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CARDIAC ADENYLATE CYCLASE, CYCLIC NUCLEOTIDE PHOSPHODIESTERASE AND LACTATE DEHYDROGENASE IN NORMOTENSIVE AND SPONTANEOUSLY HYPERTENSIVE RATS*

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Abstract—To understand altered physiological responses of hypertrophied spontaneously hypertensive rat (SHR) myocardium to beta-adrenergic receptor stimulation *in vivo*, myocardial tissues from SHR, normotensive Wistar (NR) and normotensive Wistar–Kyoto (WKY) rats were analyzed for adenylate cyclase, phosphodiesterase and lactic dehydrogenase. While WKY left ventricular adenylate cyclase activity exceeded that of SHR at low (1 and 5 μM) norepinephrine concentrations, there were no further differences. Norepinephrine stimulation of NR and SHR left ventricular adenylate cyclase was the same. In all rat strains similar responses of adenylate cyclase to glucagon were observed. Cyclic AMP phosphodiesterase activity of whole left ventricular homogenates were not significantly different in NR, WKY or SHR when assayed at either 1 mM or μM cyclic AMP. While it was not possible to entirely explain previous hemodynamic findings *in vivo* on the basis of abnormal cAMP-related enzyme activities, certain other interstrain enzymatic differences were observed. The hypertrophied SHR left ventricle contained higher levels of lactate dehydrogenase (LDH) and an altered isozymic composition as compared to both normotensive strains. These changes may indicate a shift in glycolytic enzyme needs as also seen with artificially produced cardiac hypertrophy. In all rat strains the right ventricular wall has less norepinephrine-stimulatable adenylate cyclase activity and more cyclic AMP phosphodiesterase activity than the left ventricle. These results demonstrate differences in cyclic AMP-related activities between the ventricles and increased LDH activity in the hypertrophied SHR left ventricle.

The spontaneously hypertensive rat (SHR), developed by Okamoto and Aoki [1], represents one of the most widely accepted animal models for essential hypertension in man. Like man with essential hypertension, SHR exhibits abnormal hemodynamic functions and has ventricular hypertrophy [2]. However, varied and sometimes contradictory results have been obtained in experiments concerning the hormonal reactivity of its heart [3–6]. To correlate physiological observation of cardiac function with biochemical activities, we have measured adenylate cyclase, cyclic AMP phosphodiesterase, and lactate dehydrogenase (LDH) activities in SHR and two strains of normotensive rats, the normotensive Wistar (NR) and Wistar–Kyoto (WKY).

Studies in our laboratories and those of others have indicated a lessened cardiac sensitivity *in vivo* to catecholamines or their analogs in terms of inotropic and chronotropic responses [3, 5, 6]. One possible explanation was that cardiac adenylate cyclase, the externally oriented hormone-binding portion of which is generally accepted as the β-adrenergic receptor, may be abnormally insensitive to stimulation by β-adrenergic receptor agonists such as isoproterenol or norepinephrine. Largis *et al.* [4], utilizing isolated perfused hearts from SHR and NR, have reported that there were no differences in either cardiac function or myocardial levels of adenosine 3′:5′-cyclic monophosphoric acid (cAMP) as a function of infused isoproterenol. Glucagon, however, was reportedly less effective with SHR in both the elevation of myocardial cAMP levels and the stimulation of inotropic responses. No differences in cAMP phosphodiesterase activities were found.

Amer *et al.* [7–9], in studies concerned primarily with vascular enzymes, have presented some data concerning cardiac adenylate cyclase and cyclic nucleotide phosphodiesterase activities. SHR cardiac adenylate cyclase was found to have a lesser sensitivity to isoproterenol stimulation [8, 9]. Cardiac cAMP phosphodiesterase activity was higher in the SHR [both low and high K, Michaelis constant (K_m) enzymes], while guanosine 3′:5′-cyclic monophosphoric acid (cGMP) phosphodiesterase was elevated as the high K_m form and normal as the low K_m form [7].

METHODS AND MATERIALS

The physical characteristics of the animals used in these studies are listed in Table 1. We tried to match the animals by age for each group of comparative experiments, but were unable to do so completely because of the limited size of our breeding program. These studies have, however, used SHR and WKY in a stable phase of cardiac performance.

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Table 1. Characteristics of animals studied

Experiment	No.	Strain	Age, weeks ± S. E. M.	Body wt, g ± S. E. M.	Left vent. wt (g) ± S. E. M.	Ratio of left vent. wt, mg / body wt, g
Adenylate cyclase	4	NR	40 ± 3.6	364 ± 34.6	0.733 ± 0.077	2.01
norepinephrine	4	WKY	24 ± 2.6	257 ± 28.3	0.662 ± 0.073	2.58
	5	SHR	33 ± 3.3	219 ± 23.5	0.677 ± 0.071	3.09
Glucagon	3	NR	60 ± 5.7	360 ± 32.4	0.683 ± 0.063	1.90
	3	WKY	54 ± 5.6	281 ± 36.5	0.672 ± 0.087	2.39
	4	SHR	63 ± 7.0	250 ± 35.0	0.820 ± 0.106	3.28
Cyclic AMP	5	NR	38 ± 2	238 ± 5	0.558 ± 0.016	2.34
phosphodiesterase	5	WKY	37 ± 1.5	251 ± 14	0.596 ± 0.051	2.37
	6	SHR	40 ± 0.3	231 ± 9	0.765 ± 0.021	3.31
Lactate dehydro-	3	NR	14 ± 1.6	198 ± 25.7	0.494 ± 0.069	2.49
genase	4	WKY	26 ± 2.4	232 ± 28.2	0.489 ± 0.054	2.11
	4	SHR	16 ± 2.3	188 ± 26.3	0.537 ± 0.059	2.86

Studies have shown that cardiac performance/g of left ventricle is reduced at 83 but not 63 weeks of age, even though the absolute left ventricular wt continually increases [10]. The SHR exhibited a large left ventricular mass/unit of body wt in each age group, indicating a consistent cardiac hypertrophy as a result of hypertension.

Adenylate cyclase. The assay method used in the adenylate cyclase assay was that developed by Krishna *et al.* [11], in which α-^{32}P-labeled adenosine 5′-triphosphate (ATP) is used as a substrate and the radioactive product [^{32}P]cAMP is purified by ion exchange chromatography and zinc sulfate–barium hydroxide precipitation. The enzyme source for the adenylate cyclase experiments was obtained from cardiac tissue of three strains of rats. The heart was removed through a midsternal thoracotomy incision under ether anesthesia and was then placed into a small beaker with 0.25 M sucrose and briefly perfused to wash out residual blood. The right ventricular wall, as well as any attached connective and vascular tissue, was removed, and the entire left ventricle cut into small pieces and placed in a micro VirTis homogenizer; 3.5 ml of 0.25 M sucrose was then added. The heart was then homogenized for three 15-sec intervals, with 1-min cooling time between each interval. After VirTis homogenization the suspension was poured into a 15-ml Dounce homogenizer. An additional 3 ml of 0.25 M sucrose was utilized to wash the VirTis flask and was then added to the Dounce homogenizer. The suspension was then homogenized with approximately fifteen strokes of the pestle. After this homogenization the material was filtered through a small square of cheese cloth into a 15-ml plastic centrifuge tube and centrifuged for 25 min at 10,000 *g*. After centrifugation, the supernatant solution was discarded and the pellet was resuspended in 6.5 ml sucrose. The resuspended pellet was again subjected to fifteen strokes in a Dounce homogenizer. After another centrifugation (15 min at 10,000 *g*), the supernatant solution was discarded and the pellet was resuspended in 2.5 ml sucrose. This resuspended pellet was utilized directly as a source of enzyme. The incubation mixture was composed of 1.33 mM α-^{32}P-labeled ATP (40 dis./min/*p*mole), 1.22 mM (G)-^{3}H-labeled cAMP (500 dis./min/*p*mole), 67 mM phosphocreatine, 13 I.U. creatine phosphokinase/ml, 40 mM tris(hydroxymethyl)aminomethane (Tris) acetate, pH 7.6, 4.4 mM magnesium acetate, and 44 mM caffeine. The final pH of this mixture was verified to assure that it was pH 7.6. This incubation mixture, combined with tissue and test substances where indicated, was incubated for 10 min at 37°. After this incubation the various mixtures were subjected to 100° for 3 min followed by cAMP purification [11]. After the cAMP fractions were collected, they were included in a liquid scintillation mixture (Mallinckrodt–Handi Fluor) and assayed for both tritium and the ^{32}P. The efficiency of the cAMP isolation procedure was calculated from the yields of the [^{3}H]cAMP (50–70 per cent). Under these conditions, [^{32}P]cAMP production was linear within the limits of these experiments. Product cAMP was not chromatographically characterized since the procedure is standard and well documented as valid.

Cyclic nucleotide phosphodiesterase. The experimental procedure utilized here was one which allows a ready measurement of the formation of 5′-mononucleotides from cyclic nucleotides [12]. The hearts were obtained in the same manner as with the adenylate cyclase procedure. After any connective or vascular tissue was trimmed away, the hearts were dissected into three segments: left ventricular wall, septal wall, and right ventricular wall. Each tissue was then scissored into small pieces and homogenized as described in the adenylate cyclase procedure up to the point of centrifugation. The whole homogenates were used in the phosphodiesterase assays. Assays were carried out in triplicate in all cases, as with the adenylate cyclase reactions. The reaction mixture contained 15 mM Tris–Cl, pH 7.4, 5 mM $MgCl_2$, 1 mM or 1 μM cyclic nucleotide (0.5 μCi [(G)-^{3}H]/ml), and 0.1 to 0.3 mg of heart protein preparation all in a 0.5 mg vol. After a 10-min incubation at 37° the reaction was stopped by heating up to 100° for 3 min. This was followed by treatment with *Ophiophagus hannah* venom (0.1 mg) for 10 min at 37°, whereupon the 5′-nucleotidase present converted all 5′-nucleotides to nucleosides. The mixture was then subjected to Dowex 1 chromatography and the radioactive adenosine isolated for measurement. The reaction

rates were linear with time (up to 10 min) and the doses of enzyme utilized in these experiments. For purposes of brevity, cAMP hydrolytic activity at 1 mM substrate is referred to as high K_m phosphodiesterase, and at the near physiological 1 μM concentration as low K_m phosphodiesterase [12].

Lactate dehydrogenase. Lactate dehydrogenase was assayed spectrophotometrically by measuring the oxidation of 0.12 mM reduced β-nicotinamide adenine dinucleotide (NADH) in the presence of soluble heart protein and 0.3 mM pyruvate in 100 mM potassium phosphate, pH 7 [13]. The left ventricular enzyme was prepared by the procedure described for the adenylate cyclase studies, except that the supernatant solution obtained after the first centrifugation was utilized as the enzyme source. Isozyme analyses were performed by a modification of the heat denaturation method of Wroblewski and Gregory [14]. Prior to the heating steps, the cardiac extracts were diluted (1:50) in calf serum which had been heated previously (75°, 39 min) to denature endogenous serum LDH. Dilution in serum was done to make the procedure, developed primarily for serum LDH, analogous for our analyses of cardiac tissue extracts. Each 2-ml serum sample of cardiac extract contained 0.5 mg NADH and was either left unheated or was heated for 30 min at 57 or 65°. Afte rapid cooling, aliquots (10–50 μl) were withdrawn and assayed for LDH activity. The LDH activity of the unheated sample represented total LDH; that lost at 57°, LDH_1; that lost at 65°, LDH_{2-4}; and that remaining after 65°, LDH_5.

RESULTS

Adenylate cyclase. There were only a few significant differences between either the basal or norepinephrine-stimulated left ventricular adenylate cyclase activities in the SHR and two normotensive control strains (Table 2). Namely, the WKY, but not the NR, showed more stimulation than SHR at 1 μM ($P < 0.01$) and 5 μM ($P < 0.05$) norepinephrine. These results also showed no further interstrain differences when expressed as a function of DNA content in the particulate enzyme preparation. Further, fluoride-stimulated adenylate cyclase activities, a reflection of total enzyme potential, were also about the same in each strain. Potassium fluoride was found to give the same stimulation as sodium fluoride in our experiments.

However, when right ventricular adenylate cyclase was assayed in the presence of various norepinephrine levels, it was found to be stimulated less than the enzyme from the left ventricle. All three strains of animals exhibited this decreased right ventricular response to catecholamine stimulation (Figs. 1–3). Whereas the magnitude of norepinephrine-stimulated adenylate cyclase activity was generally lower in the right ventricle, the basal and fluoride-stimulated activities and the levels of norepinephrine which caused minimal and maximal (or near maximal) stimulation were similar.

In studying the glucagon response to cardiac adenylate cyclase we found that, in this age group of rats, while SHR had slightly higher basal adenylate cyclase activity than both normal control groups, the glucagon-stimulated activities were about the same.

Cyclic nucleotide phosphodiesterase. Total cyclic AMP phosphodiesterase was measured in the three cardiac segments at 1 mM and 1 μM substrate concentrations (Table 3). Although the left ventricular high K_m activity appeared somewhat greater in SHR, there were no significant differences present between rat strains for any part of the heart at either high or low cAMP concentrations (i.e. with P less than 0.1). Right ventricular phosphodiesterase activity was, however, significantly greater than left ventricular activity in four of the six comparative experiments.

Lactate Dehydrogenase. The SHR left ventricle contained significantly more LDH activity/mg of protein than either the NR or WKY normotensive controls (Table 4). Significant differences in LDH isozyme composition as percentages of the total enzyme levels were also noted. Specifically, the

Table 2. Stimulation of left ventricular adenylate cyclase activity

Addition	Concn (μM)	(pmoles cAMP*/min/mg protein) NR	SHR	WKY
None		2.55 ± 0.32	2.27 ± 0.19	2.55 ± 0.37
L-Norepinephrine	1.0	4.44 ± 1.20	3.56 ± 0.37†	5.46 ± 0.38
	3.0	5.79 ± 0.88	5.78 ± 0.69	
	5.0	6.02 ± 0.83	6.25 ± 0.65‡	8.52 ± 0.74
	10.0	8.33 ± 1.34	8.84 ± 0.74	9.80 ± 0.76
	30.0	9.07 ± 1.06	10.40 ± 0.59	
	50.0	9.86 ± 1.39	11.41 ± 0.56	13.06 ± 0.97
	100.0	12.74 ± 1.44	11.85 ± 0.93	13.10 ± 0.88
Potassium fluoride	(10 mM)	24.18 ± 4.0	22.27 ± 1.64	25.81 ± 2.82
glucagon	None	2.17 ± 0.24	2.53 ± 0.13	2.38 ± 0.26
	0.1	2.09 ± 0.23	2.52 ± 0.17	2.21 ± 0.19
	1.0	2.53 ± 0.21	3.06 ± 0.23	2.38 ± 0.20
	10.0	4.22 ± 0.36	3.94 ± 0.13	3.60 ± 0.17

* Values for cAMP are expressed as mean ± S. E. M.
† Lower than WKY ($P < 0.01$).
‡ Lower than WKY ($P < 0.05$).

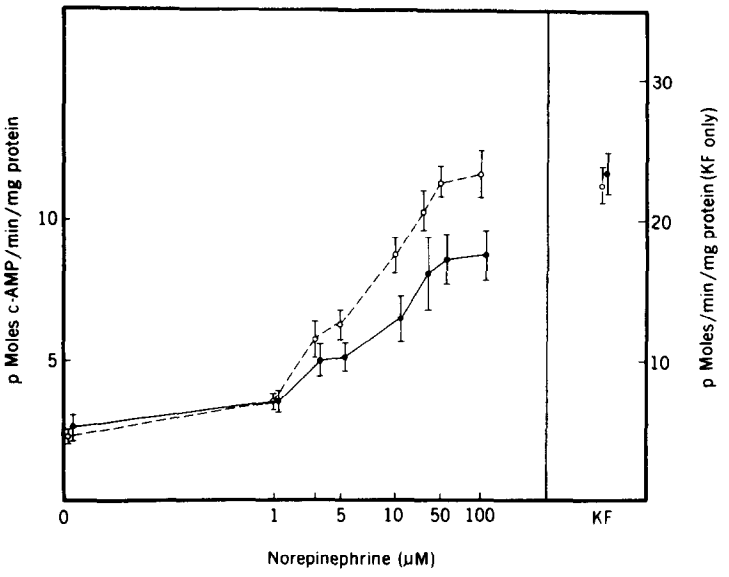

Fig. 1. Norepinephrine stimulation of adenylate cyclase from SHR left ventricle (○) or right ventricle (●). The enzyme activity was measured in the presence of 10 mM potassium fluoride (KF) where indicated.

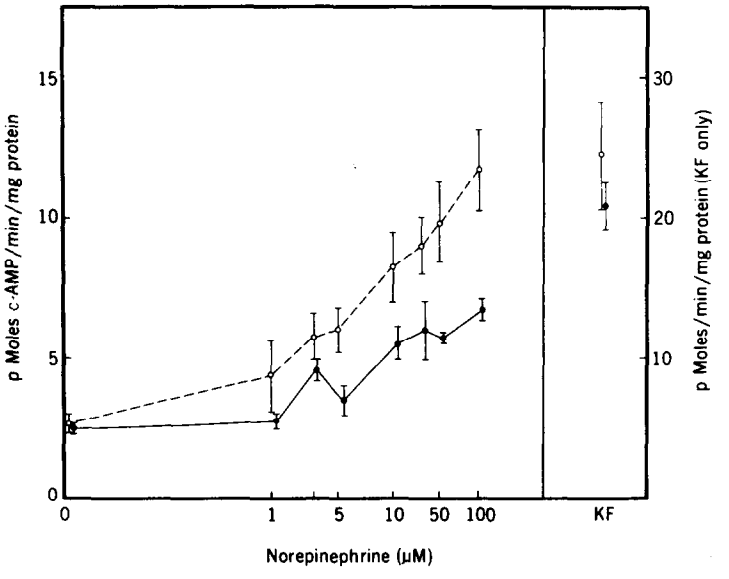

Fig. 2. Norepinephrine stimulation of adenylate cyclase from NR left ventricle (○) or right ventricle (●). The enzyme activity was measured in the presence of 10 mM potassium fluoride (KF) where indicated.

SHR left ventricle demonstrated increased levels of skeletal muscle LDH (LDH_1) isozyme, lowered levels of intermediate forms ($LDH_{2,3,4}$), and no significant changes in the cardiac type (LDH_5) (Table 4).

DISCUSSION

Two normotensive Wistar rat strains were utilized as controls in this investigation since there appear to be physical and hemodynamic differences between them, implying that neither one alone may be a completely appropriate control when investigating hypertension-related biochemical or physiological parameters.

Norepinephrine was selected as the β-adrenergic agonist because it is the physiological β-receptor agonist, and α-receptor presence in the myocardium is generally held to be negligible. Govier [15] specifically has shown that, while epinephrine and norepinephrine do mediate a positive inotropic effect at α-receptors, this effect is a minor one as compared to their β-adrenergic activity. The specific question answered by this research is whether differences in the sensitivity of cardiac β-receptors to norepinephrine may account for the decreased cardiac response *in vivo* of SHR myocardium to this catecholamine. The inability of SHR to increase heart rate and cardiac index in response to low doses of infused norepinephrine (0.5 μg/kg/min), as com-

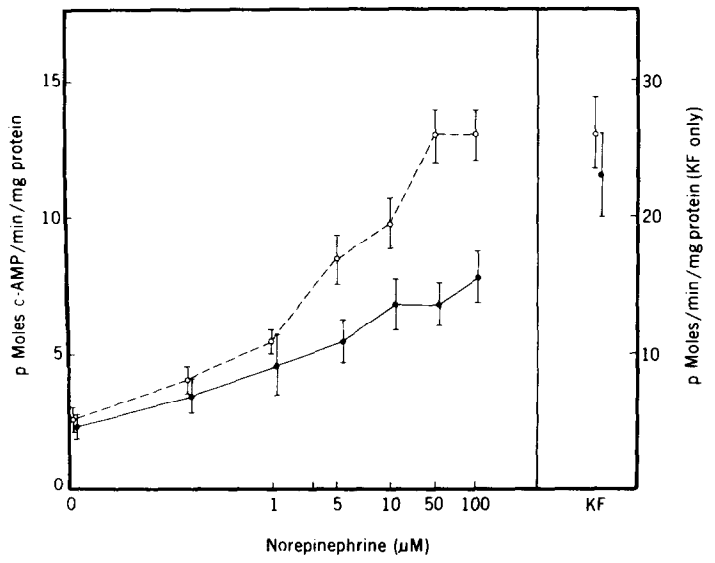

Fig. 3. Norepinephrine stimulation of adenylate cyclase from WKY left ventricle (○) or right ventricle (●). The enzyme activity was measured in the presence of 10 mM potassium fluoride (KF) where indicated.

Table 3. Cardiac cyclic AMP phosphodiesterase activity

Strain	Cyclic AMP concn	cAMP hydrolyzed* (nmoles/min/mg protein) Left ventricle	Center wall	Right ventricle
NR	1 mM	1.70 ± 0.21	2.03 ± 0.30	2.35 ± 0.25†
SHR	1 mM	2.28 ± 0.245	2.19 ± 0.163	2.95 ± 0.44
WKY	1 mM	1.76 ± 0.17	2.10 ± 0.21	2.73 ± 0.34†
NR	1 μM	0.0535 ± 0.0021	0.0558 ± 0.0034	0.0651 ± 0.0020‡
SHR	1 μM	0.0513 ± 0.0020	0.0539 ± 0.0045	0.0608 ± 0.0037†
WKY	1 μM	0.0517 ± 0.0038	0.0489 ± 0.055	0.0541 ± 0.0038

* Values for cAMP hydrolyzed are expressed as mean ± S.E.M.
† Higher than left ventricle ($P < 0.1$).
‡ Higher than left ventricle ($P < 0.02$).

Table 4. Left ventricular L-lactate dehydrogenase activities

Strain	L-Lactate dehydrogenase (I.U./mg protein ± S. D.)	Percentage LDH activity ± S. D. LDH_1	$LDH_{2,3,4}$	LDH_5
NR	6.0 ± 0.42	12.7 ± 1.0	56.4 ± 5.8	33.8 ± 3.9
SHR	8.53 ± 0.49*	16.2 ± 2.0*	47.0 ± 1.1*	37.1 ± 2.9
WKY	6.97 ± 0.68	10.8 ± 1.0	56.4 ± 5.8	32.7 ± 7.7

* Significantly different ($P < 0.05$) from both control strains.

pared to NR [5], is not explained on the basis of a differential sensitivity of cardiac adenylate cyclase. No significant differences were noted between SHR and NR at either low or high levels of norepinephrine (Table 2). With either right or left ventricular preparation, the norepinephrine concentrations necessary for one-half maximal stimulation (K_m) were different when comparing SHR (6–8 μM) and WKY (2.5–4.5 μM). However, the value for NR (6.8–8 μM) was comparable to that of SHR (Figs 1–3). Since there is no consistent correlation between hypertension and K_m values, these observations provide little understanding of the physiological differences *in vivo* in these species. These results are consistent with the data concerning the β-adrenergic receptor agonist isoproterenol reported by Largis *et al.* [4] with perfused, electrically driven hearts. They found no differences between SHR and NR in the effects of isoproterenol upon either cardiac performance or myocardial cAMP

levels. The present data extend these observations to include the natural β-adrenergic receptor agonist norepinephrine in terms of its action as an adenylate cyclase stimulant *in vitro*. However, the decreased sensitivity *in vivo* of SHR heart performance as compared to WKY [3] could be due to the relative insensitivity of SHR left ventricular adenylate cyclase to low levels of norepinephrine (1 and 5 μM), although the overall similarity of the dose–response curves argues against this. These results differ somewhat from those of Amer *et al.* [9], who reported that cardiac adenylate cyclase from SHR, stress hypertensive, and cortisone hypertensive rats was less sensitive to isoproterenol stimulation than the enzyme from NR.

Our findings that glucagon stimulation of ventricular adenylate cyclase was not significantly different in NR, WKY or SHR are not consistent with the report that the effects of glucagon upon both cardiac performance and increases in myocardial cAMP levels were less in SHR and NR [4] (Table 2). The mechanisms by which glucagon causes these differential effects are apparently not based upon cardiac adenylate cyclase responsiveness. The indices *in vivo* of cardiac performance as a function of glucagon infusion have not yet been determined with these strains of rats.

Striking differences between right and left ventricular adenylate cyclase preparations in terms of the magnitude of their responses to norepinephrine stimulation were noted. In all three rat strains the right ventricle, while having about the same K_m values, appeared to have either a lesser density of norepinephrine-activatable adenylate cyclase receptors or less stimulatable ones (Figs 1–3). While the explanation for these findings is unknown, it does seem clear that the biochemical activities of both ventricles should not be presumed identical in studies of cardiac properties.

Left ventricular cAMP phosphodiesterase activity with 1 mM or 1 μM cAMP was not significantly different in any rat strain. When assayed at a 1-μM cAMP concentration, SHR, NR and WKY left ventricles had, respectively, 2.24, 3.14 and 2.9 per cent of the activity measured at 1 mM cAMP, again not notably different. Our results closely resemble those of Largis *et al.* [4], who found no differences in cardiac phosphodiesterase activities between SHR and NR at 1 mM or 1 μM cAMP. Amer *et al.* [7, 9], however, have presented results indicating that SHR heart contains higher levels of total cAMP phosphodiesterase activity and a higher relative level of the low K_m enzyme. These latter results, although obtained under different conditions and with more sophisticated technique, appear to differ from our results and those of Largis *et al.* [4]. Our measurements of the enzymes hydrolyzing cAMP do not explain the differential cardiac responses *in vivo* of these animals to β-adrenergic receptor stimulation. (A higher level of the low K_m enzyme in SHR might have helped explain relative insensitivity to β-adrenergic stimulation.)

Again, as with adenylate cyclase, while interspecies differences were absent, left and right ventricular walls were not identical in enzymic activity. In all species and at both substrate concentrations the right ventricular wall had higher measured cAMP phosphodiesterase activity than left ventricular wall (this was, however, statistically significant in only four of six instances, Table 3). When the ventricular data for all three rat species were averaged, the phosphodiesterase activities at 1 mM substrate were 1.913±0.20 nmoles/min/mg of protein (left ventricle) and 2.68±0.34 nmoles/min/mg of protein (right ventricle), differing with a P value of less than 0.001. At 1 μM substrate the activities were 0.0522±0.0035 nmole/min/mg of protein (left ventricle) and 0.060±0.0031 nmole/min/mg of protein (right ventricle), differing with a P value of less than 0.005. Norepinephrine-stimulated adenylate cyclase activity is lower and cAMP phosphodiesterase activity is higher in the right ventricular wall as compared to the left. A reasonable prediction might be that right ventricular cAMP levels, especially as a result of norepinephrine challenge, would be lower than those of the relatively hypertrophied left ventricle. This appears to indicate a decreased reliance of the right ventricle upon a cAMP-dependent process of energy production and/or contraction.

Soluble left ventricle tissue extracts were assayed for lactate dehydrogenase activity, and the SHR left ventricle contained significantly more enzyme activity than either normotensive control strain (Table 4), thus confirming previous observations with SHR [16] and also with hypoxically induced cardiac hypertrophy [17]. Further interstrain differences in LDH activity were noted when left ventricular extracts were diluted in LDH-free serum and subjected to selective heat denaturation [14]. Distinct variations in SHR isozyme composition were apparent: a shift toward LDH_1 (muscle type) from intermediate forms (Table 4). The increased LDH_1, found usually in organs with greater glycolytic potential, may indicate a greater dependence upon glycogenolysis as a source of energy in the hypertrophied heart. These results are analogous to those of Sembrowich *et al.* [18], who found that in rat myocardium, 24–72 hr after aortic constriction, LDH_1 increased, intermediate types decreased and LDH_5 (heart type) remained the same. Similar changes in isozyme composition have also been reported in hypertrophied hearts of rats chronically exposed to hypoxia [17]. The tissue specificity of LDH isozyme patterns indicates that these isozymes play an important and specific physiological role. Just what this role is, however, remains unclear. Based upon the tissue distribution of these isozymes, some generalizations have been offered: (1) tissues with a constant and rich supply of oxygen are predominantly LDH_5, and (2) tissues subjected to transient anaerobiosis are rich in LDH_1 [19, 20]. This shift toward LDH_1 in hypertrophied hearts is consistent with a decreased vasculature in relation to the increased muscle mass. This latter phenomenon may induce transient anaerobiosis and involve a capability to utilize glycolysis in place of oxidative phosphorylation as a means of energy production. LDH_1 is thought, because of its kinetic properties, to function more efficiently than LDH_5 as pyruvate reductase [21]. This phenomenon may be related to cAMP because phosphofructokinase, the key regu-

latory enzyme in glycolysis, is directly activated by cAMP or indirectly by epinephrine [22], although this effect is open to question because other nucleotides also have this effect. Thus, although we failed to find differences in adenylate cyclase or cAMP phosphodiesterase between normal and hypertrophied SHR hearts, LDH patterns are indicative of possible alterations in cAMP-related phenomena. However, because relatively subtle changes in nucleotide levels may have magnified physiological effects, these experiments cannot entirely exclude the control of cyclic nucleotide levels as a factor in hypertension-induced changes in cardiac performance. These results also suggest that the SHR provide a physiological model for cardiac hypertrophy similar to that produced by artificial interventions.

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