Antidiuretic and pressor actions of vasopressin in age-dependent DOCA-salt hypertension

J. ZICHA, J. KUNEŠ, M. LÉBL, I. POHLOVÁ, J. SLANINOVÁ, AND J. JELÍNEK
Institute of Physiology and Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, Prague 4, CS-142 20, Czechoslovakia

ZICHA, J., J. KUNEŠ, M. LÉBL, I. POHLOVÁ, J. SLANINOVÁ, AND J. JELÍNEK. *Antidiuretic and pressor actions of vasopressin in age-dependent DOCA-salt hypertension.* Am. J. Physiol 256 (Regulatory Integrative Comp. Physiol. 25): R138–R145, 1989.—The role of antidiuretic and pressor effects of vasopressin (VP) in deoxycorticosterone acetate (DOCA)-salt hypertension was studied in young and adult Brattleboro rats. The antidiuretic VP action was a necessary prerequisite for the development of severe DOCA-salt hypertension. The insufficient expansion of extracellular fluid volume in DOCA-salt-treated VP-deficient (DI) rats was associated with the attenuation of their hypertensive response, although they had highly increased blood volume and extracellular sodium. Chronic [deamino]-D-arginine vasopressin supplementation that restored volume and distribution of body fluids in DI rats permitted the full development of DOCA-salt hypertension. Blood pressure response to DOCA-salt treatment was always greater in young than in adult Brattleboro rats (even in animals lacking pressor or both VP effects). In animals in which antidiuretic VP effects were present, the pattern of body fluid response to DOCA-salt treatment was also age dependent. There was a tendency to intravascular expansion in young hypertensive rats, whereas an increase of interstitial fluid volume was found in adult animals. The elimination of VP pressor action lowered systemic resistance much more in adult than in young hypertensive rats. We conclude that *1*) in adult but not in young rats antidiuretic VP effects are essential for the occurrence of blood pressure response to DOCA-salt treatment, *2*) the restoration of body fluids due to antidiuretic VP action enables the development of hypertension in both age groups of DI rats, and *3*) pressor VP effects contribute to the maintenance of hypertension, especially in adult animals.

Brattleboro rat; diabetes insipidus; 1-desamino-8-D-arginine vasopressin; vasopressin antagonists; blood pressure; body fluids; hemodynamics

---

THERE ARE NO DOUBTS about the important role of vasopressin (VP) in deoxycorticosterone acetate (DOCA)-salt hypertension, although its detailed involvement in the induction, development, and maintenance of this form of experimental hypertension remains to be elucidated. VP was reported to participate in the pathogenesis of salt-dependent hypertension not only through its pressor action (20) but also by its antidiuretic (11, 24) and central nervous effects (1). The age of experimental animals should be also considered because prepubertal rats are more susceptible to various forms of salt-dependent hypertension than the adult ones (32). Indeed, a moderate salt hypertension as well as DOCA-salt hypertension can be induced in young VP-deficient (DI) Brattleboro rats (6, 15, 31). On the other hand, adult DI rats are really resistant to these hypertensive stimuli (2, 4, 6, 15, 24, 25, 31).

The sensitivity of adult DI rats to DOCA-salt treatment can be reestablished by chronic supplementation with 1-desamino-8-D-arginine vasopressin (dDAVP) that has prolonged antidiuretic and minimal pressor effects (24, 25). It was proposed that VP antidiuretic action might be important for the intravascular expansion involved in the pathogenesis of this form of experimental hypertension (5, 11). However, we found that blood pressure (BP) response of DI rats to DOCA-salt treatment was attenuated, although their blood volume was markedly expanded (15).

Although a considerable participation of VP pressor effects in the maintenance of increased systemic resistance was demonstrated in DOCA-salt hypertensive rats (18, 23), the acute VP blockade did not always lower their BP (3, 4, 7, 21, 22, 25). The hemodynamic effects of the acute neutralization of VP pressor action are counteracted by the baroreceptor reflex operation (23), the efficiency of which is augmented by VP (13, 17, 28). Thus the major contribution of VP pressor effects to the maintenance of elevated BP can be observed in DOCA-salt hypertensive rats either after the impairment of the baroreceptor reflex (17, 23) or after the prevention of compensatory increase of sympathetic vasoconstriction (3, 19).

To determine the role of pressor and antidiuretic VP effects in the induction, development, and maintenance of DOCA-salt hypertension we studied the response to this hypertensive stimulus in different groups of Brattleboro rats: homozygous DI rats, DI rats chronically supplemented with dDAVP, and heterozygous (non-DI) rats with endogenous VP (Table 1). Thus we compared the animals lacking VP with those in which antidiuretic or both components of VP action were present. Young (prepubertal) and adult rats were always compared to detect the possible age-dependent participation of vasopressin in the hypertensive mechanisms studied. Other aims of our study were *1*) to elucidate the relationship of VP antidiuretic effects to the alterations of the volume and distribution of body fluids in DOCA-salt-treated Brattleboro rats, and *2*) to evaluate the contribution of VP pressor action to the maintenance of elevated sys-

temic resistance in DOCA-salt hypertensive non-DI Brattleboro animals.

METHODS

Animals. One hundred three homozygous (DI) and 74 heterozygous (non-DI) female Brattleboro rats were born in our colony, which was established in 1967 from breeding stock kindly provided by Dr. H. Valtin (Hanover, NH). Animals were kept in a temperature-controlled room on a 0700–1900 light cycle, were fed pelleted diet (DOS 2b Velaz, 170 mmol NaCl/kg), and drank tap water ad libitum. Young rats were weaned at the age of 28 days and tested for the presence of diabetes insipidus by measuring their water consumption. Daily water intake of DI rats was always >50% of body weight, whereas non-DI rats drank <25 ml water·100 g^{-1}·day^{-1}.

DOCA-salt hypertension was induced in uninephrectomized young (29 day old) and adult (75 day old) animals. Particular experimental groups of VP-deficient DI rats, DI rats chronically supplemented with dDAVP, and VP-synthetizing non-DI rats are listed in Table 1. Five days after the removal of the left kidney, the initial blood pressure was measured, and the animals were given 0.6% saline as the only drinking fluid and were injected with 20 mg DOCA/kg body wt, im, twice a week for 6 wk. Age-matched unoperated water-drinking Brattleboro rats of both genotypes served as controls.

dDAVP (Adiuretin, Spofa, Prague) was given to DI rats in the drinking fluid (1 mg dDAVP/l of 0.6% saline) (25). Fresh drinking fluid was prepared every 2nd day to prevent the decrease of dDAVP concentration to <0.3 mg/l, which still ensured effective antidiuresis (14).

Blood pressure and fluid intake measurements. During the experiment, systolic blood pressure (SBP) was measured in conscious rats once a week using the tail-cuff method. Fluid intake was monitored by daily weighing of drinking bottles. After 6 wk of the experiment the carotid artery was cannulated under light ether anesthesia. Mean arterial pressure (MAP) was recorded in conscious animals 4 h later, i.e., just before the measurement of the volume and distribution of body fluids.

Body fluid volume determination. Plasma volume (PV) was determined by the dilution of Evans blue that was injected into the exposed jugular vein of ether anesthetized animals [1 ml of 0.5% solution (wt/vol) per kg body wt]. Five minutes later, 0.2 ml of blood was taken from tail vessels to obtain the hematocrit value and a plasma sample was taken for the determination of the dye concentration. Immediately thereafter the animals were nephrectomized, and extracellular fluid volume (ECFV) was measured as the distribution space of polyfructosan (Inutest, Laevosan, Linz) that was also administered intravenously [0.2 ml of 25% solution (wt/vol) per kg body wt]. Blood was taken from the carotid artery after an additional 80 min for the equilibration of polyfructosan. Its concentration was determined by means of a modified method for inulin measurement. After deproteinization (50 μl plasma + 100 μl 5% solution of trichloroacetic acid + 100 μl water) an aliquot of the supernatant (100 μl) was incubated for 80 min at 37°C with 20 μl of β-indoleacetic acid (0.5% solution in ethyl alcohol) and with 800 μl of hydrochloric acid. After cooling, the extinction of samples was read at 535 nm. Interstitial fluid volume (IFV) was calculated by subtracting PV from ECFV value. Blood volume (BV) was calculated from PV and hematocrit values.

Plasma osmolality was measured by a Knauer semimicroosmometer and plasma sodium concentration by means of Varian atomic absorption. The amount of sodium in the total extracellular fluid (Na_{ECFV}) was calculated.

Hemodynamics. After 6 wk of DOCA-salt treatment central hemodynamics were studied in selected subgroups of young and adult hypertensive non-DI and dDAVP-supplemented DI rats. MAP, cardiac output, heart rate, and systemic resistance were determined in conscious unrestrained rats (30). The tip of a heparinized catheter (PE-50) was inserted through the carotid artery into the aortic arch while two catheters (PE-10) were placed in a jugular vein under light ether anesthesia 4 h before the experiment. All implanted catheters were exteriorized behind the rat's ears. Animals adapted to the measuring conditions for 30 min before the hemodynamic measurement. Blood pressure was monitored continuously (HP 321), and heart rate was derived from BP recordings. Systemic resistance was calculated from MAP and cardiac output that was determined repeatedly using Cardiogreen-dilution technique (30). Three to five measurements of cardiac output were done in each animal before the injection of VP antagonists. Thereafter the hemodynamic effects of the acute blockade of VP pressor action were studied in both young and adult DOCA-salt hypertensive non-DI rats for 1 h after the intravenous injection of competitive vascular V_1 antagonist [1-penicillamine, 2-(*O*-methyl)tyrosine, 8-lysine]-vasopressin (27) or combined vascular and tubular V_1V_2 antagonist [1-(β-mercapto-β,β-cyclopentamethylenepropionic acid), 2-(*O*-ethyl)tyrosine, 4-valine, 8-arginine]-vasopressin (16). Both VP antagonists were synthesized in the Institute of Organic Chemistry and Biochemistry (Czechoslovak Academy of Sciences, Prague).

Statistical analysis. Data were expressed as means ± SE and were evaluated by Student's *t* test with Bonferroni correction for multiple comparison and by Hotelling *t* test.

TABLE 1. *Experimental groups of Brattleboro rats*

Group	V_1	V_2	Drinking Fluid	DOCA	UNX
DOCA-salt treated					
Non-DI rats	+	+	0.6% saline	+	+
dDAVP-supplemented DI rats	−	+	0.6% saline with 1 mg dDAVP/l	+	+
DI rats	−	−	0.6% saline	+	+
Control					
dDAVP-DI rats*	−	+	0.6% saline with 1 mg dDAVP/l	−	+
DI rats*	−	−	0.6% saline	−	+
Non-DI rats	+	+	Tap water	−	−
DI rats	−	−	Tap water	−	−

DI, homozygous; non-DI, heterozygous; V_1, pressor (vascular) VP effects; V_2, antidiuretic (tubular) VP effects; dDAVP, 1-desamino-8-D-arginine vasopressin; UNX, uninephrectomy; DOCA, deoxycorticosterone acetate. * Only young animals were used.

RESULTS

Blood pressure response to DOCA-salt treatment. A severe DOCA-salt hypertension developed in VP-synthesizing non-DI rats in which SBP reached much higher values in young than in adult animals (Fig. 1). The development of DOCA-salt hypertension was attenuated in DI animals. Nevertheless, a moderate SBP rise was induced in young VP-deficient DI rats, whereas no BP increase occurred in adult DOCA-salt-treated DI animals. In both age groups of dDAVP-supplemented DI rats SBP rise was comparable to that of DOCA-salt hypertensive non-DI rats and their SBP was again higher in the young than in the adult group. These age-dependent SBP differences appeared after 2–4 wk of DOCA-salt regimen (Fig. 1). Saline intake of DI rats with chronic dDAVP supplementation was reduced to the level observed in non-DI rats (Fig. 2). It was demonstrated in a separate experiment that 6 wk of dDAVP administration did not influence SBP of young saline-drinking unine-

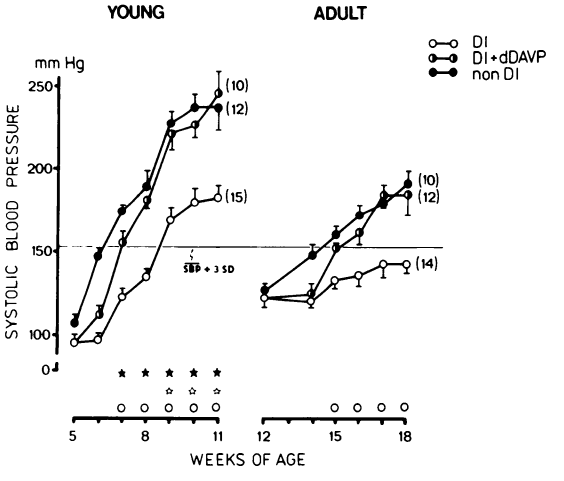

FIG. 1. Development of systolic blood pressure (SBP) in young and adult DOCA-salt-treated Brattleboro rats. Data are means ± SE. Significant differences ($P < 0.002$): open circles, vasopressin-deficient (DI) rats vs. both non-DI and 1-desamino-8-D-arginine vasopressin (dDAVP)-supplemented DI rats; full asterisks, young vs. adult non-DI and dDAVP-supplemented rats; open asterisks, young vs. adult DI rats. Numbers in parentheses, numbers of animals. Horizontal line, upper limit of normal SBP values (average SBP + 3 SD) in control pooled young and adult water-drinking non-DI and DI rats.

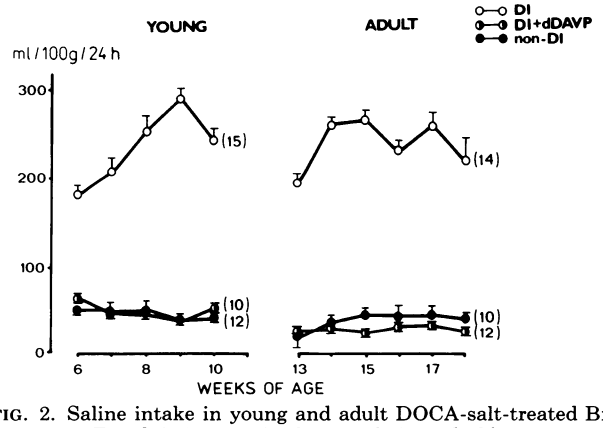

FIG. 2. Saline intake in young and adult DOCA-salt-treated Brattleboro rats. For definitions of other symbols and abbreviations see legend to Fig. 1.

phrectomized DI rats that were not injected with DOCA (Table 2).

SBP differences detected by repeated tail-cuff measurements were confirmed by the direct blood pressure determination at the end of the experiment.

After 6 wk of DOCA-salt treatment a moderate MAP elevation (+15% of control values) was found in conscious young DI rats, whereas there was no MAP change in the adult ones (Fig. 3). Markedly elevated MAP of yound dDAVP-supplemented DI rats was equal to that of hypertensive non-DI rats. On the other hand, there was slightly smaller MAP increase in adult dDAVP-supplemented DI rats than in age-matched non-DI animals. Young DOCA-salt-treated rats had always higher MAP than corresponding groups of adult animals (Fig. 3).

Volume and distribution of body fluids in DOCA-salt-treated rats. The small BP response of DI rats to DOCA-salt treatment occurred in spite of the great expansion of BV that was found in both age groups of these animals (+30 and +25% of control values). Chronic dDAVP supplementation decreased BV of DOCA-salt-treated DI rats close the values observed in hypertensive non-DI rats (Fig. 3).

Major changes of BV in both age groups of VP-deficient DOCA-salt-treated DI rats were the reason why we tried to analyze first the importance of vasopressin for the regulation of body fluids in this hypertensive model (Fig. 4). A moderate increase of both PV and ECFV was observed in young hypertensive non-DI animals. Since PV expansion was slightly greater than that of ECFV, the ratio of plasma volume to interstitial fluid volume (PV/IFV) was significantly increased. On the other hand, greatly expanded PV, decreased IFV, highly elevated PV-to-IFV ratio together with raised plasma sodium concentration and plasma osmolality (358 ± 3 vs. 319 ± 2 mosmol/kg, $P < 0.01$) were characteristic findings in DOCA-salt-treated DI rats in which ECFV was not expanded (Fig. 4). The administration of dDAVP corrected these abnormalities of body fluids in young DOCA-salt-treated DI rats so that dDAVP-supplemented DI animals did not differ from DOCA-salt hypertensive non-DI rats with the exception of a mild elevation of plasma osmolality (324 ± 3 vs. 310 ± 2 mosmol/kg, $P < 0.05$). The total pool of extracellular sodium (Na_{ECFV}) was markedly increased in all groups of young DOCA-salt-treated rats regardless of VP presence (Fig. 4).

TABLE 2. *SBP, MAP, and DBP of conscious young rats subjected to 6 wk of different experimental regimens*

Group	No. of Animals	SBP	MAP	DBP
Water-drinking DI controls	7	146±5	124±3	106±3
Saline-drinking DI rats	8	158±4	123±3	94±6
dDAVP-treated saline-drinking DI rats	6	154±3	127±2	103±3

Values are means ± SE in mmHg. SBP, systolic blood pressure; MAP, mean arterial pressure; DBP, diastolic blood pressure; DI, vasopressin deficient; dDAVP, 1-desamino-8-D-arginine vasopressin.

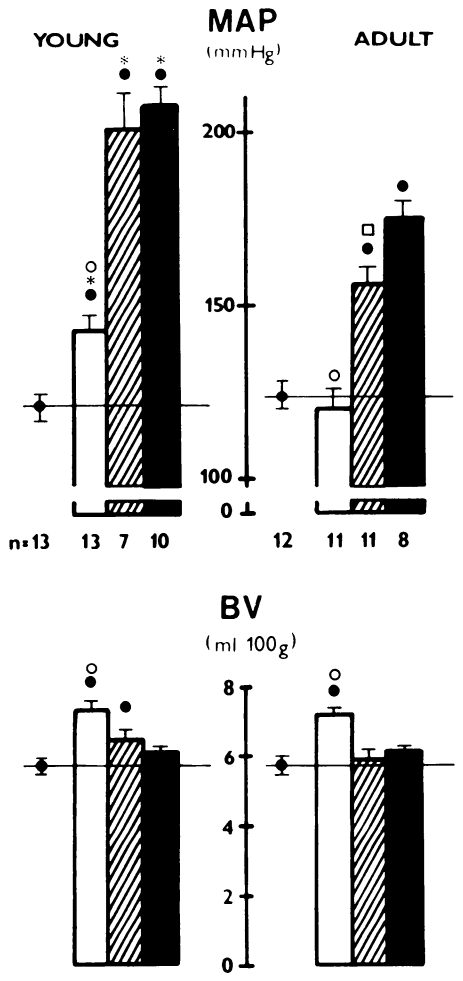

FIG. 3. Mean arterial pressure (MAP) and blood volume (BV) in young and adult Brattleboro rats subjected to DOCA-salt treatment for 6 wk. Open columns, vasopressin-deficient (DI) rats; cross-hatched columns, 1-desamino-8-D-arginine vasopressin (dDAVP)-supplemented DI rats; solid columns, non-DI rats. Solid circles on horizontal lines, control values of pooled water-drinking non-DI and DI animals. Data are means ± SE. Nos. of animals are given under respective columns. Significant differences (Hotelling t test, $P < 0.05$): full dots, from control values; asterisks, young vs. adult rats; open circles, DI rats vs. both non-DI and dDAVP-supplemented DI rats; open squares, respective group vs. non-DI hypertensive rats.

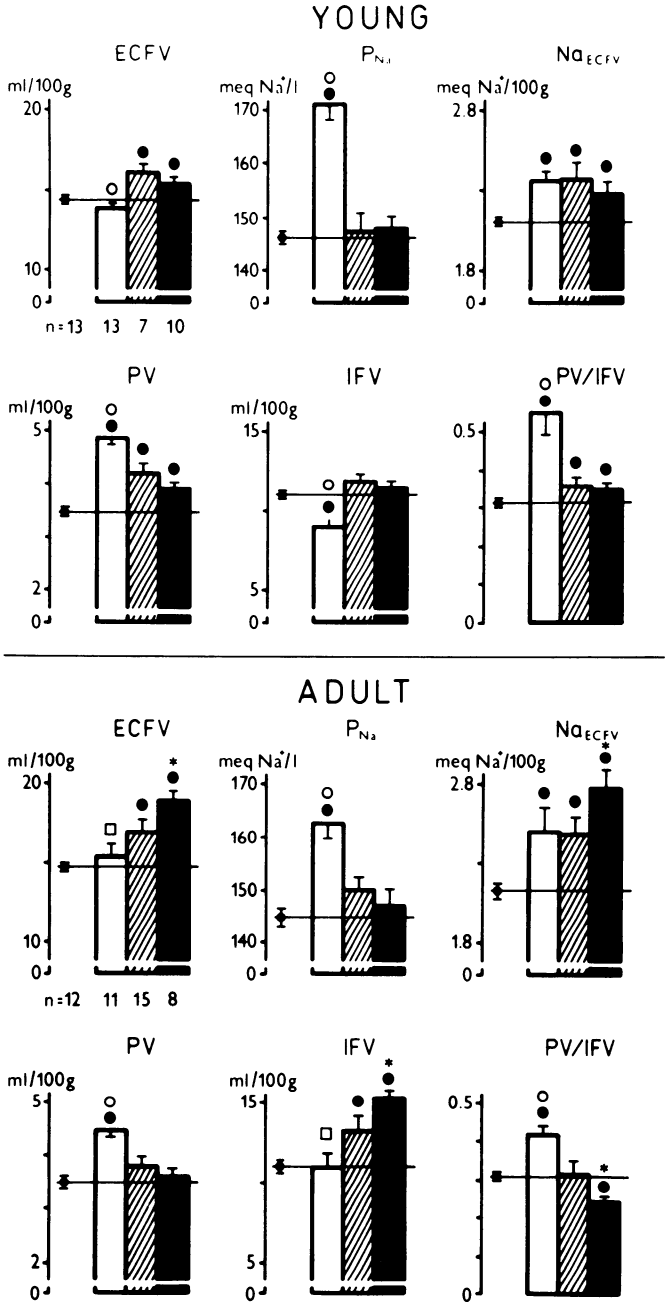

FIG. 4. Body fluids in young and adult DOCA-salt-treated Brattleboro rats. ECFV, extracellular fluid volume; P_{Na}, plasma sodium concentration; Na_{ECFV}, extracellular sodium pool; PV, plasma volume; IFV, interstitial fluid volume; and PV/IFV, plasma volume-to-interstitial fluid volume ratio. For definition of other symbols see legend to Fig. 3.

The general pattern of body fluid changes found in adult DOCA-salt-treated Brattleboro rats was similar to that observed in young animals (Fig. 4). The principal exception was the pronounced ECFV rise in adult hypertensive non-DI rats that occurred exclusively in the interstitial compartment and resulted in the significant decrease of the PV-to-IFV ratio. The chronic dDAVP administration also tended to correct the abnormalities of body fluids in adult DOCA-salt-treated DI rats.

Our data thus indicate that extracellular fluid distribution in both non-DI and dDAVP-supplemented DOCA-salt hypertensive animals was dependent on the age from which the hypertensive stimulus was applied. In young hypertensive rats PV and PV/IFV were increased, whereas this was not true in adult animals. On the other hand, interstitial fluid volume was expanded only in adult DOCA-salt hypertensive rats.

The very high plasma sodium concentration in DOCA-salt-treated DI rats led us to study the effects of mere 0.6% saline drinking on body fluids in young uninephrectomized VP-deficient and dDAVP-supplemented animals. It was evident (Fig. 5) that the pronounced increase of PV, BV, and PV/IFV as well as the elevated plasma sodium concentration and plasma osmolality also occurred in saline-drinking DI rats that were not treated with DOCA. These body fluid alterations were prevented by a chronic dDAVP supplementation that enabled the characteristic expansion of ECFV in saline-drinking DI animals (Fig. 5). Both these groups remained normotensive during 6 wk of the experiment (Table 2). The distribution of extracellular fluid in young normo-

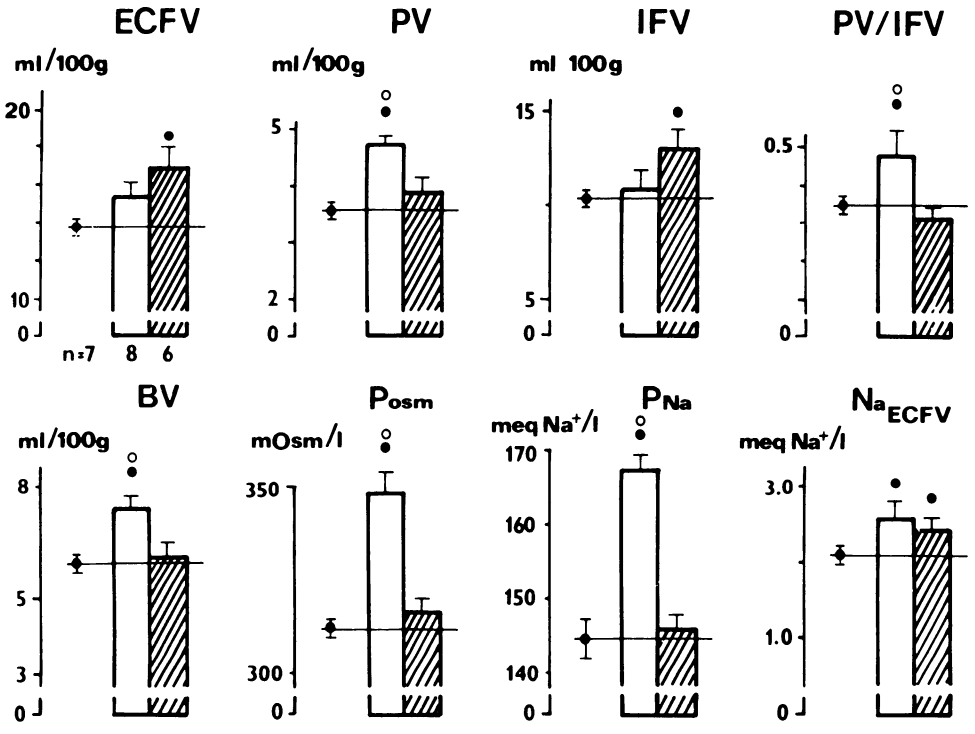

FIG. 5. Influence of chronic intake of 0.6% saline (open columns) or 0.6% saline with 1-desamino-8-D-arginine vasopressin (dDAVP) (cross-hatched columns) on body fluids in young uninephrectomized vasopressin-deficient (DI) rats that were not treated with DOCA. Solid circles on horizontal lines, control values of young water-drinking DI animals. P_{osm}, plasma osmolality. Significant differences (Hotelling t test, $P < 0.05$): full dots, from control values; open circles, from dDAVP-supplemented DI rats. For definitions of other abbreviations see legends to Figs. 3 and 4.

tensive dDAVP-supplemented saline-drinking DI rats was, however, not identical with that found in age-matched DOCA-salt hypertensive dDAVP-supplemented DI animals. It should be pointed out that PV and PV-to-IFV ratio were increased significantly only in the hypertensive group (Fig. 4), whereas IFV rose only in the normotensive one (Fig. 5).

Hemodynamics of DOCA-salt hypertensive rats. The participation of VP pressor effects in the maintenance of elevated systemic resistance (TPR) was examined under the conditions of their chronic or acute elimination. The comparison of the hemodynamics in BP-matched non-DI and dDAVP-supplemented DI rats revealed a substantial difference between young and adult DOCA-salt hypertensive animals (Fig. 6). In young animals there was an identical TPR rise in dDAVP-supplemented DI rats as in non-DI ones. This contrasted with lower systemic resistance and greater cardiac output in adult dDAVP-supplemented DI rats compared with adult hypertensive non-DI animals.

The hemodynamic effects of the acute blockade of circulating vasopressin were studied in the next experiment. The administration of V_1 or V_1V_2 antagonists produced similar acute hemodynamic changes in hypertensive animals, although those induced by V_1V_2 antagonist tended to be slightly greater.

The administration of VP antagonists decreased systemic resistance in both age groups of DOCA-salt hypertensive non-DI rats, but this hemodynamic change was more pronounced in adult than in young rats (Fig. 7). Moreover, compensatory increase of cardiac output was less efficient in the adult than in the young group. This resulted in a prompt and long-term MAP fall in adult hypertensive rats that contrasted with a mild and transient MAP decrease caused by VP antagonist in young hypertensive animals. BP- and TPR-lowering effects of VP antagonists became significantly greater in adult than in young rats at 15–30 min after their injection (Fig. 7). Thus the contribution of VP pressor action to the maintenance of elevated TPR and BP was really more important in adult than in young DOCA-salt hypertensive rats.

It is necessary to mention that none of these VP antagonists had long-term influence on the hemodynamics of either water-drinking DI rats or DOCA-salt hypertensive dDAVP-supplemented DI animals. In most animals transient CO increase and TPR decrease were observed within the 1st min after the injection of VP antagonists. These artificial hemodynamic changes disappeared soon, so that 5 min after the administration of VP antagonists TPR was decreased significantly only in hypertensive non-DI rats ($-15 \pm 3.3\%$, $n = 20$) but not in hypertensive young or adult dDAVP-supplemented DI rats ($-3 \pm 1.9\%$ of initial values, $n = 6$).

DISCUSSION

There might be several important factors involved in the pathogenesis of DOCA-salt hypertension that could be altered by the lack of vasopressin (26). Our study performed in adult Brattleboro rats confirmed the earlier concept (5) that the antidiuretic effects of vasopressin are essential for the development of DOCA-salt hypertension, whereas VP pressor action participates in its maintenance. On the other hand, we would like to point out that the role of VP is less important in young than in adult DOCA-salt hypertensive animals. This seems to be true for both components of its action. A moderate (attenuated) form of DOCA-salt hypertension could be induced even in VP-deficient rats in which this hypertensive stimulus was applied from youth, i.e., from the

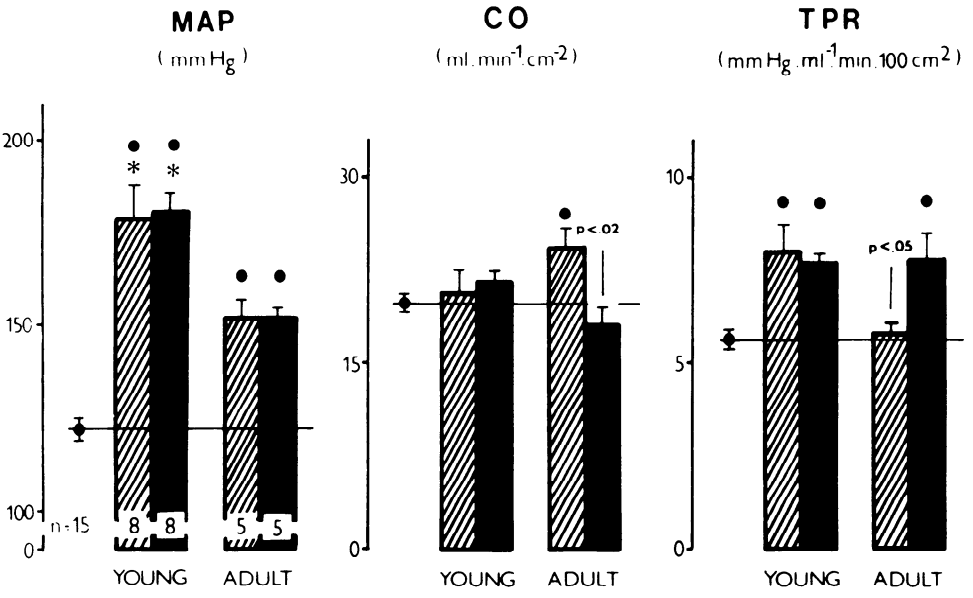

FIG. 6. Mean arterial pressure (MAP), cardiac output (CO), and systemic resistance (TPR) in conscious young and adult DOCA-salt hypertensive Brattleboro rats, a comparison of blood pressure-matched [deamino]-D-arginine vasopressin-supplemented vasopressin-deficient (DI) rats (cross-hatched columns) and non-DI rats (solid columns). Solid circles on horizontal lines, control values of pooled young and adult water-drinking non-DI animals. For definitions of other symbols see legend to Fig. 3.

5th wk of age. Moreover, the contribution of VP pressor action to the maintenance of elevated blood pressure was also less prominent in young animals than in rats subjected to DOCA-salt treatment in adulthood.

The major role of antidiuretic VP action for the development of DOCA-salt hypertension focused our attention on the possible alterations of body fluids that occurred in Brattleboro animals subjected to this hypertensive stimulus. A characteristic ECFV expansion was disclosed only in those DOCA-salt-treated rats in which antidiuretic VP action was present. In DOCA-salt-treated VP-deficient animals ECFV failed to rise above the values found in control rats, although the total pool of extracellular sodium was increased. Thus DOCA-salt-treated DI rats were lacking water but not sodium. This could be also documented by 10–15% rise of plasma osmolality and plasma sodium concentration in these animals. Consequently the chronic supplementation with an antidiuretic analogue (dDAVP) permitted not only the normalization of body fluid pattern in DOCA-salt-treated DI rats but also the full development of this form of experimental hypertension. Our findings on the importance of adequate ECFV expansion in DOCA-salt-treated animals are in good agreement with Guyton's (8) conclusion that increased volume of extracellular fluid is more important for triggering the hypertensive mechanisms than augmented body sodium accumulation. Chronic expansion of body fluids seems to be accompanied by increased vascular reactivity (9). Indeed vascular reactivity was low in DOCA-salt-treated DI rats if these animals were not supplemented with exogenous vasopressin (2). On the other hand, our data are partially at variance with the idea of Guyton et al. (8) concerning the role of blood volume expansion. It was earlier proposed (5, 11) that hypertensive response of DI rats might be blunted by their failure to expand blood volume (BV). Our measurements revealed much greater BV expansion in DOCA-salt-treated DI rats than in any other experimental group. This BV expansion due to extracellular fluid redistribution was not a sufficient trigger for hypertensive mechanisms.

Our results obtained by the comparison of VP-deficient, dDAVP-supplemented and VP-synthetizing Brattleboro rats are in good agreement with the data reported in DOCA-salt-treated Sprague-Dawley rats in which chronic nonselective (V_1V_2) or selective (V_1) blockade of VP action was produced (11). We thus confirmed the earlier suggestions (11, 24) that VP antidiuretic effects are much more important for the induction and development of DOCA-salt hypertension than VP pressor action.

The major finding of our study is that the hypertensive response, the alterations in body fluid pattern as well as the involvement of particular VP effects, depend on the age at which hypertensive stimulus is applied. There are important age-dependent differences in the role of VP effects for the induction, development, and maintenance of DOCA-salt hypertension.

The induction of DOCA-salt hypertension, i.e., the initial BP rise, depends on the presence of VP only in adult but not in young rats because a moderate BP increase occurred in young DI rats (15). This finding can explain the difference between this and previous studies (2, 4, 25) in which adult and old DI rats did not respond by BP increase to DOCA-salt treatment. Nevertheless, it is important to note that the observed hypertensive response of young VP-deficient DI rats to DOCA-salt treatment could not be only ascribed to the hypertensive effects of high salt intake per se (15).

The development of DOCA-salt hypertension was augmented in all groups of young Brattleboro animals because young rats are more susceptible to various salt-dependent forms of experimental hypertension than the adult ones (32). A characteristic redistribution of extracellular fluid toward the intravascular compartment was detected in young non-DI- and dDAVP-supplemented DOCA-salt hypertensive rats. This contrasted with the opposite shift of extracellular fluid in adult hypertensive animals in which the expansion of interstitial fluid volume was found. Thus, under the conditions of normal hydration, increased BP response of young DOCA-salt-

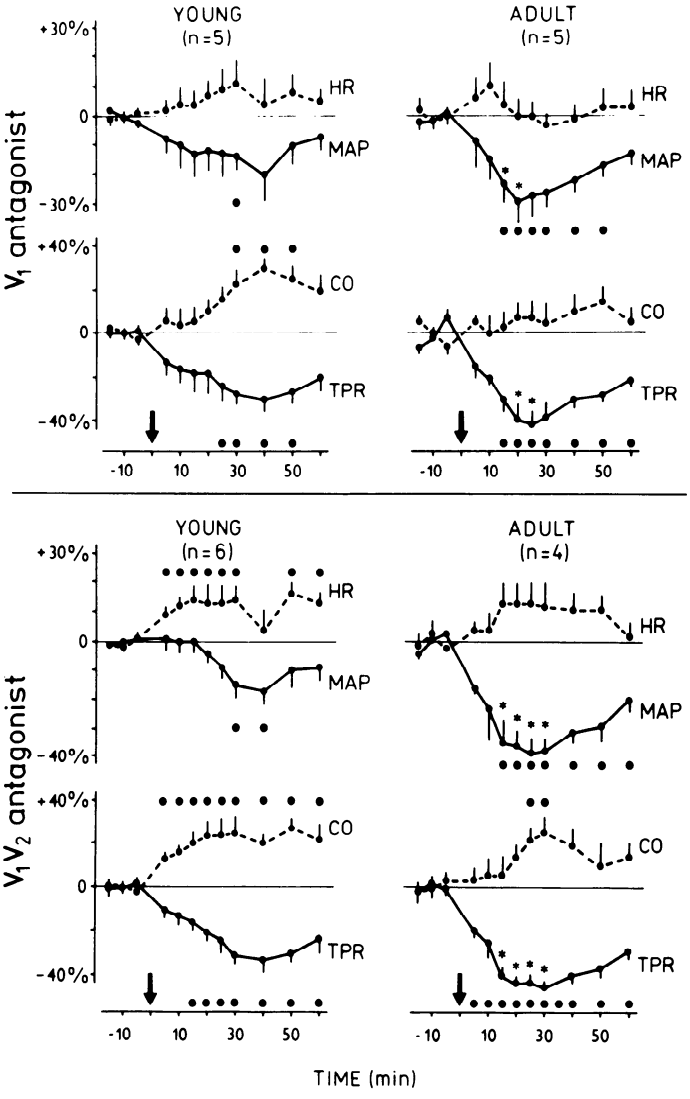

FIG. 7. Time course of changes in heart rate (HR), mean arterial pressure (MAP), cardiac output (CO), and systemic resistance (TPR) induced by vascular (V_1) and combined vascular and tubular (V_1V_2) VP antagonists (arrow) injected into conscious young and adult deoxycorticosterone acetate-salt hypertensive vasopressin-synthetizing rats. Data are expressed in percentages of mean initial values. Significant differences ($P < 0.05$): full dots, from initial values; asterisks, young vs. adult rats.

treated rats might be also related to their greater intravascular volume, triggering hemodynamic adjustments described by Guyton et al. (8). Of course, these changes were not great enough to explain completely the observed age-dependent differences in BP response to this hypertensive stimulus.

It is probable that the pathogenesis of salt-dependent experimental hypertension need not be identical in young and adult rats (32). This might be a reason why young but not adult DI animals were able to develop an attenuated form of DOCA-salt hypertension, although the body fluid pattern was similar in both age groups.

Though the experiments with chronic selective V_1 blockade demonstrated only a minor role of VP pressor action in the development of DOCA-salt hypertension (11), we have disclosed the age-dependent contribution of VP pressor effects to the maintenance of this form of experimental hypertension. Both previous hemodynamic studies (23, 29) revealed that the acute administration of V_1 antagonist lowered TPR in conscious rats with DOCA-salt hypertension. However, Rascher et al. (23) reported that TPR decrease was fully compensated by increased cardiac output. This was not true in the study of Yamamoto et al. (29) who detected a significant decrease of BP and TPR in 40% of DOCA-salt hypertensive rats.

In our experiments the acute blockade of VP pressor action lowered BP and TPR in 85% of hypertensive non-DI Brattleboro rats. Moreover, we monitored hemodynamic changes caused by VP antagonists for a much longer period (up to 60 min), because long-term BP decrease was occasionally reported after the administration of V_1 antagonists (10, 12). Thus we disclosed even mild BP-lowering effects of VP antagonists in young DOCA-salt hypertensive rats in which no significant BP change occurred within the first 30 min, although TPR was already decreased at 15 min after the injection of VP antagonists. In adult hypertensive animals the decrease of TPR was earlier, greater, and less compensated by increased cardiac output than in young rats. This resulted in a more pronounced and long-term BP fall in adult hypertensive animals. This is in good agreement with a greater chronic contribution of VP-dependent TPR increase to BP elevation in adult hypertensive animals. Thus VP pressor action participates in the maintenance of high BP more in adult than in young rats with DOCA-salt hypertension. Of course, a greater baroreceptor reflex impairment in adult rats should be also considered as an additional explanation for the different hemodynamic response of young and adult animals to the acute VP blockade. It seems from our data that the hemodynamic consequences of an acute V_2 blockade in DOCA-salt hypertensive rats were not considerable. Besides comparable effects of V_1 and V_1V_2 antagonists it should be noted that V_1V_2 antagonist lowered TPR so early that the potential reduction of body fluids induced by V_2 blockade was still negligible.

On the basis of our data we suggest that the regulatory involvement of vasopressin in the pathogenesis of DOCA-salt hypertension is age dependent. Although the absence of antidiuretic VP action limits the development of this form of experimental hypertension in both age groups, in adult rats antidiuretic VP effects are essential for hypertension induction, whereas pressor VP effects contribute substantially to hypertension maintenance.

The authors thank J. Křivánková and J. Svatůňková for excellent technical assistance, Dr. J. Křeček and Dr. B. Lichardus for valuable comments, and B. Doležalová for careful manuscript preparation.

Address for reprint requests: J. Zicha, Institute of Physiology, Czechoslovak Academy of Sciences, Videňská 1083, Prague 4, CS-142 20, Czechoslovakia.

Received 29 May 1987; accepted in final form 19 August 1988.

REFERENCES

1. BERECEK, K. H., K. W. BARRON, R. L. WEBB, AND M. J. BRODY. Vasopressin-central nervous system interactions in the development of DOCA hypertension. *Hypertension Dallas* 4, *Suppl.* II: 131–137, 1982.
2. BERECEK, K. H., R. D. MURRAY, F. GROSS, AND M. J. BRODY.

Vasopressin and vascular reactivity in the development of DOCA hypertension in rats with hereditary diabetes insipidus. *Hypertension Dallas* 4: 3–12, 1982.

3. BURNIER, M., J. BIOLLAZ, D. B. BRUNNER, H. GAVRAS, AND H. R. BRUNNER. Alpha and beta adrenoceptor blockade in normotensive and deoxycorticosterone (DOC)-hypertensive rats; plasma vasopressin and vasopressin pressor effect. *J. Pharmacol. Exp. Ther.* 224: 222–227, 1983.
4. CROFTON, J. T., L. SHARE, R. E. SHADE, W. J. LEE-KWON, M. MANNING, AND W. H. SAWYER. The importance of vasopressin in the development and maintenance of DOC-salt hypertension in the rat. *Hypertension Dallas* 1: 31–38, 1979.
5. CROFTON, J. T., L. SHARE, B. C. WANG, AND R. E. SHADE. Pressor responsiveness to vasopressin in the rat with DOC-salt hypertension. *Hypertension Dallas* 2: 424–431, 1980.
6. DLOUHÁ, H., J. KŘEČEK, AND J. ZICHA. Hypertension in rats with hereditary diabetes insipidus. The role of age. *Pfluegers Arch.* 369: 177–182, 1977.
7. FILEP, J., J. C. FRÖHLICH, AND E. FÖLDES-FILEP. Role of AVP in malignant DOC-salt hypertension: studies using vascular and antidiuretic antagonists. *Am. J. Physiol.* 253 (*Renal Fluid Electrolyte Physiol.* 22): F952–F958, 1987.
8. GUYTON, A. C., R. D. MANNING, J. E. HALL, R. A. NORMAN, D. B. YOUNG, AND Y. J. PAN. The pathogenic role of the kidney. *J. Cardiovasc. Pharmacol.* 6, *Suppl* 1: S151–S161, 1984.
9. HADDY, F. J., AND M. B. PAMNANI. Evidence for a circulating endogenous Na^+-K^+ pump inhibitor in low-renin hypertension. *Federation Proc.* 44: 2789–2794, 1985.
10. HATZINIKOLAOU, P., H. GAVRAS, H. R. BRUNNER, AND I. GAVRAS. Role of vasopressin, catecholamines, and plasma volume in hypertonic saline-induced hypertension. *Am. J. Physiol.* 240 (*Heart Circ. Physiol.* 9): H827–H831, 1981.
11. HOFBAUER, K. G., S. C. MAH, H.-P. BAUM, H. HÄNNI, J. M. WOOD, AND J. KRAETZ. Endocrine control of salt and water excretion: the role of vasopressin in DOCA-salt hypertension. *J. Cardiovasc. Pharmacol.* 6, *Suppl* 1: S184–S191, 1984.
12. HOFBAUER, K. G., W. STUDER, S. C. MAH, J.-B. MICHEL, J. M. WOOD, AND R. STADLER. The significance of vasopressin as a pressor agent. *J. Cardiovasc. Pharmacol.* 6, *Suppl* 2: S429–S438, 1984.
13. IMAI, Y., P. L. NOLAN, AND C. I. JOHNSTON. Restoration of suppressed baroreflex sensitivity in rats with hereditary diabetes insipidus (Brattleboro rats) by arginine-vasopressin and DDAVP. *Circ. Res.* 53: 140–149, 1983.
14. KINTER, L. B., AND R. BEEUWKES. Oral antidiuretic therapy: studies in the diabetes insipidus rat. *Am. J. Physiol.* 243 (*Regulatory Integrative Comp. Physiol.* 12): R491–R499, 1982.
15. KUNEŠ, J., AND J. ZICHA. DOCA-salt hypertension in young and adult Brattleboro rats: the role of endogenous vasopressin. *IRCS Med. Sci. Libr.* 14: 738–739, 1986.
16. MANNING, M., B. LAMMEK, A. M. KOLODZIEJCZYK, J. SETO, AND W. H. SAWYER. Synthetic antagonists of in vivo antidiuretic and vasopressor responses to arginine-vasopressin. *J. Med. Chem.* 24: 701–706, 1981.
17. MATSUGUCHI, H., AND P. G. SCHMID. Pressor response to vasopressin and impaired baroreflex function in DOC-salt hypertension. *Am. J. Physiol.* 242 (*Heart Circ. Physiol.* 11): H44–H49, 1982.
18. MATSUGUCHI, H., AND P. G. SCHMID. Acute interaction of vasopressin and neurogenic mechanisms in DOC-salt hypertension. *Am. J. Physiol.* 242 (*Heart Circ. Physiol.* 11): H37–H43, 1982.
19. MENTO, P. F., H.-H. WANG, AND W. H. SAWYER. Contributions of vasopressin and other pressor systems to DOC-salt hypertension in rats. *Proc. Soc. Exp. Biol. Med.* 175: 58–63, 1984.
20. MÖHRING, J. Neurohypophyseal vasopressor principle. Vasopressor hormone as well as antidiuretic hormone? *Klin. Wochenschr.* 56, *Suppl.* I: 71–79, 1978.
21. MÖHRING, J., B. MÖHRING, M. PETRI, AND D. HAACK. Vasopressor role of ADH in the pathogenesis of malignant DOC hypertension. *Am. J. Physiol.* 232 (*Renal Fluid Electrolyte Physiol.* 1): F260–F269, 1977.
22. RABITO, S. F., O. A. CARRETERO, AND A. G. SCICLI. Evidence against a role of vasopressin in the maintenance of high blood pressure in mineralocorticoid and renovascular hypertension. *Hypertension Dallas* 3: 34–38, 1981.
23. RASCHER, W., R. E. LANG, D. GANTEN, H. MERFLE, M. TAUBITZ, T. UNGER, AND F. GROSS. Vasopressin in deoxycorticosterone acetate hypertension of rats: a hemodynamic analysis. *J. Cardiovasc. Pharmacol.* 5: 418–425, 1983.
24. SAITO, T., AND Y. YAJIMA. Development of DOCA-salt hypertension in the Brattleboro rat. *Ann. NY Acad. Sci.* 394: 309–317, 1982.
25. SAITO, T., Y. YAJIMA, AND T. WATANABE. Involvement of AVP in the development and maintenance of hypertension in rats. In: *Antidiuretic Hormone*, edited by S. Yoshida, L. Share, and K. Yagi. Baltimore, MD: University Park, 1980, p. 215–225.
26. SHARE, L., AND J. T. CROFTON. The role of vasopressin in hypertension. *Federation Proc.* 43: 103–106, 1984.
27. ŠIMEK, P., T. BARTH, F. BRTNÍK, J. SLANINOVÁ, AND K. JOŠT. Penicillamine-containing analogues of neurohypophysial hormones. In: *Peptides 1982*, edited by K. Bláha and P. Maloň. Berlin: de Gruyter, 1983, p. 461–464.
28. UNGER, T., P. ROHMEISS, G. DEMMERT, D. GANTEN, R. E. LANG, AND F. C. LUFT. Differential modulation of the baroreceptor reflex by brain and plasma vasopressin. *Hypertension Dallas* 8, *Suppl.* II: 157–162, 1986.
29. YAMAMOTO, J., Y. YAMANE, Y. UMEDA, T. YOSHIOKA, M. NAKAI, AND M. IKEDA. Cardiovascular hemodynamics and vasopressin blockade in DOCA-salt hypertensive rats. *Hypertension Dallas* 6: 397–407, 1984.
30. ZICHA, J., P. KAREN, V. KRPATA, H. DLOUHÁ, AND J. KŘEČEK. Hemodynamics of conscious Brattleboro rats. *Ann. NY Acad. Sci.* 394: 409–413, 1982.
31. ZICHA, J., J. KŘEČEK, AND H. DLOUHÁ. Age-dependent salt hypertension in Brattleboro rats: a hemodynamic analysis. *Ann. NY Acad. Sci.* 394: 330–340, 1982.
32. ZICHA, J., J. KUNEŠ, AND J. JELÍNEK. Experimental hypertension in young and adult animals. *Hypertension Dallas* 8: 1096–1104, 1986.