Antihypertensive Effect of Vasopressin Withdrawal in Young and Adult Spontaneously Hypertensive Rats

Edward K.Y. Chiu and J. Robert McNeill

The extent to which age influences the effect of prolonged intravenous infusion and withdrawal of arginine vasopressin (AVP) on blood pressure was investigated in spontaneously hypertensive rats (SHR) and their normotensive Wistar-Kyoto controls (WKY) of 6-, 10-, 14-, 18-, and 22-week age groups. The pressor response to AVP (20 ng/kg/min for 3 hours) was relatively well maintained in WKY but showed an age-dependent tachyphylaxis in SHR. After cessation of the infusion, arterial pressure of SHR fell in all age groups. In contrast, withdrawal of AVP in WKY resulted in little or no hypotensive response. Thus, a withdrawal-induced antihypertensive phenomenon (WAP) to AVP was specific to SHR. The magnitude of the WAP was significantly correlated with the level of initial blood pressure in SHR (r = -0.81, p < 0.001). The magnitude of the tachyphylaxis during the AVP infusion was also correlated with the level of initial blood pressure in SHR (r = -0.66, p < 0.001). Accordingly, a significant correlation was found between the magnitude of the WAP and the degree of tachyphylaxis to the pressor activity of AVP in SHR (r = 0.69, p < 0.001). The significance of this is unknown, but it might mean that a common underlying mechanism existed in the expression of the tachyphylactic phenomenon and the WAP in SHR. Finally, an apparent enhancement in the baroreceptor reflex sensitivity was observed in both SHR and WKY during the infusion of AVP, but the magnitude of this enhancement appeared to be greater in SHR than in WKY. We conclude that in all age groups, a WAP to AVP is observed in SHR but not in WKY; the magnitude of the WAP appears to depend on the level of the hypertension in SHR. (Hypertension 1989;14:66-72)

Previously,1-2 we described a hypotensive response that occurred in spontaneously hypertensive rats (SHR) after the cessation of a prolonged intravenous infusion of a pressor dose of arginine vasopressin (AVP). This fall of arterial pressure below basal control levels did not occur in normotensive Wistar-Kyoto rats (WKY). Furthermore, the hypotensive response in SHR was of a magnitude (approximately 45–50 mm Hg) sufficient to reduce arterial pressure in these SHR to normotensive levels. Thus, a withdrawal-induced antihypertensive phenomenon (WAP) was specific to SHR. The WAP was reduced or absent when angiotensin II or phenylephrine was infused at pressor doses.1-3 Accordingly, the WAP appeared to be specific for AVP in SHR. The specificity in AVP may lie in the fact that AVP, among pressor agents, has the strongest vasoconstrictor activity,4 has a natriuretic action,5 and enhances baroreceptor reflex activity6; one or more of these actions of AVP may form the basis of the mechanism for the WAP. Because there is no evidence that these actions of AVP exist in SHR alone, one needs to postulate that SHR are more sensitive than WKY to these actions of AVP.

An obvious attribute of SHR that may contribute to their greater sensitivity is the hypertensive state. Because the original findings were obtained from animals of the 22–28-week age group, an important unanswered question is whether the presence of long-term hypertension in SHR had somehow predisposed the rats to the actions of AVP. Additionally, it was important to determine if the magnitude of the WAP was related to the level of hypertension. In the present study, we sought to address these issues by studying the WAP in five age groups of SHR and WKY.

Materials and Methods

SHR and WKY were purchased from Taconic Farms (Germantown, New York) and raised in our

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animal quarters under standardized conditions. Rats were selected randomly for use in our experiments when they reached the age of 6, 10, 14, 18, or 22 weeks. Except for rats in the 6-week age groups, which were purchased at 4 weeks of age, all rats were obtained from Taconic Farms at 6 weeks of age; this allowed the rats enough time to acclimate to the animal quarters and laboratory surroundings before experimentation. One week before any surgical intervention, each group of rats was brought into the recording room where experiments would be performed. Under light ether anesthesia, each rat underwent catheterization of its femoral artery and vein for blood pressure recording and intravenous drug administration, respectively. Rats 6 weeks old were catheterized with PE-10 polyethylene tubing (Clay Adams, Parsippany, New Jersey); rats of other age groups were catheterized with PE-50 tubing. Pulsatile and mean arterial pressures were measured with the arterial catheter connected to a Gould-Statham Model P23 pressure transducer (Statham Laboratories, Inc, Hato Rey, Puerto Rico). These pressure signals were recorded with a Grass Model 7 polygraph (Grass Instrs. Co., Quincy, Massachusetts) with a Model 7P1 low-level DC preamplifier and a Model 7DAF DC driver amplifier. Heart rate recordings were obtained with a Model 7P44 tachograph preamplifier receiving pressure signals from the DC driver amplifier.

All experiments were performed in conscious, unrestrained rats 1 day after the implantation of the catheters. Each rat was initially allowed 2–3 hours to settle in a single animal cage, during which time the basal blood pressure and heart rate values were recorded. Blood pressure and heart rate were also monitored during the 3-hour intravenous infusion of AVP (Peninsula Labs., Inc., Belmont, California) at a dose of 20 ng/kg/min as well as during the 5-hour period after cessation of the infusion.

Changes in blood pressure and heart rate were calculated as the differences between the values obtained in the experimental period (during either the infusion or the withdrawal of AVP) and the basal values obtained in the control period. The magnitude of the WAP was defined as the difference between the pressure level attained 5 hours after AVP withdrawal and that recorded under basal conditions. Tachyphylaxis during the AVP infusion was determined by the difference in the pressor effect (pressure rise above control level) at the end of the 3-hour infusion and the maximal pressor effect achieved during the initial period of the infusion. Baroreceptor reflex function was assessed by calculating a baroreceptor reflex index, defined as the change in heart period in relation to the change in mean arterial pressure at any particular time during AVP infusion. Comparison of the baroreceptor reflex functions in SHR and WKY was achieved by expressing the baroreceptor reflex index in SHR as a fraction of that in WKY.

All values in the text, figures, and table are expressed as mean±SEM. The time course characteristics of the pressure and heart rate responses were tested by analysis of variance with repeated measures using BMDP2V.7 Simultaneous multiple comparisons of experimental and control values were performed using modified t tests. Critical t values were determined with Bonferroni’s inequality. The association between selected variables was tested by correlation analysis.

Results

Control Values

The values of mean arterial blood pressure and heart rate recorded during the control period in rats of the various age groups are presented in Table 1. Pressure of SHR was higher than that of WKY as early as 6 weeks of age (p<0.01). Pressure reached the highest level in WKY at 10 weeks of age. In contrast, pressure continued to rise beyond 10 weeks of age in SHR and became established at a plateau hypertensive level at 14 weeks of age. Thereafter, pressure rose only minimally. Heart rate was elevated in the younger rats. There was a trend toward a slowing heart rate as the rat aged, but the drop in basal heart rate occurred in large part between growth from the 6- to the 10-week age group. SHR and WKY of the 6-week age group showed comparable heart rate levels. There was a

<table>
<thead>
<tr>
<th>Age (wk)</th>
<th>WKY</th>
<th>SHR</th>
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<tr>
<td></td>
<td>n</td>
<td>MAP (mm Hg)</td>
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<tr>
<td>6</td>
<td>6</td>
<td>104±1.4*</td>
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<tr>
<td>10</td>
<td>7</td>
<td>109±2.4</td>
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<td>14</td>
<td>8</td>
<td>107±2.1</td>
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<tr>
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<td>106±1.8</td>
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<td>22</td>
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Values are mean±SEM. SHR, spontaneously hypertensive rats; WKY, Wistar-Kyoto rats; n, number of animals; MAP, mean femoral arterial pressure; HR, heart rate.

*p<0.01 for comparison of values between the following groups in the same strain of rat: 6- vs. 10-week-old, 10- vs. 14-week-old, 14- vs. 18-week-old, and 18- vs. 22-week-old.

†p<0.01, values in SHR compared with those in age-matched WKY.
small but significant resting tachycardia in SHR of older age groups compared with age-matched WKY.

Time Course of Changes in Blood Pressure and Heart Rate

Figure 1 presents the results obtained with the prolonged infusion and withdrawal of AVP in SHR and WKY of the five age groups. The maximal pressor effect of AVP was observed at the 10-minute mark of the infusion. The pressor effect was not well maintained in the SHR over the course of the AVP infusion. This tachyphylaxis toward the pressor effect of AVP appeared to be age dependent so that pressure was still elevated significantly ($p<0.01$) by the end of the infusion in younger age groups (6 and 10 weeks), whereas pressure had returned to levels not significantly different from control basal values in the two oldest age groups (18 and 22 weeks). In contrast, although pressure dropped slightly after the maximal pressor response at the 10-minute mark, pressure in WKY was still markedly elevated by the end of the infusion in all age groups. During the AVP infusion, heart rate dropped more markedly in WKY than in SHR. When the infusion of AVP ceased, blood pressure dropped precipitously and remained below basal levels throughout the entire withdrawal period in SHR of all age groups. The extent of this fall in pressure was greater in the older than in the younger age groups. Contrarily, in WKY, all groups (except for the 10-week-old group in which there was a small and sustained hypotensive response) displayed only small and transient falls in pressure during AVP withdrawal. After AVP withdrawal, a tachycardia was uniformly observed in SHR and WKY of all age groups.

Relation Between Blood Pressure Changes and Initial Pressures

The association between the magnitude of the WAP and the initial control blood pressures for each animal is illustrated in Figure 2. A strong correlation ($r=-0.81$, $p<0.001$) between the magnitude of the WAP and the level of initial blood pressure existed in SHR (Figure 2, left panel). In contrast, no correlation was found between the WAP and initial blood pressure in WKY (Figure 2, right panel). The association between the degree of tachyphylaxis and the initial control pressures is shown in Figure 3. As for the WAP, the magnitude of tachyphylaxis showed a significant correlation ($r=-0.66$, $p<0.001$) with the level of initial blood pressure in SHR (Figure 3, left panel) but not in WKY (Figure 3, right panel).

Comparison of Withdrawal-Induced Antihypertensive Phenomenon With Tachyphylaxis

The relation between the magnitude of the WAP and the degree of tachyphylaxis is illustrated in Figure 4. A significant correlation ($r=0.69$, $p<0.001$) was observed between these two variables in SHR (Figure 4, left panel) but not in WKY (Figure 4, right panel).

Baroreceptor Reflex Function

The time course relation of baroreceptor reflex index with age during the infusion of AVP is shown in Figure 5 (SHR, left panel; WKY, right panel). The baroreceptor reflex index of SHR expressed as a fraction of that of WKY is shown in Figure 6. At the 10-minute mark of the infusion, baroreceptor reflex activity was depressed in SHR compared with WKY in all age groups, and the degree of impairment appeared age related. Over the period of the AVP infusion, baroreceptor reflex activity apparently increased in both SHR and WKY of all age groups. The apparent enhancement with AVP infusion, however, was greater in SHR than in WKY.

Discussion

In our present study, we demonstrated that a WAP to AVP occurred in young as well as old SHR. The magnitude of the WAP was not dependent on the magnitude of the pressor response to AVP because, despite similar initial pressor responses in all age groups, older SHR appeared to manifest a greater hypotensive response after AVP withdrawal. It was, however, dependent on the level of initial blood pressure, such that the higher the initial blood pressure, the larger the magnitude of the WAP. Thus, the larger magnitude of the WAP in older SHR was as effective as the smaller magnitude in younger SHR in returning blood pressure levels toward normotensive levels. This observation suggests that either the level or the duration of the hypertensive state has an influence on the expression of the WAP to AVP. Recently, however, we were able to demonstrate the WAP to AVP in the deoxycorticosterone acetate (DOCA)-salt hypertensive rat. Because the hypertensive state in the DOCA-salt rat was produced over a period of 3 weeks on an experimental regimen, it appears that the duration of hypertension is a relatively unimportant determinant for the expression of the WAP. On the other hand, we observed a strong correlation between the magnitude of the WAP and the level of the initial control blood pressure. At an age as young as 6 weeks, SHR have pressure values higher than those in age-matched WKY and may have pressures at levels higher than those ever attained in older WKY. Thus, younger SHR already attain hypertensive pressure levels important for the development of WAP to AVP. On the contrary, in WKY, despite a relatively wide range of pressure across both young and old age groups, a WAP to AVP was not observed. This difference is not strain related because a WAP can be elicited in WKY when they are rendered hypertensive by a DOCA-salt regimen. Taken together, our data in the SHR and the DOCA-salt hypertensive rat suggest that the WAP is related neither to strain nor to the duration of hypertension; rather, it appears that it is
FIGURE 1. Plots of time course of changes in mean arterial pressure (BP) and heart rate (HR) induced by intravenous infusions of arginine vasopressin (AVP) at a dose of 20 ng/kg/min for 3 hours. Values are mean±SEM. *p<0.05; **p<0.01, absolute values compared with corresponding basal values. SHR, spontaneously hypertensive rats; WKY, normotensive Wistar-Kyoto rats.
related to the level of hypertension. Accordingly, we suggest that the term "antihypertensive" effect of AVP withdrawal is apt.

The degree of tachyphylaxis toward the pressor response to AVP was also correlated with the degree of hypertension in the SHR. Not surprisingly, therefore, a significant correlation between the degree of tachyphylaxis and the magnitude of the WAP was observed in SHR but not in WKY. Accordingly, it is tempting to suggest that the tachyphylactic phenomenon and the WAP may share a common mechanism, but we have no evidence to support this notion.

The observation of the WAP to AVP in SHR, but not in WKY, requires an explanation based on a specific interaction between SHR and AVP. Because a WAP to AVP was similarly demonstrated in the DOCA-salt hypertensive rat, it follows that a specific interaction with AVP may not be restricted to the SHR but rather may be generally found in all hypertensive animals. Despite extensive literature on the cardiovascular actions of AVP, a specific interaction of this nature had never been demonstrated. Recently, however, Imai and coworkers reported that a prolonged infusion of AVP (2 pg/min/kg for 21 hours) into the cerebral ventricles of the stroke-prone strain of SHR (SHRSP) elicited a hypotensive response and bradycardia. In contrast, a brief hypertensive response and tachycardia were observed in the normotensive WKY. Furthermore, in the few SHRSP that underwent extended observation, the fall in pressure and bradycardia recovered slowly over 48-72 hours after the cessation of the AVP infusion. Such a finding bears special relevance to our study, in which we found a specific hypotensive response in SHR but not in WKY. Evidently, the study of Imai et al involved central administration of AVP, whereas our study used peripheral administration of AVP. Because centrally and peripherally administered AVP may reach very different brain areas critically involved in cardiovascular function, it is difficult to suggest that the hypotensive responses observed in our studies and those of Imai et al involved the same mechanisms. Nevertheless, the studies of Imai et al lend strong support to the notion of a specific interaction between SHR and AVP, perhaps even one involving the central action of AVP. The idea that a central AVP system might play a depressor or an antihypertensive function was suggested by the observation that the AVP content of the brainstem of SHRSP and the paraventricular nuclei of SHR is much reduced. Although unproven, it is at least plausible that during the prolonged intravenous administration of AVP in our experiments, some AVP did gain access to important brain areas accessible to the centrally administered AVP in the

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

**Figure 2.** Plots of relation between the magnitude of withdrawal-induced antihypertensive phenomenon (WAP) and initial basal blood pressure in spontaneously hypertensive rats (n=38, left panel) and normotensive Wistar-Kyoto rats (n=36, right panel). The magnitude of WAP, on the vertical axis, is defined as the blood pressure change (ΔBP) at the end of withdrawal period compared with control basal values. r, correlation coefficient.

![Figure 3](https://hyper.ahajournals.org/)

**Figure 3.** Plot of relation between the degree of tachyphylaxis and initial basal blood pressure in spontaneously hypertensive rats (n=38, left panel) and normotensive Wistar-Kyoto rats (n=36, right panel). The degree of tachyphylaxis is defined as the difference between the pressure level at the end of arginine vasopressin (AVP) infusion and that attained during the peak pressor response to AVP. r, correlation coefficient.
studies of Imai et al.\textsuperscript{10} Consistent with this possibility is the report that an intravenous injection of lysine vasopressin suppressed the pressor response to electrical stimulation of the posterior hypothalamus in the anesthetized rat long after the peripheral pressor response had subsided.\textsuperscript{15}

The site at which circulating AVP exerts a central influence is unknown but one likely possibility is the area postrema, a brain area that has been found to contribute substantially to the overall cardiovascular effects of circulating AVP. Recent studies in dogs, rabbits, and humans, have demonstrated that elevations of the circulating levels of AVP are associated with increased sensitivity of baroreceptor reflex activity, thereby buffering the pressor activity of the peptide.\textsuperscript{6,16-19} These actions of AVP are abolished by lesioning of the area postrema.\textsuperscript{20,21}

In rats, the baroreceptor reflex control of heart rate may be enhanced by AVP through V\textsubscript{2} receptors,\textsuperscript{22} whereas the pressor activity of AVP may be buffered through a nonbaroreceptor reflex withdrawal of sympathetic tone.\textsuperscript{23}

Interestingly, sympathetic hyperactivity\textsuperscript{24} and impairment of baroreceptor reflex function\textsuperscript{25} are found in SHR. Unlike the normotensive dog\textsuperscript{26} and rat\textsuperscript{27}, in which baroreceptor reflex function improves with age, SHR has an age-dependent impairment of baroreceptor reflex function.\textsuperscript{27} In the present study, we also observed an impairment of baroreceptor reflex sensitivity in SHR compared with that in WKY at an age as early as 6 weeks. Furthermore, our findings confirmed earlier reports regarding the
progressive increase in baroreceptor reflex sensitivity in WKY and the lack of baroreceptor reflex enhancement with age in SHR. Additionally, we observed that there was a progressive decrease in the pressor response to AVP despite continuous infusion of the peptide in SHR. The drop in pressure during infusion was not associated with a corresponding decrease in the bradycardia, such that during AVP infusion there appeared to be an enhancement of baroreceptor reflex sensitivity, calculated by a change in heart period in relation to a change in pressure. A small enhancement in baroreceptor reflex sensitivity in fact also appeared in the WKY, but the magnitude of such enhancement was much reduced in contrast to that in the SHR. Of importance, the apparent enhancement of baroreceptor reflex sensitivity during AVP infusion appeared to increase with age in SHR. Unfortunately, our impression of an enhancement of baroreceptor reflex sensitivity was at best based on indirect evidence as our study was not designed to measure baroreceptor reflex sensitivity by a method independent of our AVP infusion. Although the enhancement effect of AVP on baroreceptor reflexes makes an attractive mechanism in explaining the tachyphylaxis and the WAP to AVP in SHR, any suggestion of such must remain a highly speculative one at the present.

Our present study demonstrated an age-dependent WAP to AVP in SHR. The expression of the WAP is dependent on the existence of the hypertensive state, and the magnitude of the WAP appears dependent on the level of initial blood pressure achieved in the hypertensive animal. The results are consistent with the view that the WAP is dependent on either the level or the duration of hypertension in the animal. Taken with our results obtained in the DOCA-salt hypertensive animal, however, we conclude that the level, but not the duration, of hypertension is a more important determinant in the manifestation of the WAP.

References

Key Words • pressor response • hypotension • age • tachyphylaxis • baroreceptor reflex • spontaneously hypertensive rats
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