Interaction between alpha 2-adrenergic and angiotensin II systems in the control of glomerular hemodynamics as assessed by renal micropuncture in the rat.

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Research Article

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Interaction between α_2-Adrenergic and Angiotensin II Systems in the Control of Glomerular Hemodynamics as Assessed by Renal Micropuncture in the Rat

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Abstract

The hypothesis that renal α_2 adrenoceptors influence nephron filtration rate (SNGFR) via interaction with angiotensin II (AII) was tested by renal micropuncture. The physical determinants of SNGFR were assessed in adult male Munich Wistar rats 5–7 d after ipsilateral surgical renal denervation (DNX). DNX was performed to isolate inhibitory central and presynaptic α_2 adrenoceptors from end-organ receptors within the kidney. Two experimental protocols were employed: one to test whether prior AII receptor blockade with saralasin would alter the glomerular hemodynamic response to α_2 adrenoceptor stimulation with the selective agonist B-HT 933 under euvolemic conditions, and the other to test whether B-HT 933 would alter the response to exogenous AII under conditions of plasma volume expansion. In euvolemic rats, B-HT 933 caused SNGFR to decline as the result of a decrease in glomerular ultrafiltration coefficient (LpA), an effect that was blocked by saralasin. After plasma volume expansion, B-HT 933 showed no primary effect on LpA but heightened the response of arterial blood pressure, glomerular transcapillary pressure gradient, and LpA to AII. The parallel results of these converse experiments suggest a complementary interaction between renal α_2-adrenergic and AII systems in the control of LpA. (*J. Clin. Invest.* 1992. 90:604–611.) Key words: B-HT 933 • saralasin • glomerular ultrafiltration coefficient • renal nerves • glomerular filtration rate

Introduction

The renal glomerulus is replete with α_2 adrenoceptors (1), but the physiological role of these receptors is not easily demonstrated. Conflicting data have resulted from various attempts to study the potential hemodynamic effects of α_2 receptor stimulation at either the whole kidney or single nephron level. We previously suspected that inconsistent renal hemodynamic responses to α_2 receptor stimulation might result from opposing hemodynamic effects of stimulating central or presynaptic versus post- or extrajunctional α_2 receptors. This hypothesis was confirmed by comparing the glomerular hemodynamic effects of the α_2 agonist, B-HT 933, in rats previously subjected to renal denervation versus rats with the renal nerves intact (2). When B-HT 933 was administered to animals with normally innervated kidneys, single nephron GFR (SNGFR) increased due to an increase in nephron plasma flow, but when it was administered to animals after renal denervation, SNGFR decreased because of a decrement in ultrafiltration coefficient. Renal denervation thus appeared to unmask effects of α_2 agonist administration on the kidney that are not dependent upon renal nerves and that cause ultrafiltration coefficient and SNGFR to decrease.

The present studies were undertaken to ascertain whether these effects of α_2 receptor stimulation in the denervated kidney might involve a functional interaction with angiotensin II (AII), since AII is well known to exert local control over the determinants of SNGFR through effects on vascular resistances and glomerular ultrafiltration coefficient (LpA) (3).

Glossary

DNX	Denervation of the left (ipsilateral) kidney
EUV	Euvolemia
PVE	Plasma volume expansion
AII	Angiotensin II
BHT	α_2 Adrenoceptor agonist, B-HT 933
SAR	AII receptor antagonist, 1-SAR, 8-ALA AII
Hct	Fractional hematocrit
BP	Mean arterial pressure
P_{GC}	Glomerular capillary hydrostatic pressure
ΔP	Trans-glomerular capillary hydrostatic pressure gradient
P_E	Efferent arteriolar hydrostatic pressure
C	Plasma protein concentration
π	Plasma oncotic pressure
EFP	Effective filtration pressure (ΔP-π)
GFR	Whole kidney glomerular filtration rate
SNGFR	Single nephron GFR
SNPF	Nephron plasma flow
LpA	Glomerular ultrafiltration coefficient
$V_{L,R}$	Urine flow
V_{LP}	Late proximal flow rate
AR_P	Absolute proximal reabsorption (SNGFR-V_{LP})
FR_P	Fractional proximal reabsorption (AR_P/SNGFR)

Subscripts

L	Left
R	Right
a	Afferent
e	Efferent

Methods

The potential for the AII and α_2-adrenergic systems to interact at the single nephron level was assessed by in vivo micropuncture in male Munich-Wistar rats 5–7 d after surgical denervation of the ipsilateral kidney. Measurement of SNGFR and each of its determinants were obtained during each of two experimental periods in four different groups of animals as follows:

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Table I. Effects of B-HT 933 in Euvolemic Rats with and without Saralasin

Group	Hct	BP	P_{GC}	ΔP	P_e	EFP_A	SNGFR	SNPF	LpA	V_{LP}	AR_P	FR_P	GFR_L	GFR_R	V_L	V_R
				mmHg			*nl/min*		*nl/s/mmHg*	*nl/min*			*ml/min*		*μl/min*	
SAR	0.51±0.01	98.2±3.4	53.5±1.3	37.4±0.9	19.2±0.6	20.2±1.5	42.4±1.8	159±9	0.051±0.007	30.7±1.4	12.8±0.7	0.294±0.011	1.25±0.14	1.08±0.14	3.5±0.4	2.5±0.3
SAR + BHT	0.50±0.01	90.5±3.1*	48.2±1.1*	34.3±1.0*	15.9±0.8*	20.1±2.0	41.8±1.8	152±7	0.066±0.015	28.2±1.7	14.2±0.8	0.343±0.015*	1.30±0.13	1.51±0.12	6.3±1.1*	8.1±1.7*
CON	0.51±0.01	102.6±3.0	50.4±1.1	35.1±0.7‡	19.3±1.4	18.7±1.4	49.9±1.8‡	159±7	0.080±0.015	33.4±1.2	16.5±1.3	0.323±0.018	1.21±0.08	1.34±0.13	3.0±0.4	2.9±0.3
CON + BHT	0.51±0.01	91.6±1.9*	48.5±0.9	34.1±0.9	16.7±0.4	18.4±1.3	40.4±1.9*	157±10	0.054±0.007*	23.7±1.5*	16.7±1.4	0.413±0.024*	0.89±0.10*‡	0.91±0.14‡	9.3±0.1*	10.7±2.4*
Effect of interaction between SAR and BHT																
P	NS	NS	NS	NS	NS	NS	0.016	NS	0.077 (0.030)	0.015	NS	NS	0.024	0.011	NS	NS

Effects of B-HT 933 (BHT) in euvolemic rats with (SAR) and without (CON) saralasin. Values expressed as mean ± SEM. Parameters with one data point per experimental period (BP, EFP_A, SNPF, LpA, GFR_{LR}, and V_{LR}) were analyzed by one-way ANOVA with design for repeated measures. Parameters with multiple data points per experimental period (P_{GC}, ΔP, HP_e, SNGFR, V_{LP}, AR_P, and FR_P) were analyzed by two-way ANOVA. Statistical significance of effects on LpA were determined from animals in filtration pressure disequilibrium. *P* value shown in parentheses is result of ANOVA performed on Log(LpA). Refer to Glossary for definitions.
* $P < 0.05$ vs. pre-BHT. ‡ $P < 0.05$ vs. respective SAR-treated group. NS, not significant.

In Group 1A (n = 7), measurements were obtained before and during systemic infusion of AII (70 ng/kg per min) in plasma volume expanded animals receiving the α_2-adrenergic agonist, B-HT 933 (1 mg/kg per h). Plasma volume expansion was carried out to suppress the endogenous renin-angiotensin system.

Group 1B (n = 7) was the control for group 1A, with Ringers' saline in place of B-HT 933.

In Group 2A (n = 6), measurements were obtained before and during systemic infusion of B-HT 933 (1.3 mg/kg per h) in euvolemic animals receiving the AII receptor antagonist 1-SAR, 8-ALA AII (saralasin [SAR]; 10 μg/kg per min).

Group 2B (n = 7) was the control for group 2A, with Ringers' saline in place of SAR.

Denervation procedure. Renal denervation was carried out 5–7 d before micropuncture under sterile operating conditions according to protocols as previously described (2). We have previously demonstrated uniform success in achieving renal sympathetic denervation by these means as documented by a > 90% reduction in renal tissue norepinephrine (4, 5).

Micropuncture experiments. Micropuncture was performed under Inactin (Andrew Lockwood Assoc., Ann Arbor, MI) anesthesia according to protocols previously described in publications from this laboratory (6). Animals studied under euvolemic conditions received donor rat plasma as surgical replacement (11 ml/kg body wt over 60 min) followed by continuous infusion (1.5 ml/kg per h). Animals undergoing plasma volume expansion received donor rat plasma (25 ml/kg body wt over 60 min) followed by continuous infusion of Ringers' saline (4.8 ml/h). All animals received an additional infusion of Ringers' saline containing 80 μCi/ml [^{3}H]inulin (1.5 ml/h) as a marker of glomerular filtration.

Arterial blood pressure was monitored from a femoral artery catheter. Hydrostatic pressures were measured directly in glomerular capillaries (P_{GC}), Bowman's space (P_{BS}), and efferent arterioles (P_E) with a servo-nulling pressure device using micropipettes filled with hypertonic saline. Systemic blood was sampled from the femoral artery. Efferent arteriolar blood was obtained by direct micropuncture. A microadaptation of the Lowry technique (7) was used to determine the protein concentrations of systemic (C_A) and efferent arteriolar (C_E) plasma. Plasma oncotic pressure (π) was calculated from protein concentration by the Landis–Pappenheimer equation (8). Nephron filtration fraction was computed from C_A and C_E. Inulin clearance and volumetric measurement of fluid collected from late proximal tubules (five per experimental period) were used to calculate SNGFR and late proximal flow rate (V_{LP}). Absolute and fractional rates of proximal reabsorption were calculated from SNGFR and V_{LP}.

Mathematical models. The determinants of SNGFR are as follows: (*a*) nephron plasma flow, SNPF = $(SNGFR \times C_E/C_E - C_A)]$; (*b*) afferent effective filtration pressure, $EFP_A = \Delta P - \pi_A$; and (*c*) glomerular ultrafiltration coefficient, *LpA,* such that;

$$LpA = \frac{SNGFR}{\int_0^1 [EFP(x)]dx},$$

where x is the axial position along a nondimensionalized glomerular capillary,

$$EFP(x) = \Delta P - \pi(x)$$

$$\pi(x) = 1.73C(x) + 0.28C^2(x)$$

and the plasma protein concentration, $C(x)$, is calculated according to standard formulas (4) with the boundary conditions $C(0) = C_A$ and $C(1) = C_E$.

Statistical analysis. To take best advantage of the paired nature of the experiments, the effects of treatments were analyzed when appropriate by one-way analysis of variance (ANOVA)[1] with design for re-

1. *Abbreviations used in this paper:* ANOVA, analysis of variance.

peated measures (9). For parameters measured more than once during an experimental period (SNGFR, V_{LP}, FR_P, AR_P, P_{GC}, P_E, and ΔP), the mean for that period was used. For these parameters, groups were also compared by standard two-way ANOVA using individual measurements. The results of analyses by these two methods were similar.

As has been previously discussed (4), LpA, as estimated by the above method, is likely not to be a normally distributed. Despite the limitation imposed by small sample sizes, an indication of whether or not a variable is normally distributed may be ascertained from the linearity of a Normal Probability Plot (10). Such plots constructed for LpA indicated that LpA was as likely to be distributed log-normally as normally. For this reason values of Log(LpA) as well as LpA were subjected to repeated measures ANOVA.

Results

Experimental results are depicted in Tables I and II and Figs. 1 and 2.

Systemic and whole kidney effects

Effects of B-HT 933 in euvolemia with and without saralasin. Among euvolemic animals, arterial pressure (BP) did not differ significantly between those receiving saralasin and controls. B-HT 933 reduced BP by ~10 mmHg in both groups ($P = 0.001$). Saralasin did not alter the effect of B-HT 933 on blood pressure. B-HT 933 exerted a similar diuretic effect in left and right kidneys, independent of saralasin. In the denervated left kidney, GFR declined with B-HT 933 administration in control, but not saralasin-treated, animals. Similar effects on GFR were observed in the innervated right kidney, although the effect of B-HT 933 in control animals did not achieve statistical significance ($P = 0.06$ by paired t test).

Effects of AII after plasma volume expansion with and without B-HT 933. Before receiving AII, volume-expanded animals treated with B-HT 933 tended toward lower blood pressures commensurate with the expected central sympatholytic effect of the α_2 agonist. AII caused BP to increase by an amount similar to that previously reported with this dose (5). After AII infusion, the mean BP was similar between B-HT 933–treated and control groups but the incremental increase in BP after AII administration was greater in animals pretreated with B-HT 933.

B-HT 933 exerted a diuretic effect that was most pronounced in the innervated right kidney, whereas a pressure diuresis after AII administration was noted only in the left kidney. Fractional hematocrit increased slightly with AII administration. This effect was not dependent on B-HT 933, suggesting that B-HT 933 administration was not a determinant of plasma volume. The rate of saline infusion exceeded the rate of urine flow by ~ 30 and ~ 70 μl/min in B-HT 933 and control animals, respectively.

Glomerular hemodynamics

Effects of B-HT 933 in euvolemia with and without saralasin. In euvolemic animals, P_{GC} was not affected by saralasin but declined somewhat with the administration of B-HT 933, perhaps reflecting incomplete autoregulation. The first period mean ΔP was 2.3 mmHg higher in the saralasin group, a finding of stochastic ($P = 0.05$), but not quantitative significance. EFP_a and SNPF, however, were unaffected by either treatment. Filtration pressure disequilibrium prevailed throughout both experimental periods in 5/7 control animals and in 6/6 animals receiving saralasin, enabling calculation of unique values

Table II. Effects of Angiotensin II after Plasma Volume Expansion with and without B-HT 933

Group	Hct	BP	P_{GC}	ΔP	P_e	EFP_a	SNGFR	SNPF	LpA	V_{LP}	AR_P	FR_P	GFR_L	GFR_R	V_L	V_R
				mmHg			*nl/min*		*nl/s per mmHg*	*nl/min*			*ml/min*		*μl/min*	
BHT	0.44±0.01	92.9±1.2	58.8±1.4	35.9±1.0	26.4±0.9	17.3±1.5	44.4±1.4	144±5	0.086±0.014	30.4±1.3	14.4±1.4	0.318±0.024	1.03±0.08	1.42±0.09	13.5±4.3	57.2±3.6
BHT + AII	0.47±0.01	131.2±2.9*	60.4±1.8	48.0±1.4*	18.4±1.0*	31.4±2.1*	29.6±1.4*	84±5*	0.023±0.002*	19.0±1.3	10.7±0.7	0.373±0.025	1.00±0.06	1.29±0.04	24.8±5.0	52.8±14.8
CON	0.45±0.01	102.1±6.3	54.5±1.0‡	37.0±0.9	23.2±0.9‡	17.6±1.4	45.8±1.8	165±8‡	0.081±0.015	31.6±1.4	15.0±1.4	0.316±0.017	1.22±0.04	1.32±0.05	12.1±2.1	14.7±4.4‡
CON + AII	0.47±0.01	128.4±4.3*	54.5±1.2	41.0±1.2*	17.2±0.6*	26.3±1.3*	32.5±1.4*	82±4*	0.034±0.004*‡	21.7±1.0	11.0±0.8	0.336±0.016	1.00±0.05*	1.02±0.14	19.7±4.5	16.44±3.9‡
Interaction between BHT and AII																
P	NS	0.006	NS	0.001	NS	0.086	NS	0.042	0.47 (0.006)	NS	NS	NS	0.088	NS	NS	NS

Effects of AII in plasma volume expanded rats with (BHT) and without (CON) B-HT 933. Values expressed as mean ± SEM. Parameters with one data point per experimental period (BP, EFP_a, SNPF, LpA, $GFR_{L,R}$, and $V_{L,R}$) were analyzed by one-way ANOVA with design for repeated measures. Parameters with multiple data points per experimental period (P_{GC}, ΔP, HP_e, SNGFR, V_{LP}, AR_P, and FR_P) were analyzed by two-way ANOVA. Statistical significance of effects on LpA were determined from animals in filtration pressure disequilibrium. *P* value shown in parentheses is result of ANOVA performed on Log(LpA). Refer to Glossary for definitions.
* $P < 0.05$ vs. per-AII. ‡ $P < 0.05$ vs. respective BHT-treated group. NS, not significant.

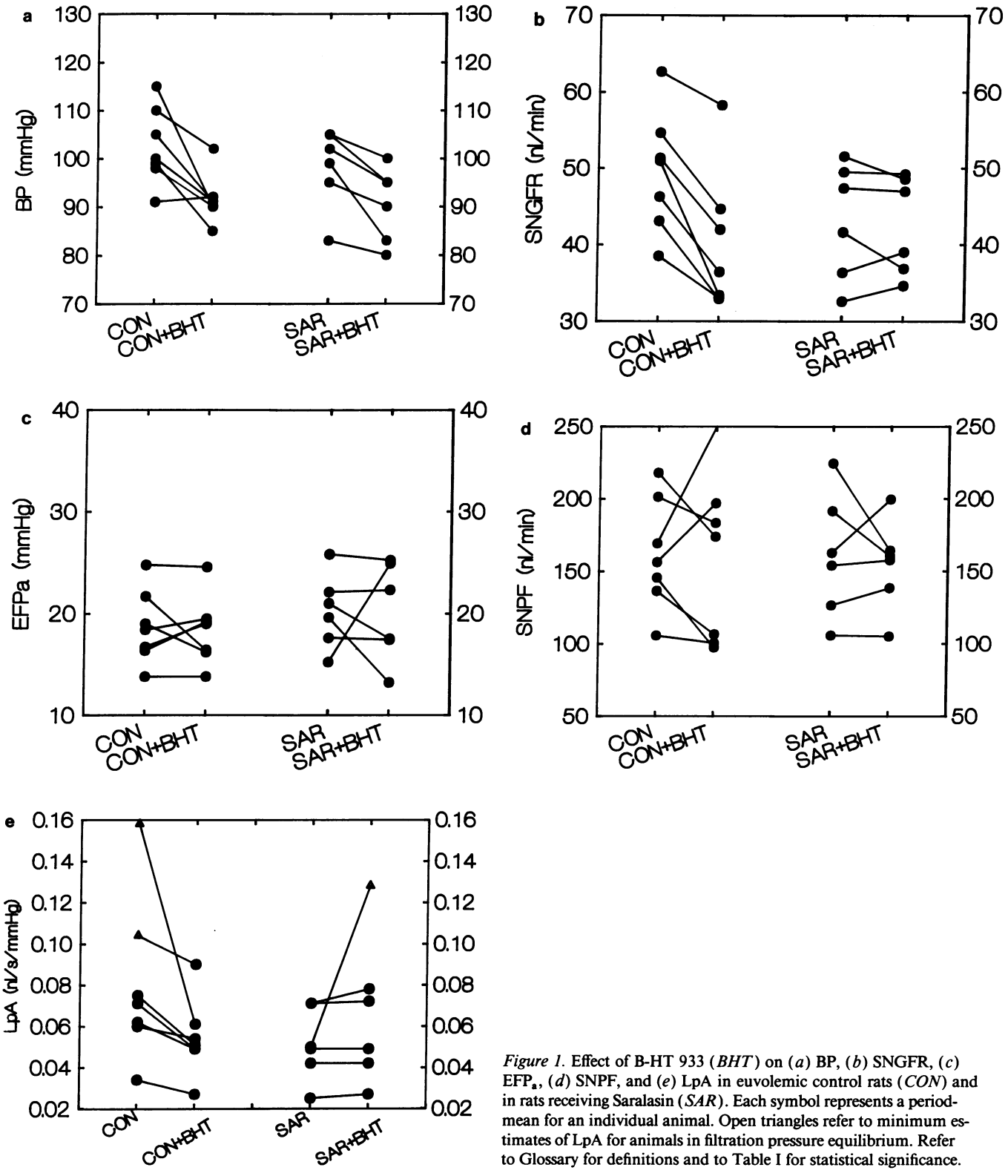

Figure 1. Effect of B-HT 933 (*BHT*) on (*a*) BP, (*b*) SNGFR, (*c*) EFP_a, (*d*) SNPF, and (*e*) LpA in euvolemic control rats (*CON*) and in rats receiving Saralasin (*SAR*). Each symbol represents a period-mean for an individual animal. Open triangles refer to minimum estimates of LpA for animals in filtration pressure equilibrium. Refer to Glossary for definitions and to Table I for statistical significance.

for LpA in those animals. The effect of B-HT 933 on LpA was dependent on pretreatment with saralasin such that LpA increased by 30±25% in saralasin-treated animals but decreased by 23±4% in controls ($P = 0.077$ and $P = 0.030$ for saralasin to inhibit the effect of B-HT 933 on ultrafiltration coefficient as defined by LpA or log[LpA], respectively). Both control animals excluded from analysis because of filtration pressure equilibrium were in disequilibrium during the second experimental period, enabling calculation of minimum estimates for the effect of AII on LpA in those animals. The minimum estimate of the effect of AII in each of those two cases exceeded the group mean effect derived during their exclusion, further strengthen-

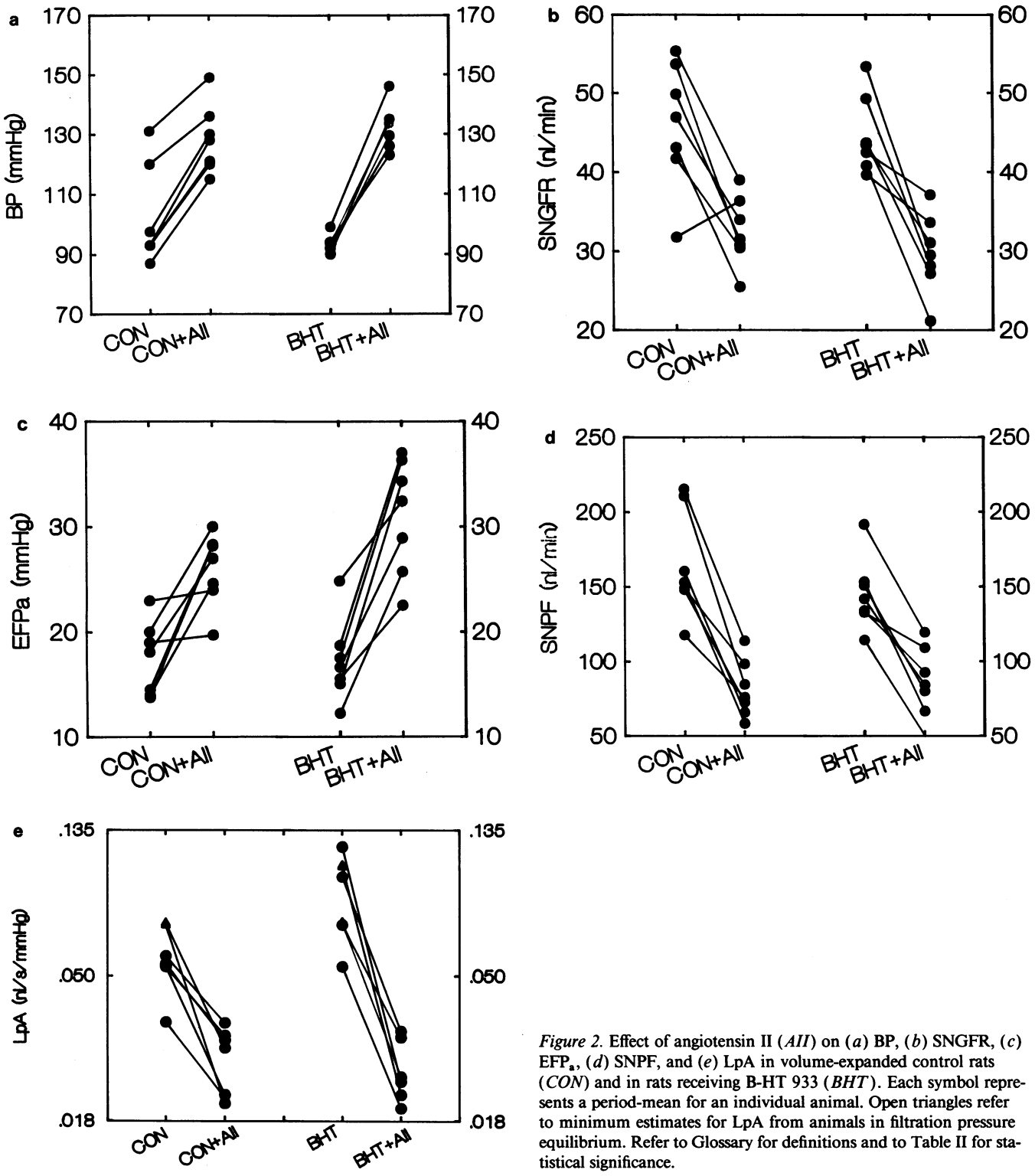

Figure 2. Effect of angiotensin II (*AII*) on (*a*) BP, (*b*) SNGFR, (*c*) EFP_a, (*d*) SNPF, and (*e*) LpA in volume-expanded control rats (*CON*) and in rats receiving B-HT 933 (*BHT*). Each symbol represents a period-mean for an individual animal. Open triangles refer to minimum estimates for LpA from animals in filtration pressure equilibrium. Refer to Glossary for definitions and to Table II for statistical significance.

ing the difference between saralasin and control groups with respect to the effect of AII on LpA. As the result of a decline in LpA, B-HT 933 caused SNGFR to decrease by 21±4% in control, but not saralasin-treated animals.

Effects of AII after plasma volume expansion with and without B-HT 933. Despite a tendency toward lower BP, P_{GC} was higher among volume expanded animals receiving B-HT 933, suggesting an effect on the ratio of pre- and postglomerular vascular resistances. Before AII administration ΔP did not differ between the two groups. AII caused ΔP and EFP_a to increase by amounts which were greater in animals receiving B-HT 933. Before AII, SNPF was slightly lower in animals treated with B-HT 933. AII caused SNPF to decline to similar values in both groups such that the net effect was greater among controls ($P = 0.042$). Filtration pressure disequilibrium prevailed during both experimental periods in five B-HT

933–treated and four control animals, allowing precise estimates of LpA in those experiments. Before AII infusion, B-HT 933 had no effect on LpA in plasma volume–expanded animals. AII caused a reduction in LpA in all animals, with a greater decline observed among those pretreated with B-HT 933. The integrated effects of treatments on the determinants of SNGFR resulted in no net difference in SNGFR between B-HT 933 and control groups before AII administration. AII caused SNGFR to decline by a similar amount in both groups.

Proximal tubular reabsorption

Effects of B-HT 933 in euvolemia with and without saralasin. The effects of B-HT 933 and saralasin on the delivery of fluid to the late proximal tubule tended to parallel the effects on SNGFR. Fractional reabsorption was enhanced by B-HT 933 in both groups and tended to be less in animals receiving SAR. Net fluid reabsorption from the proximal tubule was diminished in the presence of saralasin but unaffected by B-HT 933.

Effects of AII after plasma volume expansion with and without B-HT 933. In volume-expanded animals, no independent effect of B-HT 933 was demonstrated on absolute or fractional reabsorption of fluid from the proximal tubule. Absolute reabsorption fell along with the filtered load whereas fractional reabsorption increased with AII administration in both groups. The increase in fractional reabsorption after AII was numerically greater in the B-HT 933–treated group, although this effect of B-HT 933 was not statistically significant.

Discussion

Although the physiological role of renal α_2 adrenoceptors remains to be fully established, they have been reported to constrict (11–13) or relax (2) the renal vasculature, suppress renin secretion (14, 15), and stimulate reabsorption of sodium from the proximal nephron by stimulating Na/H exchange (16–18) and from the loop of Henle by suppressing furosemide- (19) or prostaglandin- (20) mediated increases in cAMP. α_2 Receptors also inhibit reabsorption of salt and water from the distal nephron by antagonizing the effects of vasopressin (21–25) and potentiating the effect of atrial natriuretic peptide (26). In many of these cases, α_2 adrenoceptors function by modulating the activity of other effector systems (16–18, 27–33). In situations where α_2 receptors modulate the influence of multiple effectors, the physiological outcome of α_2 receptor stimulation or blockade will depend upon the previous activities of potentially competing systems that are individually conditioned by interactions with α_2 adrenoceptors.

The present studies were formulated to ascertain whether previously reported effects of α_2 adrenoceptor stimulation on glomerular dynamics involve an interaction with AII. The basis for this hypothesis derives in part from similarities between the recently reported glomerular hemodynamic response to B-HT 933 (2) and the well-known response to AII (3), as well as from past reports that angiotensin-converting enzyme inhibitors will block α_2-mediated vasoconstriction (34–36). Studies were performed after renal denervation to isolate the effects of stimulating renal α_2 receptors from the sympathoinhibitory actions of systemic α_2 agonist administration. Although changes may occur in the density and distribution of renal α_2 adrenoceptors when nerve signaling is interrupted by α_1 receptor blockade (37), subacute surgical denervation does not alter the density of α_2 adrenoceptors within glomeruli (2) so that glomerular hemodynamic response to B-HT 933 observed in the denervated kidney are not mere reflections of denervation hypersensitivity.

To block the effects of the renin-AII system, saralasin was chosen in preference to a converting enzyme inhibitor in order to avoid the potentially confounding influence of the latter on kinin degradation (38). The dose of saralasin used was sufficient to decrease by > 90% the pressor response to a bolus injection of AII (70 ng/kg intravenously).

Given that α_2 and AII receptors are both widely distributed and that each may exert influence over vascular tone and epithelial transport at numerous sites it is not surprising that the various experimental treatments altered systemic hemodynamics, nephron plasma flow, glomerular ultrafiltration coefficient, proximal tubular reabsorption, and urine flow. The effects of administering AII (5) and B-HT 933 (2) to control animals after subacute renal denervation are similar to those previously reported. The enhanced diuretic effect of α_2 receptor stimulation associated with volume expansion has also been previously reported (39). Statistically significant interactions between the α_2-adrenergic and AII systems were observed in euvolemic animals with regard to nephron and whole kidney GFR and glomerular ultrafiltration coefficient. In volume-expanded animals, significant interactions were noted with regard to effects on systemic blood pressure, nephron plasma flow, ΔP, whole kidney GFR, and glomerular ultrafiltration coefficient. Among the physiological determinants of SNGFR, therefore, the α_2 and AII systems manifest interdependence in their control of nephron plasma flow, intraglomerular hydrostatic pressures, and glomerular ultrafiltration coefficient. Each of these interactions is complementary except for that involving nephron plasma flow after volume expansion.

In a complex physiological model, in which the α_2 and AII systems interact to control multiple parameters, it is likely that they do so through multiple mechanisms. Several investigators have undertaken to delineate the roles of the adrenergic receptor subtypes in the control of renal blood flow. A number of functional and pharmacological studies in anesthetized animals have suggested that renal vasoconstriction, whether elicited by renal sympathetic nerve activity or adrenergic agonist infusion, is mediated by α_1 receptors (40–42). In fact, administration of B-HT 933 to euvolemic rats with intact renal nerves resulted in an actual increase in nephron plasma flow despite a decline in blood pressure (2), probably because of suppression of efferent renal sympathetic nerve activity by central (30) or peripheral presynaptic α_2 receptors (29, 30, 43, 44). α_2-Mediated renal vasoconstriction has been demonstrated, however, in awake rats (13, 45), sheep (11), and humans (12), suggesting the possibility of a saturable vasomotor response that is obscured by the increase in circulating catecholamines accompanying general anesthesia (46). The present study confirms the previous finding, that α_2 agonist administration does not alter nephron plasma flow in the euvolemic anesthetized rat after renal denervation (2). After 2.5% plasma volume expansion, however, nephron plasma flow is somewhat less among animals receiving B-HT 933 than among controls. Since P_{GC} and P_E were both elevated despite a lower arterial blood pressure in the group receiving the α_2 agonist, the difference in SNPF appears to have been mediated by a combination of lower arterial blood pressure and a greater vascular resistance in segments downstream from the efferent arteriole. The differ-

ence in SNPF between the two groups of volume-expanded animals does not depend on differences in the resistance of vascular segments between the aorta and peritubular capillary. The fact that this finding was limited to volume-expanded animals probably reflects a decreased residual capacitance of the venous system and, therefore, greater sensitivity to α_2-mediated venoconstriction under this condition. In contrast, when B-HT 933 was given to euvolemic animals, P_{GC} and P_E actually declined along with BP while SNPF was preserved, findings which exclude selective postrenal vasoconstriction in euvolemia.

An inhibitory interaction between renal α_2 adrenoceptors and the renin-angiotensin system has been previously documented (15). Renin secretion is stimulated by antagonists and inhibited by agonists of the α_2 adrenoceptor. A heightened response to exogenous AII during α_2 receptor stimulation could, therefore, result from a true positive interaction or from the administration of exogenous AII against a diminished endogenous background. In our model, for the interaction to be merely apparent, the α_2-inhibitable component of renin secretion must be independent of the renal nerves. However, α_2 agonists appear to suppress β-adrenergic–mediated renin release by binding to presynaptic receptors on the renal nerves (14). Additionally, suppression of background AII activity by B-HT 933 would not have accounted for the ability of saralasin to eliminate the effect of the α_2 agonist on LpA.

In previous studies designed to dissociate the effects of stimulating central or presynaptic from post- or extrasynaptic renal α_2 receptors, systemic infusion of B-HT 933 resulted in a decrease in SNGFR mediated by an effect on LpA in a denervated, but not in an innervated kidney (2). This effect of B-HT 933 was prevented by previous administration of the α_2 receptor antagonist, yohimbine, thus substantiating its mediation by α_2 adrenoceptors. This consequence of administering B-HT 933 to euvolemic animals is confirmed in the present study and is now shown to be inhibitable by an AII receptor antagonist, suggesting a facilitory role for AII in the response to B-HT 933. Furthermore, after plasma volume expansion, the effect of administering B-HT 933 on LpA was eliminated, whereas B-HT 933 amplified the effect of administered AII. Plasma volume expansion may alter the hormonal milieu in a number of ways, among them diminishing the tonic influence of AII over LpA. It is plausible that the response to α_2 adrenoceptor stimulation is diminished under volume-expanded conditions because of effects of volume expansion on intrarenal angiotensin.

The phenomenological nature of micropuncture limits the usefulness of these observations in distinguishing between interactions that occur at the cellular versus those which occur at the systemic level. Nonetheless, such data do provide information regarding the physiological relevance of these interactions and the plausibility of hypotheses to explain them. For instance, the likelihood that an interaction is mediated locally rather than via events in distant organs increases if it holds under different conditions or with contradictory perturbation of the components under study. Among the parameters measured, only LpA manifested a statistically significant interdependence between the AII and α_2 systems during both stimulation and inhibition of AII activity. Although not excluding the possibility of other local interactions between the two systems, these findings enhance the plausibility of the notion that the two systems could interact within the glomerulus to govern LpA.

A facilitory interdependence has been previously observed between the AII and α_2-adrenergic systems in the arterial vasculature (35, 36, 47) where inhibition of AII will blunt α_2-mediated vasoconstriction by mechanisms that remain to be elucidated. Since certain shared properties of the contractile mesangium and vascular smooth muscle could account for the functional control that the former, as a site of action for various hormones and autacoids, may exert over the glomerular ultrafiltration coefficient (48), it is conceivable that the mechanism of interaction between AII and the α_2-adrenergic subsystem in the renal glomerulus and arterial vasculature are the same.

To summarize, α_2 adrenoceptor stimulation in euvolemic rats after ipsilateral renal denervation causes SNGFR to decrease as the result of a decrease in glomerular ultrafiltration coefficient. The effects of α_2 agonist administration on glomerular ultrafiltration coefficient and SNGFR under these conditions are eliminated by previous treatment with the AII receptor antagonist saralasin or by plasma volume expansion. α_2 Adrenoceptor stimulation in volume-expanded rats after ipsilateral renal denervation amplifies the well-known effects of AII on blood pressure, glomerular capillary pressure gradient, and glomerular ultrafiltration coefficient. A positive interaction between the α_2-adrenergic and AII systems in the control of LpA seems particularly likely, having been demonstrated by two converse means, first as a tendency for B-HT 933 to heighten the response to AII and then as a proclivity for saralasin to inhibit the response to B-HT 933. Furthermore, the effect of the α_2 agonist on LpA was eliminated by plasma volume expansion. Since suppression of endogenous renin is among the hormonal effects of plasma volume expansion, the role of volume status in conditioning the effect of B-HT 933 on LpA provides additional circumstantial evidence that α_2 adrenoceptors function within the glomerulus to amplify the local physiological response to AII. Whether interactions between the α_2-adrenergic and angiotensin systems are mediated by events within single cells as well as at the end-organ level is a subject for further investigation.

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