there was no significant correlation (r = 0.02) between the stimulated PRA and the degree of agonistic response in the recumbent position in these 97 hypertensive subjects. This suggests that it was not the level of PRA per se which determined the agonistic responses. Other evidence that the level of the PRA (and thus A II) does not directly determine the agonistic response is shown in Figure 5. The mean value for recumbent PRA was almost identical in normal subjects on a high sodium diet and hypertensive subjects with agonistic responses to saralasin on a low sodium diet (1.0 and 1.1 ng/ml per hour, respectively); but the hypertensive subjects on the low sodium diet showed more than twice the change in mean blood pressure compared to the normal subjects on the high Na diet when they were receiving the same dose of saralasin.

Results presented here show that there is a strong association between NaCl loading and the production of the agonistic response to saralasin. This raises the possibility that the agonistic response in the hypertensive subjects is related to sodium, either via an increase in plasma volume or through an effect of sodium on vascular sensitivity to A II. The first possible mechanism cannot be confirmed or excluded, because plasma volume was not measured in these studies. There is indirect and direct support for the second possibility. It has been reported that hypertensive patients do have an increased vascular Na content. NaCl is also known to increase vascular sensitivity to A II both in vivo and in vitro, and the present studies showed a significantly greater pressor sensitivity to A II in the agonistic responders than in the nonresponders to saralasin. The agonistic response to saralasin and increased sensitivity to A II might be induced by sodium chloride through a change in one of the following: affinity or character of A II vascular receptors, membrane potentials, calcium movement, or contractile proteins. There is evidence that an increased vascular sodium content increases the concentration of ionized calcium reaching the contractile protein. Sodium has also been shown to increase the concentration of arterial wall muscle in response to ionized calcium. As presented in Table 2, the ratio of the saralasin infusion rate required to block the pressor action of A II and the pressor dose of A II were similar in both hypertensive groups (agonistic responders and nonresponders); thus it is likely that the affinity of the A II vascular receptors for saralasin was greater in the agonistic hypertensive group. It is still possible that there is a functional difference in excitation of the A II receptor or in the consequent arteriolar contraction in the two hypertensive groups.

Although the agonistic response to saralasin in the hypertensive subjects may not be directly determined by the level of the PRA (and thus A II), it is possible that the final response of the blood pressure to saralasin is the net result of the simultaneous agonistic and antagonistic properties of the analogue. This is possible because saralasin, under certain conditions described above, has an A II-like action on the vascular system and, at the same time, by occupying A II vascular receptors is able to block the action of the more potent A II. This property of saralasin is termed a partial agonistic one and has been described for several other drugs. Thus, a nonresponse to saralasin in a patient might not necessarily rule out an A II-mediated hypertension. A combined effect might be the explanation for the initial nonresponse in two patients with renovascular hypertension whose hypertension later was shown to fall during saralasin infusion on a low sodium diet and also after nephrectomy. We have noted a similar phenomenon in two hypertensive patients.

Finally, two other possible explanations for the pressor response to saralasin in hypertensives should be considered. One is that the response is mediated through the sympathetic nervous system. A II can inhibit the uptake of norepinephrine liberated at the nerve terminals in response to a nerve activity and thus potentiate the stimulus. Saralasin, when it acts like A II, might also potentiate a sympathetic response. However, there was no significant change in pulse rate during the agonistic response to saralasin. In addition, the principal pressor action of A II presumably is exerted through its own receptors on the plasma membrane of vascular smooth muscle. One would expect the same with a highly specific analogue of A II acting as a partial agonist.

Another possibility is that under certain circumstances a metabolic product of saralasin might exert its own pressor action like the metabolic product of A II, des-asp-angiotensin II (A III). However, A III has less pressor action than A II and the concentration of A III in arterial and venous blood is only 1/4 that of A II in man.

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References

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