CLIN. AND EXPER.-THEORY AND PRACTICE, A6(9), 1543-1558 (1984)

LOW SODIUM DIET AUGMENTS PLASMA AND TISSUE CATECHOLAMINE LEVELS IN PITHED RATS

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Key words: Dietary sodium, Sympathetic nervous system, Plasma catecholamines, Tissue catecholamines, Adrenal catecholamines, Norepinephrine

ABSTRACT

Plasma and tissue (cardiac, vascular, renal, and adrenal) catecholamine concentrations were measured in pithed male Wistar rats maintained on low (10 mEq/kg diet), basal (115 mEq/kg diet), or high (1200 mEq/kg diet) sodium test diets for five weeks. Significant differences in catecholamine disposition were observed only in response to sodium restriction; responses to basal and high sodium intakes were consistently similar. Baseline plasma catecholamine levels ($p < 0.01$) as well as those in response to stimulation of the entire sympathetic outflow at 4 Hz were markedly enhanced in low sodium rats ($p < 0.001$). The facilitation of stimulation-induced increments in plasma norepinephrine levels in low sodium rats may be related to the finding that norepinephrine content was also elevated in noradrenergically innervated tissues (atria, ventricles, mesenteric artery, and kidneys) ($p < 0.01$). Adrenal catecholamine levels, however, were not affected by dietary sodium restriction. Despite the peripheral catecholamine changes associated with a low sodium intake, pressor and tachycardic responses to sympathetic nerve stimulation were similar across dietary sodium groups. The results indicate that a low sodium intake enhances plasma and tissue catecholamine levels, adaptations that may be important in the maintenance of sympathetic responsiveness.

0730-0077/84/0609-1543$3.50/0

INTRODUCTION

Numerous adaptations occur during changes in the state of sodium balance that preserve circulatory homeostasis. The alterations produced by dietary sodium in hormonal control mechanisms such as the renin-angiotensin system and aldosterone release have been well characterized (7,10). Little is known, however, about the interactions between dietary sodium and another system important in the maintenance of cardiovascular function, the sympathetic nervous system.

One approach used to assess the effects of dietary sodium on sympathetic activity has been to measure plasma and urinary catecholamine levels. In clinical studies, plasma (16,17,18, 24,27) and urinary (1,13,27) catecholamine levels were reported to be elevated in individuals on a low sodium diet. The influence of a high sodium diet on catecholamine levels is less clear. No change (27), an increase (2,9,19,25), and a decrease (18) in plasma and urinary catecholamines have been reported.

Dietary sodium has also been observed to affect the capacity of sympathetic neurons to store norepinephrine although the results of such experiments have been equivocal. A low sodium intake resulted in a disappearance of norepinephrine from nerve terminals (15) and a reduction in cardiac norepinephrine content (6). In contrast, cardiac norepinephrine content was shown to be elevated in normotensive rats maintained on a low sodium diet plus a diuretic (5). In a preliminary study, we reported that cardiac norepinephrine levels were increased in rats maintained on a low sodium diet (4).

In view of the existing uncertainty regarding the effects of dietary sodium intake on catecholamine disposition, the present experiments were undertaken with the following two major objectives: first, to evaluate the effects of dietary sodium on tissue catecholamine content; and second, to investigate the influence of sodium intake on the increments in plasma catecholamines elicited by stimulation of sympathetic neurons using the pithed rat as the experimental model.

METHODS

General

Male Wistar rats (Hilltop Laboratories, Scottdale, PA), weighing 200-225 g upon arrival, were housed in animal quarters maintained at 23°C, with a 12 hr light-dark cycle. Animals were randomly assigned to a low (10 mEq/kg diet), basal (115 mEq/kg diet), or high (1200 mEq/kg diet) sodium test diet (Ralston Purina, Co., St. Louis, MO) for five weeks.

Pithed Rats

After five weeks on the test diets, rats were treated with atropine, 1.0 mg/kg, i.p. and anesthetized with ether. After tracheal cannulation, animals were respirated with room air using a Palmer rodent respirator set at a volume of 1 ml/100 g body weight at a rate of 100 strokes/min. Rats were pithed by passing a stainless steel pithing rod through the right orbit and down the spinal column (8). The pithing rod was insulated with teflon except for a 9 cm section at the tip to allow for stimulation of preganglionic neurons in the thoracolumbar region of the spinal cord. A second stainless steel rod passed subcutaneously from the left shoulder to the left hindlimb served as the indifferent electrode. Body temperature was maintained at 37°C by a heating lamp and monitored with a rectal thermometer (Yellow Springs Instrument Co., Model 44TG, Yellow Springs, OH). Cannulae (PE-50 polyethylene tubing) were inserted into the jugular vein for administration of drugs and into the carotid artery for collection of blood samples and blood pressure measurement. Blood pressure and heart rate were recorded continuously on a Grass Model 7 polygraph (Grass Instrument Co., Quincy, MA). Skeletal muscle paralysis was sustained with gallamine triethiodide, 20 mg/kg, i.v.

The preganglionic neurons were stimulated at a single frequency of 4 Hz (50 V, 1 msec impulse duration) for a duration of 40 sec. The frequency of stimulation was selected from the

linear portion of the frequency-blood pressure response curve (0.25 - 8.0 Hz) (3). In addition, it has been previously reported that a similar frequency, 3.0 Hz, produced increments in plasma catecholamines that were easily detectable (29).

During the course of the experiment, three blood samples (1 ml) were obtained from the carotid cannula for the determination of plasma catecholamine levels: (1) after completion of all surgical procedures when the preparation had stabilized (defined as a stable blood pressure and heart rate for 15 min, control 1); (2) during the last 20 sec of a 40 sec stimulation at 4 Hz; (3) 10 min after stimulation (control 2). Immediately after each sampling, heparinized donor blood (1 ml) was infused into the jugular cannula.

After withdrawing the third blood sample, the tissues were removed and immediately frozen in a dry ice-acetone bath for determination of catecholamine content. The tissues selected for analysis were atria, ventricles, mesenteric artery, kidneys, and adrenals. A separate experiment was conducted to control for differences among the diets that might be attributable to the pithing procedure. Intact rats maintained on low, basal, or high sodium test diets for five weeks were decapitated and the same tissues removed for determination of catecholamine content.

Assay of Plasma Norepinephrine and Epinephrine

During the blood sampling protocol outlined above, blood samples were collected from carotid artery cannulae by free flow in iced glass tubes containing 20 ul/ml of 0.20 M glutathione and 0.24 M EGTA. Samples were centrifuged at 5000g for 10 min at 4°C and aliquots of supernatant were stored at -20° C until assayed. Plasma was assayed for norepinephrine and epinephrine according to the method of Passon and Peuler (1973) as utilized in a commercially available radioenzymatic assay kit (Cat-A- Kit, Upjohn, Kalamazoo, MI). Briefly, four 50 ul aliquots of plasma (two of which contained internal catecholamine standard) were incubated at 37°C for 1 hr with catechol-O-methyl-transferase and

S-adenosyl-methionine-(^{3}H-methyl). The resulting ^{3}H-labeled-O-methylated catecholamines were extracted into toluene-isoamyl alcohol (3:2) and then into 0.1 M acetic acid. The tritiated products were separated by thin layer chromatography, the appropriate areas identified under ultraviolet light and scraped into counting vials. After periodate oxidation of the tritiated O-methylated catecholamines to vanillin and extraction into phosphor-containing toluene, the tritium content was determined by liquid scintillation spectrometry. The values obtained for each internal standard were used to calculate the endogenous catecholamine content in that respective sample. Values are expressed as pg/ml of plasma.

Assay of Tissue Norepinephrine and Epinephrine

Atria, ventricles, mesenteric artery, kidneys, and both adrenals were assayed for norepinephrine and epinephrine using high performance liquid chromatography with electrochemical detection, according to a method modified from Keller et al. (1976). Tissues were weighed and homogenized in 0.2 M perchloric acid containing 3 mM sodium metabisulfite and 10 mM EDTA. Homogenization was carried out on ice for 30 sec using a polytron homogenizer (Brinkmann Inst., Westbury, NY). After a 10 min centrifugation at 15,000 g, the supernatant was frozen at -20° C until assayed. At the time of assay, aliquots of supernatant and internal standard, 3,4-dihydroxybenzylamine, in 0.1 M perchloric acid were eluted onto alumina at pH 8.6 and desorbed with 0.1 M perchloric acid. An appropriate volume of eluate was injected onto the liquid chromatographic column. Separation of catecholamines was achieved using a C18 reverse phase column with the mobile phase being an aqueous solution of methanol (9.4%), acetate (5.0%), citrate (2.5%), octyl sodium sulfate (0.6%) as the counter ion, and EDTA (0.4%). Detection is based on the current produced when the separated catecholamines are oxidized during exposure to a glassy carbon electrode (+0.72 V vs the Ag/AgCl reference electrode). Catecholamines were quantified by

comparing the relative heights of the sample and internal standard peaks to the appropriate standards treated in the same way. Results are expressed as ug/g fresh tissue weight, except the adrenal (total ug in both adrenals).

Statistics

The presence of statistically significant differences among dietary sodium groups was determined by one-way analyses of variance. In the event of a significant main effect, differences between pairs of means were evaluated using the Scheffe test for multiple comparisons. Results are presented as mean ± S.E.

RESULTS

Maintenance on a low or high sodium diet for five weeks did not affect normal growth as evidenced by similar body weights in the three groups (low 405 ± 4, basal 423 ± 8, high 408 ± 10).

Effects of Dietary Sodium on Blood Pressure and Heart Rate in the Pithed Rat

During control periods 1 and 2, blood pressures and heart rates were not significantly different in low, basal, or high sodium rats (figure 1). Moreover, the blood pressure and heart rate increases in response to stimulation at 4 Hz were similar among the sodium groups (figure 1).

Effects of Dietary Sodium on Plasma Catecholamines in the Pithed Rat

During control period 1, norepinephrine levels were significantly elevated in low as compared to basal but not high sodium rats (figure 2). In addition, there were no significant differences between the basal and high sodium groups. The same relationships were observed during the second control period. Epinephrine levels were significantly higher in low than in basal and high sodium rats during control periods, while epinephrine levels were similar in basal and high sodium animals (figure 2).

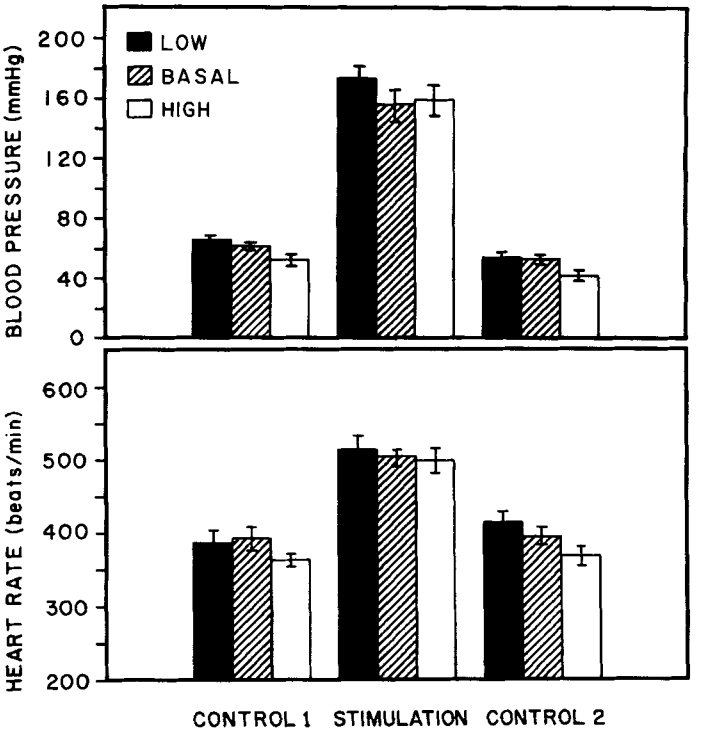

FIG. 1. Control and stimulated (4 Hz, 50 V for 40 sec) mean arterial blood pressures and heart rates in pithed rats. Animals were maintained on low, basal, or high sodium test diets (n=7/diet) for five weeks.

In response to sympathetic stimulation, plasma catecholamine levels increased significantly above the control levels in all three dietary sodium groups (figure 3). However, the increments in both norepinephrine and epinephrine were significantly greater in low sodium in contrast to animals on the basal and high sodium diets. In fact, the norepinephrine level during stimulation in low sodium rats was 168% higher than in basal and 116% higher than in high sodium rats. The epinephrine level during stimulation in low sodium rats was increased 130% over basal and 111% over high sodium rats.

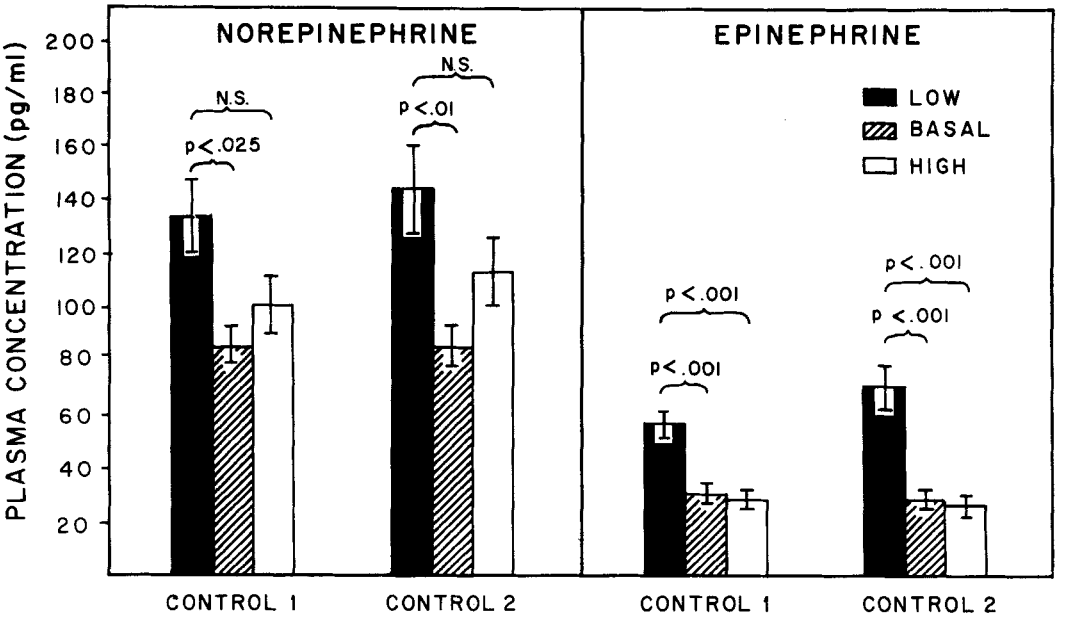

FIG. 2. Control (unstimulated) plasma norepinephrine and epinephrine concentrations in pithed rats. Animals were maintained on low, basal, or high sodium test diets (n=7/diet) for five weeks.

Effects of Dietary Sodium on Tissue Catecholamines in the Pithed Rat

Norepinephrine content in atria, ventricles, kidneys and mesenteric arteries was significantly elevated in low sodium in comparison to basal or high sodium animals (Table 1). There were no significant differences between basal and high sodium animals. Across the tissues, the average increase in low above basal sodium rats was 60%. The finding of elevated tissue content in the low sodium group could not be attributed to the pithing procedure, since the relationship among sodium groups was maintained in rats that were sacrificed by decapitation (intact groups).

In contrast to norepinephrine in these tissues, adrenal norepinephrine and epinephrine contents were not affected by dietary

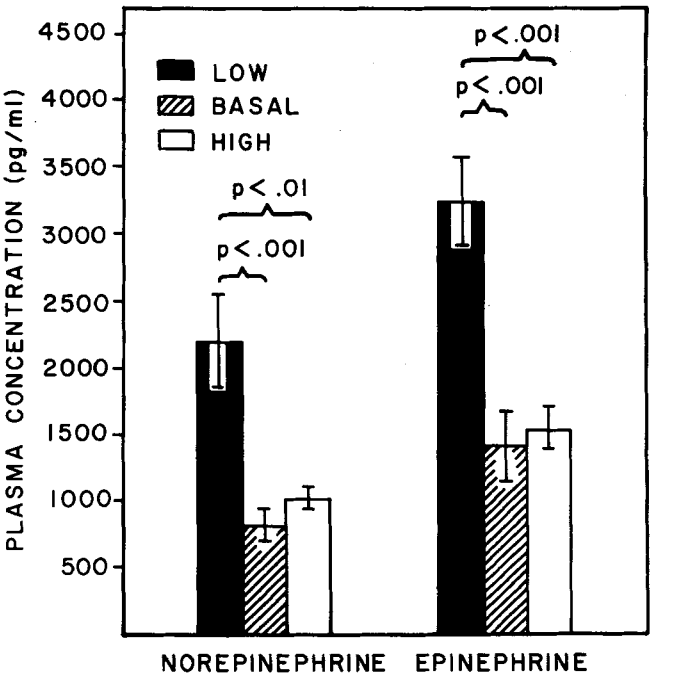

FIG. 3. Stimulated (4 Hz, 50 V for 40 sec) plasma norepinephrine and epinephrine concentrations in pithed rats. Animals were maintained on low, basal, or high sodium test diets (n=7/diet) for five weeks.

sodium intake (Table 1). Similar values for each catecholamine were obtained across diets as well as in the intact and pithed states.

DISCUSSION

The results of the present study provide evidence that catecholamine disposition in the peripheral sympathetic nervous system is sensitive to the chronic level of dietary sodium intake. Two major alterations in catecholamine disposition were observed. First, a low dietary sodium intake was associated with elevated tissue norepinephrine levels and, second, the increments

TABLE 1

Tissue Catecholamine Content (± S.E.) in Pithed and Intact Rats Maintained on Low, Basal, or High Sodium Test Diets for Five Weeks, n=7/Dietary Group in Pithed Rats; n=8/Dietary Group in Intact Rats

		DIET			p VALUES	
TISSUE	GROUP	LOW (LS)	BASAL (BS)	HIGH (HS)	LS vs BS	LS vs HS
ATRIAL NE (ug/g)	PITHED	3.29 ± 0.31	1.94 ± 0.19	1.90 ± 0.27	.01	.01
	INTACT	2.50 ± 0.31	1.51 ± 0.11	1.70 ± 0.11	.01	.05
VENTRICULAR NE (ug/g)	PITHED	1.04 ± 0.07	0.65 ± 0.05	0.67 ± 0.05	.001	.001
	INTACT	0.78 ± 0.03	0.64 ± 0.05	0.63 ± 0.03	.05	.05
KIDNEY NE (ug/g)	PITHED	0.19 ± 0.01	0.12 ± 0.01	0.12 ± 0.01	.001	.001
	INTACT	0.16 ± 0.01	0.11 ± 0.01	0.10 ± 0.01	.001	.001
MESENTERIC ARTERIAL NE (ug/g)	PITHED	16.22 ± 2.79	10.63 ± 2.01	7.24 ± 0.94	N.S.	.05
	INTACT	14.25 ± 2.32	8.07 ± 1.36	9.75 ± 2.04	.05	N.S.
ADRENAL NE (ug in both glands)	PITHED	7.70 ± 1.09	6.11 ± 0.87	7.07 ± 1.10	N.S.	N.S.
	INTACT	6.37 ± 0.74	6.24 ± 0.83	5.47 ± 0.64	N.S.	N.S.
ADRENAL EPI (ug in both glands)	PITHED	29.93 ± 2.08	26.64 ± 1.69	27.16 ± 4.10	N.S.	N.S.
	INTACT	25.65 ± 1.65	28.59 ± 1.55	23.18 ± 0.73	N.S.	N.S.

in plasma levels of norepinephrine and epinephrine resulting from stimulation of the entire sympathetic outflow in pithed rats were markedly enhanced in low sodium rats.

Tissue norepinephrine levels measured in atria, ventricles, mesenteric artery, and kidneys were consistently elevated in pithed rats maintained on the low sodium diet. A high sodium intake, however, did not alter tissue norepinephrine levels, a finding consistent with previous investigations (5,28). The increases seen in these noradrenergically innervated tissues in response to a low sodium intake could not be attributed to the pithing procedure since comparable increases were evident in the same tissues taken from intact low sodium animals, i.e., animals sacrificed by decapitation.

In a previous study, deChamplain (5) found that the norepinephrine content of cardiac tissue tended to be elevated in rats kept on a sodium restricted diet for three weeks. However, the elevation was only significant if a diuretic, meralluride, was administered in combination with a low sodium intake. Our study extends these observations by indicating that a low sodium diet alone is capable of causing a significant increase in norepinephrine content. Moreover, the increases in norepinephrine content were found in other noradrenergically innervated tissues in addition to the heart. A possible reason that a low sodium intake alone elicited such a marked effect was that the animals in the present study were kept on the diets for a longer period of time, five weeks.

In addition to the alterations in tissue norepinephrine levels, both baseline and stimulated plasma catecholamines were affected by dietary sodium intake. Plasma catecholamines were measured in the pithed rat so that the variable influence of tonic neuronal discharge could be eliminated through the destruction of the brain and spinal cord during placement of the pithing rod. Baseline norepinephrine and epinephrine concentrations in plasma were markedly higher in low than in basal or high sodium rats; no difference between the basal and high sodium groups was

seen. Moreover, plasma catecholamine increments in response to sympathetic nerve stimulation were also increased by a low sodium intake. The plasma norepinephrine level during sympathetic stimulation in low sodium rats was 168% greater than in basal and 116% greater than in high sodium rats. Similarly, the plasma epinephrine level during stimulation in low sodium rats was 130% greater than in basal and 111% greater than in high sodium rats. There were no differences in plasma catecholamine increases to nerve stimulation between basal and high sodium rats.

The observations that both baseline and stimulated levels of plasma catecholamines were augmented in low sodium animals may be of clinical significance since similar findings of increased catecholamine levels have been reported in humans maintained on a low sodium intake (16,17,18,24,27). In these clinical studies, it was not determined if the enhanced plasma catecholamine levels simply reflected an increase in central nervous system outflow or a change within the peripheral sympathetic nervous system. In our study it is apparent that the enhanced plasma catecholamine response to nerve stimulation in the low sodium group is due to a modification of peripheral sympathetic neural function since stimulation was conducted at the spinal level near the origin of preganglionic neurons. Although it is quite possible that some change in central nervous system outflow may initiate the peripheral alteration. Moreover, the enhanced plasma norepinephrine response to nerve stimulation in the pithed rat maintained on a low sodium diet may be causally related to the increased norepinephrine content seen in cardiac, vascular, and kidney tissues.

Since all plasma epinephrine originates from the adrenal gland, the results indicate that the low sodium intake enhances both basal and neurally mediated adrenal epinephrine release. The augmentation of the plasma epinephrine cannot be accounted for by enhanced medullary storage since adrenal gland content of both epinephrine and norepinephrine was not different from either basal or high sodium animals. Several endogenously produced

factors, such as bradykinin and angiotensin II, are known to be capable of stimulating adrenal catecholamine release via a direct action on the chromaffin cells (14,21,22,23,26). These findings are of particular interest to the present investigation since a low sodium intake is associated with increased plasma renin activity and, hence, increased angiotensin II formation (11).

Despite the increased plasma catecholamine response to sympathetic stimulation in the low sodium rat, the blood pressure and heart rate responses to stimulation were similar in low and basal sodium animals. This finding is in agreement with a prior study in which stimulation was conducted over a wider range of frequencies (3). The increased release of norepinephrine and epinephrine during stimulation in the low sodium animal may be necessary to maintain blood pressure and heart rates responses. The physiological significance, however, of this increase in catecholamine concentration during nerve stimulation remains to be established.

Low sodium regimens are thought to be generally beneficial in controlling hypertension. Yet the findings of the present study suggest that the augmented catecholamine release produced by a low sodium diet might directionally oppose any blood pressure reduction resulting from dietary sodium restriction. This may represent a normal physiological control mechanism which seeks to preserve blood pressure at a normal level in the face of diminished sodium intake. In this way it would be similar to the activation of the renin angiotensin system which also counters the reduction in blood pressure that can be achieved by dietary sodium restriction.

In summary, these experiments identified two major alterations in peripheral catecholamine disposition that were induced by maintenance on a low dietary sodium intake. 1) Cardiac, vascular, and kidney norepinephrine content were significantly increased and 2) plasma catecholamine responses to stimulation of sympathetic preganglionic neurons were enhanced. The blood pressure and heart rate responses to nerve stimulation, however,

were equivalent in all three dietary sodium groups. Therefore, the increased norepinephrine content and enhanced catecholamine increments to sympathetic stimulation during sodium restriction may represent a physiological adaptation important in maintaining cardiovascular function. It is of further interest that maintenance of animals on a high sodium diet did not measurably alter catecholamine disposition.

ACKNOWLEDGEMENTS

The authors are grateful to Sue Meyers for her technical assistance; to Dr. Robert J. Ertel for his help in the radioenzymatic assay; and to Mrs. Andrea Tassick for her secretarial assistance. These studies were supported in part by the National Institutes of Health, HL-26212.

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