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Pulmonary Vascular Efflux of Norepinephrine in Dahl Rats Susceptible or Resistant to Salt-Induced Hypertension (42730)

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Abstract. The purpose of these studies was to determine whether the accumulation of norepinephrine by the pulmonary circulation is altered in the Dahl model of genetic hypertension. Pulmonary norepinephrine accumulation was evaluated by performing a compartmental analysis of the efflux of L-[^{3}H]norepinephrine from perfused lungs after inhibition of the norepinephrine-metabolizing enzymes. The lungs were isolated from Dahl salt-hypertension-susceptible (S) and salt-hypertension-resistant (R) rats that had been on a high sodium diet for 3 weeks. In both S and R rats, norepinephrine was accumulated into a single compartment with an efflux half-time of approximately 23 min, in addition to its distribution in the extracellular space. The size of the extracellular space was significantly increased in the S rats, but there was no difference in the size of the compartment of L-[^{3}H]norepinephrine efflux between S (6.4 ± 1.2 ml/g) and R (3.7 ± 0.7 ml/g) rats. These data indicate that impaired accumulation and efflux of norepinephrine by the lungs does not contribute to the pathogenesis of hypertension in Dahl S rats.

The sympathetic nervous system and circulating catecholamines have long been known to be involved in the regulation of arterial blood pressure, and thus have been implicated in the pathogenesis of hypertension. In the 1960s, Dahl *et al.* (1) developed two strains of rats with markedly different genetic propensities for development of hypertension during excess salt intake. The salt-hypertension-susceptible (S) strain of the Dahl rats exhibit characteristics similar to those of human hypertension and have therefore been used as an animal model in the study of this disease (2, 3). The pathogenesis of the hypertension of Dahl S rats has not been fully elucidated, but several lines of evidence implicate the importance of the sympathetic nervous system (2, 4–6) and catecholamines (7, 8) in the development and/or maintenance of the elevated arterial pressure in this model.

The postulated mechanisms by which an alteration in adrenergic function can cause or sustain high blood pressure include (i) an increased vascular reactivity to norepinephrine due to either an increased sensitivity of the vascular smooth muscle to norepinephrine (9) or to an increase in wall tension developed in response to norepinephrine (10), (ii) increased synthesis (11) or release (12) of norepinephrine from sympathetic nerve terminals, and (iii) a decrease in the inactivation of norepinephrine via impaired uptake or metabolism of the amine (9, 13–19). Takeshita and Mark (4) demonstrated that Dahl S rats fed a high-salt diet have greater vascular responses to sympathetic nerve stimulation compared with those of the salt-resistant (R) rats. These findings suggest that S rats have a greater sensitivity to released neurotransmitter that may result from reduced inactivation of norepinephrine released from or available to nerve endings (13).

The purpose of this study was to determine if the pulmonary vascular inactivation of norepinephrine is altered in the Dahl model of genetic hypertension. Inactivation of norepinephrine by the lungs was examined because it is quantitatively important in modifying the concentration of circulating norepinephrine (20), and a neuronal uptake mechanism may be important in this process (21). Pulmonary vascular inactivation of norepinephrine involves uptake of the amine by a carrier-mediated transport process and subsequent metabolism by both monoamine oxidase (MAO) and catechol-*O*-methyltransferase (COMT) (22). The initial and apparently rate-limiting step in the pulmonary

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inactivation of norepinephrine is its uptake by the lungs (23, 24). Previous experiments have shown that an estimate of the original distribution of labeled norepinephrine taken up into various tissue compartments can be obtained by compartmental analysis of the efflux curves from tissue pretreated to inhibit norepinephrine-metabolizing enzymes (21, 25–27). When MAO and COMT are inhibited, the half-time for the approach to steady-state accumulation of norepinephrine in tissue during exposure to the amine equals the half-time for efflux of the amine (25, 26). Therefore, we evaluated pulmonary norepinephrine accumulation in inbred Dahl S and R rats by performing a compartmental analysis of the efflux of L-[^{3}H]norepinephrine from isolated perfused lungs pretreated to block metabolism of norepinephrine. Our data suggest that a decrease in the pulmonary vascular accumulation and efflux of norepinephrine does not contribute to the pathogenesis of hypertension in the Dahl model.

Material and Methods. *Isolated lung preparation.* Male inbred Dahl S and R rats were obtained at the time of weaning from the colony of Dr. John P. Rapp, Medical College of Ohio, Toledo, Ohio. The official designation of these inbred Dahl rats is SS/Jr and SR/Jr for the S and R rats, respectively (28). The rats were housed in individual cages, and maintained in the Animal Research Facility in a controlled temperature, humidity, and light environment. After weaning, the rats were placed on a high salt diet (8% sodium chloride per dry wet; Teklad Test Diets, Madison, WI; Diet TD 82050) for a 3-week period. Potassium chloride content in the chow was 0.79%. Tap water was provided for drinking *ad libitum.*

For isolation and perfusion of the lungs, the rats were anesthetized with pentobarbital sodium (50 mg/kg, ip) and given heparin (500 U iv) to prevent clotting. A tracheostomy was performed, and the lungs were ventilated with a humidified gas mixture of 95% O_2–5% CO_2, delivered at a rate of 80 cycles/min and a tidal volume of 2 ml (Harvard Apparatus Model 680 respirator, Millis, MA). The femoral artery was cannulated with PE 50 tubing for direct measurement of arterial blood pressure using a strain gauge transducer (Statham Instruments Model P23Db, Puerto Rico). Arterial pressure was recorded on a Sensormedics dynograph (Model R611, Anaheim, CA).

A midline thoracotomy was performed and the pulmonary artery was cannulated *in situ* through an incision in the right ventricular wall. After constant flow perfusion of the lungs was initiated (Masterflex Pump Model 7013, Cole-Parmer, Chicago, IL) at 7.5 ml/min, the lungs were carefully removed from the animal and suspended in a jacketed chamber maintained at 37°C with a recirculating water bath. Perfusion pressure was measured continuously with a Statham P23Db pressure transducer and recorded on the Sensormedics dynograph.

The lungs were perfused initially in a nonrecirculating system for approximately 10–15 min with a Krebs–bicarbonate solution to wash the blood out of the lungs. The Krebs solution had the following composition: 117 m*M* NaCl, 4.7 m*M* KCl, 2.5 m*M* $CaCl_2$, 1.2 m*M* KH_2PO_4, 1.2 m*M* $MgSO_4$, 24.4 m*M* $NaHCO_3$, 10 m*M* glucose, 0.03 m*M* disodium ethylenediamine tetraacetate (EDTA), 0.28 m*M* ascorbic acid, and 4.5% bovine serum albumin (Pentex, Fraction V, Miles Laboratories, Elkhart, IN) in glass-distilled water. The solution was adjusted to pH 7.4, maintained at 37°C, and equilibrated with an atmosphere of 95% O_2–5% CO_2.

Efflux studies. Following the initial washout, the lungs were treated to block NE metabolism. The lungs were perfused for 10 min with Krebs solution containing 100 μM pargyline (Sigma Chemical Co., St. Louis, MO) to inhibit MAO (21, 29, 30). Because pargyline is an irreversible MAO inhibitor, the pargyline pretreatment was followed by a 10 min washout with Krebs solution. Next, 100 μM U-0521 (3′,4′-dihydroxy-2-methyl-propriophenone, Upjohn Co., Kalamazoo, MI) was infused for 10 min to inhibit COMT (21, 30). U-0521 was present in the perfusion solution throughout the rest of the experiment.

Following pretreatment, the lungs were perfused with Krebs solution containing 0.3 μM L-[^{3}H]norepinephrine (New England Nuclear, Boston, MA) in a recirculating system with a 50 ml volume. The solution also contained [^{14}C]sorbitol (0.1 μCi/ml, New

England Nuclear, Boston, MA) as a tracer for extracellular space. The recirculating perfusion was continued for 30 min so that a steady-state concentration of the tracers was achieved (21). A sample of the perfusion solution was taken at the end of the recirculation time to determine the concentrations of [^{14}C]sorbitol and [^{3}H]norepinephrine in the perfusate at time 0 of efflux. The lungs were then washed out with tracer-free Krebs solution at a flow rate of 7.5 ml/min for 30 min. The venous effluent was collected every 3 sec from 0 to 2 min, every 6 sec from 2 to 5 min, and every 15 sec from 5 to 30 min for a total of 170 efflux samples.

The lungs were then weighed and homogenized in chilled 0.4 *M* perchloric acid. After centrifugation at 10,000g for 10 min, the supernatant was analyzed by liquid scintillation spectrometry to determine the amount of [^{14}C]sorbitol and L-[^{3}H]norepinephrine remaining in the tissue. An aliquot of the sample was added to 10 ml of Triton X-100 counting solution [6 g 2,5-diphenyloxazole (PPO), 0.4 g *p*-bis[2-(4-methyl-5-phenyloxazolyl)]benzene (dimethyl-POPOP), and 352 g Triton X-100 per liter of toluene] and counted in a Packard Model 4530 spectrometer. Quench correction was by internal standardization.

The total amount of each tracer in the tissue at the beginning of the efflux protocol was calculated from the sum of the amount of the tracer remaining in the tissue at the end of the efflux and the amount of the tracer in each of the efflux samples. The tissue level of the tracer at each sampling interval was then calculated by sequentially subtracting the amount of tracer in each efflux sample from the tissue level at the previous sampling interval. These values were then plotted vs the time of efflux.

A compartmental analysis was performed on the efflux curves so prepared as previously described (21). The best-fit kinetic constants were obtained for the set of n first-order linear differential equations

$$Y = X_1[\exp(-\lambda_1 t)] + X_2[\exp(-\lambda_2 t)] + \cdots + X_n[\exp(-\lambda_n t)],$$

where Y is the tissue level of the tracer at time t and n is the number of exponential terms (compartments). The exponent (λ_i) of each term was interpreted as the individual efflux rate constant (k_i) for compartment i. The $t_{1/2}$ of compartment i was calculated as $(\ln 2)/k_i$. The coefficient (X_i) of each exponential term was treated as the quantity of material in compartment i, which was divided by the concentration of the substance at time 0 of efflux to obtain the volume of compartment i. This volume was expressed as a fraction of blotted lung weight to give compartment size in milliliters per gram.

Compartmental analysis was performed using nonlinear least-squares regression analysis with a computer program (BMD P3R) written at the Health Science Computing Facility, University of California, Los Angeles (Grant RR3). The computer program provided the best estimate of each parameter and an asymptotic standard deviation of each parameter estimate. The standard deviation is an estimate of the precision with which that parameter can be determined from the given data set. Coefficients of variation of the parameter estimates were determined from the values of the standard deviations expressed as a percentage of the parameter estimate.

Student's t test for nonpaired values was used to compare the mean values of the total [^{14}C]sorbitol space, total L-[^{3}H]-norepinephrine space, and the size and rate of efflux for each compartment of norepinephrine efflux between lungs of S and R rats. Statistical significance was taken at $P < 0.05$. Grouped data are presented as means ± 1 SE.

Results. Table I summarizes some of the physical characteristics of the rats studied. Following 3 weeks of high salt intake, mean arterial pressure was significantly elevated in salt-sensitive compared to salt-resistant rats. The S rats appeared otherwise healthy, and there was no difference in body weight between the S and R rats. The lung-to-body weight ratios of the two groups were not different, and were within the range of previously reported normal values (21, 31). There were no differences in the perfusion pressures of lungs from S vs R rats, and the absolute pressure values indicate the soundness of the perfused lung preparations. Although the lungs of S rats did not differ from

TABLE I. CHARACTERISTIC VARIABLES OF INBRED DAHL SALT-SENSITIVE (S) AND SALT-RESISTANT (R) RATS AFTER 3 WEEKS OF HIGH SALT INTAKE

	R rats (n = 6)	S rats (n = 6)
Body wt (g)	239 ± 6	221 ± 13
Mean blood pressure (mm Hg)	104 ± 7	142 ± 5*
Lung wt/body wt (%)	0.91 ± 0.004	0.74 ± 0.001
Lung perfusion pressure (mm Hg)		
Initial	8 ± 2	5 ± 1
Final	11 ± 3	6 ± 1
ΔP	3 ± 1	1 ± 1
[^{14}C]Sorbitol space (ml/g lung wt)	0.76 ± 0.11	1.67 ± 0.33*

Note. Values are means ± SE.
* $P < 0.05$.

those of R rats in their tendency to accumulate fluid during perfusion, the volume of the [^{14}C]sorbitol space (marker for extracellular space) was significantly increased in S rats.

Table II summarizes the results of the compartmental analysis of L-[^{3}H]-norepinephrine efflux from the perfused lungs. In both S and R rats, the efflux curves of L-[^{3}H]norepinephrine content in the lungs vs time were best described by a single exponential compartment system. The compartment parameters were estimated with coefficients of variation approximating 1% for the coefficients (compartment size) and less than 3% for the exponents (rate of efflux). In general, a coefficient of variation of about 5% is considered very good for biological data (32); thus, the parameter estimates were precise for each individual experiment. Radiolabeled norepinephrine was accumulated into a slowly equilibrating compartment with a size greater than that for [^{14}C]sorbitol. There was no difference in the half-times of L-[^{3}H]-norepinephrine efflux from the lungs of S and R rats, and the average $t_{1/2}$ was approximately 23 min. Likewise, there was no significant difference in the size of the pulmonary vascular norepinephrine compartment between S and R rats (P = 1.09). This was true when the compartment size was evaluated independently or when expressed as the ratio of L-[^{3}H]norepinephrine space to [^{14}C]-sorbitol space.

Discussion. The uptake of norepinephrine constitutes a major means of inactivation of this amine (33). A decrease in the efficiency of the uptake mechanisms responsible for inactivation of norepinephrine would increase the amount of norepinephrine in the biophase resulting in a tendency for blood pressure to increase. Thus, impaired norepinephrine uptake has been examined as a possible factor contributing to the pathogenesis of several models of hypertension (13–17, 19, 31).

The pulmonary circulation has the potential to regulate the concentration of norepinephrine in the arterial blood because of its large capacity to take up and metabolize circulating norepinephrine (20, 22). Alteration in the magnitude of the removal of norepinephrine by the lungs has been reported in pulmonary hypertension (34, 35), in monocrotaline-induced lung injury (36), and in spontaneously hypertensive rats (31).

The purpose of this study was to determine whether the pulmonary vascular accumulation of norepinephrine is decreased in the Dahl model of genetic salt-susceptible hypertension. We are unaware of any previous studies of norepinephrine uptake in Dahl rats, although it has been postulated that changes in norepinephrine uptake may contribute to the increased neurogenic tone (13) and to the intrarenal distribution of norepinephrine (7) in Dahl S rats. Also, decreased norepinephrine uptake has been reported in heart and vascular tissue in other models of salt-dependent hypertension (13, 14, 17).

TABLE II. PARAMETER ESTIMATES FOR A SINGLE COMPARTMENT OF L-[^{3}H]NOREPINEPHRINE (NE) EFFLUX FROM PERFUSED LUNGS OF DAHL SALT-SENSITIVE (S) AND SALT-RESISTANT (R) RATS

Strain	$t_{1/2}$ (min)	Size (ml/g)	NE space/ sorbitol space*
R	24.8 ± 1.5	3.7 ± 0.7	5.22 ± 2.45
S	22.1 ± 3.2	6.4 ± 1.2	4.16 ± 1.32

Note. Values are means ± S.E.
* Ratio of size of norepinephrine compartment (ml/g) to size of the extracellular space (ml/g).

In the present study, norepinephrine accumulation was evaluated by performing a compartmental analysis of the efflux of L-[^{3}H]norepinephrine from isolated perfused lungs of Dahl rats after inhibition of norepinephrine-metabolizing enzymes (21, 25–27). Our data indicate that norepinephrine is taken up by one slowly equilibrating compartment with an efflux half-time of approximately 23 min. No differences were detected in the amount or rate of norepinephrine efflux from the lungs of hypertensive (S) vs normotensive (R) rats. These findings indicate that the pulmonary accumulation and efflux of norepinephrine does not contribute to the pathogenesis of hypertension in inbred Dahl S rats.

Although the pulmonary disposition of norepinephrine has not been studied previously in the Dahl rats, Roth and Wallace (31) found that the lungs from spontaneously hypertensive rats (SHR) removed significantly more norepinephrine than lungs from normotensive controls. In the present study, there also seemed to be a tendency for an increased size of the norepinephrine compartment in S rats; this may have been related to the distribution of norepinephrine in the extracellular space which was increased in the S rats because the apparent differences between S and R rats were not evident when the norepinephrine space was normalized to the size of the extracellular ([^{14}C]sorbitol) space.

The increase in the extracellular space of S rats on a high salt diet is consistent with the findings of an increase in plasma and total blood volumes in S rats by Overbeck *et al.* (37). However, those investigators did not detect a change in the extracellular fluid volume of S rats. We do not attribute the increased extracellular space in the S rats to excessive fluid accumulation from the perfusion because there was no associated increase in lung perfusion pressures or lung weight and no visible signs of pulmonary edema.

Pulmonary vascular accumulation of norepinephrine may include uptake into both neuronal and extraneuronal tissue. In several models of salt-dependent hypertension, LeLorier *et al.* (14) demonstrated that norepinephrine uptake was decreased in vascular tissues, but increased in extravascular tissue. It is possible that the neuronal uptake process in the lungs is impaired in S rats, but is compensated for by an increase in extraneuronal norepinephrine transport. Our data do not differentiate between the contributions of neuronal and extraneuronal uptake, and we were unable to identify two norepinephrine compartments despite our attempts to force such a model by specifying initial estimates appropriate for efflux rates from neuronal vs extraneuronal sites. Examination of the compartmental analysis in the presence and absence of known inhibitors of neuronal vs extraneuronal uptake would help to resolve this question. Nonetheless, in the present study, the compartment efflux half-time of 23 min is faster than that we previously found in normotensive Sprague–Dawley rats (21), and has a value closer to that previously reported for extraneuronally accumulated norepinephrine (25, 27). If there is a compensatory increase in extraneuronal uptake in the Dahl rats, however, it is likely a function of the high salt intake because the efflux half-time was comparable in both S and R rats. This suggestion is consistent with previous studies in spontaneously hypertensive rats by Ely *et al.* (12) who concluded that a high salt diet reduces norepinephrine stores in adrenergic nerves.

Finally, our data only examine the contribution of uptake (accumulation) mechanisms to norepinephrine inactivation in the pulmonary circulation because the lungs were pretreated to block norepinephrine metabolism. These studies reveal that the pulmonary vascular accumulation of norepinephrine is not different between S and R rats. The metabolic fate of norepinephrine subsequent to uptake in the lungs should also be investigated in Dahl S and R rats during high salt intake in order to rule out any contribution of pulmonary vascular norepinephrine inactivation to the genesis or maintenance of the hypertension in this model.

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