Effects of Adrenoceptor Blockade on Cardiac Hypertrophy and Myocardial Phospholipids (43399)

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Abstract. **Catecholamines have been proposed as a stimulus for the hypertrophic response to pressure overload of the heart and could also mediate the membrane lipid changes associated with cardiac hypertrophy. To address both of these possibilities, cardiac hypertrophy was induced by aortic constriction in the presence or absence of chronic α- or β-adrenoceptor blockade. Heart weights and heart weight to body weight ratios in aortic-constricted rats of the adrenoceptor-blocked and vehicle-treated groups were elevated to the same extent when compared with values in sham-operated rats of each group. Analysis of the fatty acyl composition of the major phospholipid classes revealed that similar changes occurred in vehicle-treated, α-blocked, and β-blocked aortic-constricted rats when compared with respective groups of sham-operated rats. Specifically, linoleic acid was reduced in the phosphatidylcholine, phosphatidylethanolamine (PE), and cardiolipin (CL) fractions in all groups of aortic-constricted rats. This reduction was accompanied by increased docosahexaenoic acid, arachidonic acid, or palmitic acid in phosphatidylcholine; docosahexaenoic acid in phosphatidylethanolamine; and oleic acid in cardiolipin fractions. Adrenoceptor blockade did not prevent or attenuate the major changes in the fatty acyl composition of phospholipids or the increase in heart weight associated with aortic constriction. This suggests that a change in the level of adrenoceptor stimulation is not the stimulus for cardiac hypertrophy or the observed alterations in phospholipid composition in the pressure-overloaded rat heart.** [P.S.E.B.M. 1992, Vol 200]

The ultimate trigger for the hypertrophic response in a heart subjected to chronic pressure overload is presently unknown. Induction of protein synthesis in cardiac cells during hypertrophy has been explained in terms of a number of possible mechanisms including: (i) induction by direct mechanical deformation, such as increased wall tension or stretch of the myocardium (1–3); (ii) an alteration of the energy state of the tissue (4); and (iii) alterations in the local or systemic release of mediators such as catecholamines (5–7), adrenocorticosteroids (8), angiotensin (9), atrial natriuretic peptide (10, 11), prostaglandins (12), or an unidentified hypertrophy-inducing factor (13–15).

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Continued interest has been directed toward catecholamines as potential mediators of hypertrophy. Several investigators have shown that circulating catecholamine levels increase following aortic constriction in animals (16–19). Furthermore, chronic injection of norepinephrine (5) or isoproterenol (6) in subhypertensive doses leads to cardiac hypertrophy in adult animals, while stimulation of α-adrenoceptors induces growth in cultured neonatal cardiomyocytes (20, 21). Additional evidence supporting a role for catecholamines in the cardiac response to pressure overload has been reported by Womble *et al.* (19), who showed that adrenal medulla denervation prevents cardiac hypertrophy in dogs subjected to aortic constriction. More recently, Tamai *et al.* (22) reported that chronic infusion of an α-adrenoceptor antagonist attenuates cardiac hypertrophy in aortic-constricted guinea pigs. In contrast, an early study by Overbeck (23) suggested that peripheral sympathectomy does not prevent the development of hypertrophy in aortic-constricted rats. Subsequent studies employing adrenal demedullation (8), α- or β-adre-

noceptor blockade (1), or chemical sympathectomy (17) have generally supported the view that adrenergic intervention has little or no effect on the hypertrophic response to pressure overload. Similarly, sympathectomy or β-adrenoceptor blockade does not prevent cardiac hypertrophy in spontaneously hypertensive rats (24–26), renal hypertensive rats (27), or rabbits subjected to hypoxia (28, 29).

In addition to an increase in myocardial protein synthesis in response to pressure overload, membrane phospholipids increase as the heart enlarges. Although the content of phospholipid increases in proportion to heart weight in the hypertrophied myocardium, the fatty acyl composition of myocardial phospholipids is altered (30). The possibility that the changes in fatty acyl composition could be caused by an alteration in the level of catecholamine stimulation is suggested by reports of similar changes in myocardial phospholipids following chronic administration of norepinephrine to rats (31, 32). The mechanisms involved with the phospholipid changes that occur in the hypertrophied heart are of interest, since alterations in the fatty acyl composition of phospholipids can influence a number of membrane functions, including the activities of membrane-bound enzymes, the number and affinity of receptors, and carrier-mediated transport processes (33, 34).

The present study used chronic receptor blockade by specific antagonists of α- and β-adrenoceptors to clarify the possible role of catecholamines in mediating cardiac enlargement and the corresponding remodeling of membrane phospholipids in response to pressure-overload in aortic-constricted rats.

Materials and Methods

Adrenoceptor Blockade and Aortic Constriction. Male Sprague-Dawley rats weighing 134–145 g were injected intraperitoneally twice daily with either 1 mg/kg of the α_1-adrenoceptor antagonist prazosin HCl (Pfizer Laboratories, New York, NY; α-blocked group), 15 mg/kg of the β-adrenoceptor antagonist DL-propranolol HCl (Sigma Chemical Co., St. Louis, MO; β-blocked group), or an equal volume of 0.9% NaCl (vehicle-treated group). Ten days after beginning the injections, rats were anesthetized with chloral hydrate (0.36 g/kg, ip) and pressure-overload cardiac hypertrophy was induced by constriction of the abdominal aorta (aortic-constricted [AC]) using the ligature-needle technique of Morkin and Ashford (35). Sham-operated (SO) rats were subjected to the identical surgical procedure, excluding aortic constriction.

Prazosin, propranolol, or NaCl injections were continued for 10 days following surgery, at which time the rats were anesthetized with sodium pentobarbital (Nembutal; 50 mg/kg, ip) and the left carotid artery was cannulated to measure heart rate and blood pressure. Hearts were subsequently excised and weighed. After trimming away the atria and right ventricular free wall, the left ventricle and septum were frozen between clamps precooled in liquid nitrogen.

Prior to sacrifice, four rats from each of the groups were given either the α-agonist phenylephrine HCl (25 μg/kg/min, iv) or the β-agonist isoproterenol HCl (1 μg/kg/min, iv). Mean arterial pressure responses to infusions of the α- or β-agonists were reduced by 80–90% in the corresponding α- or β-adrenoceptor-blocked groups of rats, suggesting effective receptor antagonism by the drug treatments.

Phospholipid Analysis. Lipid extractions were carried out on the frozen, pulverized cardiac tissue as described previously (30). Individual phospholipid classes were isolated by spotting lipid extracts on Silica Gel G thin-layer chromatography plates (Analtech, Newark, DE) and separating in one dimension with the solvent system chloroform/methanol/petroleum ether/acetic acid/boric acid (40:20:30:10:1.8, v/v/v/v/w), as described by Gilfillan *et al.* (36). Phospholipid spots were visualized with 0.05% 2′,7′-dichlorofluorescein in ethanol and scraped into vials for methylation. Fatty acid methyl esters were prepared by reaction with 14% boron trifluoride in methanol, as described by Morrison and Smith (37), and analyzed on a Perkin-Elmer Sigma 300 gas chromatograph with a glass column (2 mm i.d., 6 ft long) packed with 10% diethylene glycol succinate on 80/100 mesh Supelcoport (Supelco, Inc., Bellefonte, PA) at a constant temperature of 185°C and a helium flow rate of 60 ml/min. Peak area percentages were computed with a Perkin-Elmer LCI-100 integrator. Results are expressed as fatty acid weight percent, and only those fatty acids in excess of 1% of the total are reported. Fatty acids are designated by chain length:number of double bonds. In Tables II–IV, the numbers in parentheses, e.g., (n-6), refer to the number of carbon atoms (i.e., 6) between the last double bond and the terminal methyl group of the fatty acid.

Statistical Analysis. The experimental data in all tables are expressed as the mean ± SE for the number of determinations denoted in the legends. The data from AC and SO rats for each individual treatment group were compared using a two-tailed unpaired Student's *t* test. Between-group comparisons of values from the drug-treated groups with values from the vehicle-treated group were carried out using analysis of variance in conjunction with Dunnett's multicomparison test. A 95% confidence limit was used to determine significance.

Results

As shown in Table I, heart weight to body weight ratios were significantly increased in all groups of AC rats compared with respective SO rats. The increase was entirely due to increased ventricular weight, since

Table I. Heart Weight, Body Weight, Heart Rate, and Mean Arterial Pressure in Sham-Operated and Aortic-Constricted Rats Treated with Adrenoceptor-Blocking Drugs[a]

Group	Body wt (g)	Heart wt (mg)	Heart wt/body wt (mg/g)	Heart rate (bpm)	Mean arterial pressure (mm Hg)
Vehicle					
SO	247 ± 7	665 ± 19	2.70 ± 0.08	403 ± 14	120 ± 5
AC	236 ± 5	843 ± 30[b]	3.55 ± 0.15[b]	392 ± 10	146 ± 5[c]
α-Blocked					
SO	248 ± 6	676 ± 25	2.73 ± 0.10	391 ± 12	100 ± 5[d]
AC	237 ± 5	818 ± 18[b]	3.45 ± 0.10[b]	357 ± 11	137 ± 9[c]
β-Blocked					
SO	244 ± 3	659 ± 16	2.70 ± 0.06	323 ± 29[d]	104 ± 6
AC	239 ± 5	791 ± 14[b]	3.32 ± 0.09[b]	334 ± 16[e]	144 ± 9[c]

[a] Each value represents the mean ± SE of at least six determinations. Rats were chronically treated with saline (vehicle), prazosin (α-blocked), or propranolol (β-blocked) before and after surgery.
[b] $P < 0.001$, AC compared with SO of same treatment group.
[c] $P < 0.01$, AC compared with SO of same treatment group.
[d] $P < 0.05$, SO or AC of vehicle-treated group compared with SO or AC, respectively, of blocked groups.
[e] $P < 0.01$, SO or AC of vehicle-treated group compared with SO or AC, respectively, of blocked groups.

body weight was unchanged by aortic constriction. Furthermore, the drug treatments did not affect the cardiac enlargement, since there was no significant difference in heart weight to body weight ratios between the vehicle and α- or β-blocked AC groups.

There were no significant differences in heart rate between SO and AC rats within any treatment group; however, both the SO and AC β-blocked rats exhibited significantly lower heart rates when compared with respective SO or AC rats in the vehicle-treated group. This reduction in heart rate is indicative of β-adrenoceptor blockade *in vivo*.

Mean arterial pressure was significantly reduced in SO rats of the α-blocked group compared with SO rats in the vehicle-treated group, which reflects *in vivo* blockade of α-adrenoceptors. Mean arterial pressure was significantly elevated as a result of aortic constriction in every treatment group. Mean arterial pressure of AC rats in the α- or β-blocked groups was not different from that in AC rats of the vehicle-treated group.

Chronic α- or β-adrenoceptor blockade alone did not affect the fatty acyl composition of myocardial phospholipids. Intergroup comparison of the phospholipid composition of vehicle-treated SO animals with compositions of SO animals in the α- or β-blocked groups revealed no significant differences in fatty acyl profiles.

The fatty acyl composition of myocardial phosphatidylcholine (PC) is shown in Table II. Linoleic acid (18:2) in the PC fraction of hearts from AC rats was reduced to 64%, 61%, and 54% of that in SO animals for the vehicle-treated, α-blocked, and β-blocked groups, respectively. These reductions were associated with significant elevations of docosahexaenoic acid (22:6) and arachidonic acid (20:4) in hearts of AC rats in the α- and β-blocked group. These fatty acids also tended to be elevated and palmitic acid (16:0) was significantly elevated in hearts of AC rats in the vehicle-treated group.

The reduction of linoleic acid in the hearts of AC rats was also evident in the phosphatidylethanolamine fraction (Table III), in which 18:2 in AC rats was reduced to 62%, 43%, and 54% of that in SO animals for the vehicle-treated, α-blocked, and β-blocked groups, respectively. These reductions were accompanied by significant increases in 22:6 in hearts of AC rats of all groups. Also evident in this fraction was a significant reduction in oleic acid (18:1) in AC rats of the α-blocked group and a small increase in docosapentaenoic acid (22:5) in the vehicle-treated group.

The fatty acyl composition of cardiolipin in hearts of SO and AC rats of each group is shown in Table IV. In this fraction, myocardial 18:1 was significantly increased by aortic constriction in each group. As in the other phospholipid classes, 18:2 was reduced and 22:6 was increased in AC rats of every group, although these changes were statistically significant only for 22:6 in the β-blocked group. Additionally, 16:0 was significantly increased in hearts of AC rats in the vehicle-treated group and tended to be elevated in AC rats of the α- and β-blocked groups as well.

In summary, marked alterations in the fatty acyl composition of the major myocardial phospholipids occurred as a result of aortic constriction in all three treatment groups. Analysis of the individual phospholipid classes, phosphatidylcholine, phosphatidylethanolamine, and cardiolipin, which together comprise more than 90% of the total phospholipids of the rat heart (30), revealed a general reduction in 18:2 in hearts of AC rats of every group. This decrease was accompanied by increases in either 16:0, 20:4, or 22:6.

Table II. Fatty Acyl Composition of Phosphatidylcholine in Hearts of Sham-Operated and Aortic-Constricted Rats Treated with Adrenoceptor-Blocking Drugs[a]

Fatty acid	Fatty acid (wt%)					
	Vehicle		α-Blocked		β-Blocked	
	SO	AC	SO	AC	SO	AC
16:0	18.85 ± 0.34	21.20 ± 0.76[b]	20.42 ± 0.92	19.62 ± 0.71	20.47 ± 0.55	21.40 ± 1.89
18:0	24.76 ± 0.68	25.06 ± 0.65	26.57 ± 0.28	25.96 ± 0.96	26.54 ± 0.31	26.06 ± 0.72
18:1 (n-9)	9.56 ± 0.20	9.14 ± 0.33	9.81 ± 0.12	9.20 ± 1.19	9.52 ± 0.31	8.89 ± 0.34
18:2 (n-6)	13.81 ± 0.73	8.91 ± 0.69[c]	13.18 ± 0.34	8.02 ± 0.60[c]	12.74 ± 1.00	6.92 ± 0.49[c]
20:4 (n-6)	20.37 ± 0.57	22.25 ± 0.85	19.59 ± 0.66	23.51 ± 0.99[d]	19.69 ± 0.49	22.58 ± 1.09[b]
22:5 (n-3)	2.08 ± 0.10	1.95 ± 0.16	1.83 ± 0.16	1.95 ± 0.24	1.72 ± 0.08	1.73 ± 0.35
22:6 (n-3)	7.79 ± 0.44	8.60 ± 0.43	6.26 ± 0.55	9.07 ± 0.81[b]	6.73 ± 0.40	9.17 ± 0.77[b]

[a] Each value represents the mean ± SE of at least six determinations. Rats were chronically treated with saline (vehicle), prazosin (α-blocked), or propranolol (β-blocked) before and after surgery. Fatty acids are designated as described in Materials and Methods.
[b] $P < 0.05$, AC compared with SO of the same treatment group.
[c] $P < 0.001$, AC compared with SO of the same treatment group.
[d] $P < 0.01$, AC compared with SO of the same treatment group.

Table III. Fatty Acyl Composition of Phosphatidylethanolamine in Hearts of Sham-Operated and Aortic-Constricted Rats Treated with Adrenoceptor-Blocking Drugs[a]

Fatty acid	Fatty acid (wt%)					
	Vehicle		α-Blocked		β-Blocked	
	SO	AC	SO	AC	SO	AC
16:0 DMA	4.07 ± 0.56	2.38 ± 0.58	3.29 ± 0.15	3.22 ± 0.77	4.38 ± 0.43	3.50 ± 0.91
16:0	8.60 ± 0.44	7.10 ± 0.99	8.81 ± 0.67	7.61 ± 1.38	8.98 ± 0.53	8.11 ± 1.16
18:0 DMA	2.22 ± 0.33	2.58 ± 0.32	2.04 ± 0.12	2.67 ± 0.51	2.46 ± 0.21	2.80 ± 0.19
18:0	29.96 ± 0.97	29.16 ± 0.68	29.75 ± 0.55	29.91 ± 1.04	30.80 ± 0.80	29.46 ± 0.78
18:1 (n-9)	5.47 ± 0.49	5.17 ± 0.50	5.37 ± 0.23	3.13 ± 0.12[b]	4.36 ± 0.41	3.64 ± 0.30
18:2 (n-6)	6.03 ± 0.53	3.77 ± 0.48[c]	5.86 ± 0.59	2.52 ± 0.19[b]	5.06 ± 0.64	2.73 ± 0.19[d]
20:4 (n-6)	15.75 ± 0.62	16.51 ± 1.26	16.43 ± 0.37	15.53 ± 1.20	15.74 ± 0.56	15.04 ± 0.70
22:5 (n-3)	2.36 ± 0.10	2.75 ± 0.13[c]	2.54 ± 0.14	2.86 ± 0.21	2.04 ± 0.13	1.92 ± 0.26
22:6 (n-3)	23.67 ± 0.92	28.84 ± 0.99[d]	24.17 ± 0.56	30.23 ± 2.19[c]	23.99 ± 1.46	30.61 ± 1.35[d]

[a] Each value represents the mean ± SE of at least six determinations. Rats were chronically treated with saline (vehicle), prazosin (α-blocked), or propranolol (β-blocked) before and after surgery. Fatty acids are designated as described in Materials and Methods. DMA, dimethylacetal derivative from plasmalogen.
[b] $P < 0.001$, AC compared with SO of the same treatment group.
[c] $P < 0.05$, AC compared with SO of the same treatment group.
[d] $P < 0.01$, AC compared with SO of the same treatment group.

Discussion

Chronic α- or β-adrenoceptor blockade resulted in lower basal mean arterial pressures in SO animals. This is in accordance with the known hypotensive actions of these drugs. However, the extent of hemodynamic overload following aortic constriction was similar in each experimental treatment group, since there were no differences in the mean arterial pressures attained after aortic constriction. Moreover, heart weight to body weight ratios were not affected by either α- or β-adrenoceptor blockade.

The role of catecholamines in the development of pressure-overload cardiac hypertrophy has been studied in various models using surgical or chemical adrenergic intervention. Adrenal demedullation or chemical sympathectomy does not prevent or attenuate the development of cardiac hypertrophy in aortic-constricted rats (8, 17). The present results provide evidence demonstrating that specific blockade of α-adrenoceptors with intact β-adrenoceptors or vice versa does not influence the extent of the inciting hemodynamic stress nor alter the degree of cardiac enlargement in aortic-constricted rats. The results are also in agreement with previous findings for chronically adrenoceptor-blocked cats subjected to right ventricular overload (1).

In contrast, a reduced hypertrophic response to aortic constriction by adrenal medulla denervation in dogs (19) and α-adrenoceptor blockade in guinea pigs (22) has been reported. These conflicting results may be due to differences in species, experimental intervention protocol, or differences in the severity of the hemodynamic overload.

Alterations in myocardial membrane functions have been observed in pressure-overloaded hearts as

Table IV. Fatty Acyl Composition of Cardiolipin in Hearts of Sham-Operated and Aortic-Constricted Rats Treated with Adrenoceptor-Blocking Drugs[a]

Fatty acid	Fatty acid (wt%)					
	Vehicle		α-Blocked		β-Blocked	
	SO	AC	SO	AC	SO	AC
16:0	1.19 ± 0.10	1.77 ± 0.20[b]	1.33 ± 0.11	1.73 ± 0.16	1.59 ± 0.07	1.85 ± 0.16
18:0	1.43 ± 0.24	2.28 ± 0.45	2.16 ± 0.49	1.89 ± 0.49	1.68 ± 0.13	1.51 ± 0.34
18:1 (n-9)	6.84 ± 0.29	8.93 ± 0.75[b]	6.57 ± 0.24	9.66 ± 0.40[c]	6.62 ± 0.39	9.59 ± 0.71[d]
18:2 (n-6)	83.14 ± 1.31	76.82 ± 2.61	80.54 ± 0.92	76.13 ± 1.74	81.20 ± 0.60	77.35 ± 2.20
20:4 (n-6)	1.39 ± 0.16	1.99 ± 0.42	1.77 ± 0.28	2.04 ± 0.30	1.50 ± 0.15	1.73 ± 0.25
22:6 (n-3)	1.95 ± 0.42	3.44 ± 0.62	2.24 ± 0.41	4.01 ± 0.73	1.81 ± 0.23	3.71 ± 0.80[b]

[a] Each value represents the mean ± SE of at least six determinations. Rats were chronically treated with saline (vehicle), prazosin (α-blocked), or propranolol (β-blocked) before and after surgery. Fatty acids are designated as described in Materials and Methods.
[b] $P < 0.05$, AC compared with SO of the same treatment group.
[c] $P < 0.001$, AC compared with SO of the same treatment group.
[d] $P < 0.01$, AC compared with SO of the same treatment group.

evidenced by alterations in Ca^{2+} uptake by sarcoplasmic reticulum (38), sarcolemmal Ca^{2+} influx (39), and adrenoceptor function (40). The changes in myocardial phospholipids that we observe in pressure-overloaded hearts could contribute to altered membrane function.

In the present study, the general pattern and magnitude of the phospholipid alterations in hypertrophied rat hearts did not differ appreciably in the presence of α- or β-adrenoceptor blockade. Only minor differences in the composition of PC in AC rats were observed between blocked and vehicle-treated groups. Thus, the data suggest that an alteration in the level of adrenergic receptor stimulation of the rat myocardium during the development of pressure-overload cardiac hypertrophy is not responsible for the observed changes in the fatty acyl profile of phospholipids.

Interesting similarities exist between the myocardial phospholipid changes observed in pressure-overload hypertrophied hearts and those obtained with chronic administration of noradrenaline in rats. Emilsson and Gudbjarnason (31) have shown that 18:1 and 18:2 are reduced in the phospholipids of hearts from noradrenaline-treated rats. The reductions were accompanied by increases in the levels of stearic acid (18:0), 20:4, and 22:6. These investigators did not address the possibility that the noradrenaline treatment could have induced cardiac hypertrophy. In fact, the dose of noradrenaline used in their study was well above the dose required to induce hypertrophy (20). In light of the present study, it is not clear whether the lipid alterations reported to occur after norepinephrine treatment are a direct result of myocardial adrenoceptor stimulation or are linked to other factors that are altered during the development of cardiac hypertrophy. We have demonstrated that the sequence of events leading to remodeling of the cell membrane cannot be dissociated from the cardiac hypertrophic response by removing the influence of catecholamines in our model of overload. It remains to be seen whether the specific lipid changes can, in fact, be isolated from the growth response or always occur in concert with it.

The possibility that hormones other than catecholamines could mediate the phospholipid changes in the hypertrophied heart has not been fully explored. Thyroxine treatment, which can induce hypertrophy (41, 42), has been shown to alter the percentage of unsaturation of myocardial phospholipids in the rat heart (43); however, the role of cardiac enlargement was not discussed in the latter study. Other factors which may be altered during the development of cardiac hypertrophy include adrenal corticosteroids (8), angiotensin (9), atrial natriuretic factor (10, 11), and prostaglandins (12). Their effects on membrane lipid composition remain to be investigated.

The results of the present study suggest that increased adrenoceptor stimulation is not required for cardiac enlargement and does not mediate the changes in fatty acyl composition of myocardial phospholipids associated with cardiac hypertrophy in the aortic-constricted rat.

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1. Cooper G, Kent RL, Uboh CE, Thompson EW, Marino TA. Hemodynamic versus adrenergic control of cat right ventricular hypertrophy. J Clin Invest **75**:1403–1414, 1985.
2. Frolich ED. Hemodynamics and other determinants in development of left ventricular hypertrophy. Fed Proc **42**:2709–2715, 1983.
3. Morgan HE, Gordon EE, Kira Y, Siehl DL, Watson A, Chua BHL. Biochemical correlates of myocardial hypertrophy. The Physiologist **28**:18–27, 1985.
4. Meerson Z, Pomoinitsky VD. The role of high-energy phosphate compounds in the development of cardiac hypertrophy. J Mol

Cell Cardiol **4**:571–597, 1972.
5. Laks MM, Morady BA, Swan HJC. Myocardial hypertrophy produced by chronic infusion of subhypertensive doses of norepinephrine in the dog. Chest **64**:75–78, 1973.
6. Cohen J. Role of endocrine factors in the pathogenesis of cardiac hypertrophy. Circ Res **34–35**(suppl II):1149–1157, 1974.
7. Genovese A, Chiariello M, Bozzaotre M, Latte S, De Alfieri W, Condorelli M. Adrenergic activity as a modulating factor in the genesis of myocardial hypertrophy in the rat. Exp Mol Pathol **41**:390–396, 1984.
8. Nichols JR, Clancy RL, Gonzalez NC. Role of adrenals on development of pressure-induced myocardial hypertrophy. Am J Physiol **244**:H234-H238, 1983.
9. Baker KM, Chernin MI, Wixson SK, Joseph AF. Renin-angiotensin system involvement in pressure-overload cardiac hypertrophy in rats. Am J Physiol **259**:H324-H332, 1990.
10. Franch HA, Callahan LT, Blaine EH. Plasma and atrial content of atrial natriuretic factor in cardiomyopathic hamsters. Life Sci **39**:1151–1159, 1986.
11. McKenzie JC, Tanaka I, Inagami T, Misono KS, Klein RM. Alterations in atrial and plasma atrial natriuretic factor (ANF) content during development of hypoxia-induced pulmonary hypertension in the rat. Proc Soc Exp Biol Med **181**:459–463, 1986.
12. Chazov EI, Pomoinetsky VD, Geling NG, Orlova TR, Nekrasova AA, Smirnov VN. Heart adaptation to overload. Circ Res **45**:205–211, 1979.
13. Hammond GL, Wieben E, Markert CL. Molecular signals for initiating protein synthesis in organ hypertrophy. Proc Natl Acad Sci USA **76**:2455–2459, 1979.
14. Hammond GL, Lai Y-K, Markert CL. The molecules that initiate cardiac hypertrophy are not species-specific. Science **216**:529–531, 1982.
15. Yazawa K, Sen S. Characterization of a factor which stimulates protein synthesis of cardiac myocytes. Fed Proc **45**:1040, 1986.
16. Siri FM, Smith RM. Effects of plasma norepinephrine elevation on the heart's adaptation to chronic aortic constriction in rats. Can J Physiol Pharmacol **164**:934–939, 1986.
17. Siri FM, McNamara JJ. Effects of sympathectomy on heart size and function in aortic-constricted rats. Am J Physiol **252**:H442-H447, 1987.
18. Womble JR, Haddox MK, Russell DH. Epinephrine elevation in plasma parallels canine cardiac hypertrophy. Life Sci **23**:1951–1958, 1978.
19. Womble JR, Larson DF, Copeland JG, Brown BR, Haddox MK, Russell DH. Adrenal medulla denervation prevents stress-induced epinephrine plasma elevation and cardiac hypertrophy. Life Sci **27**:2417–2420, 1980.
20. Simpson P, Bishopric N, Coughlin S, Karliner J, Ordahl C, Starksen N, Tsao T, White N, Williams L. Dual trophic effects of the alpha$_1$-adrenergic receptor in cultured neonatal rat heart muscle cells. J Mol Cell Cardiol **18**(suppl 5):45–58, 1986.
21. Simpson P. Norepinephrine-stimulated hypertrophy of cultured rat myocardial cells is an alpha$_1$-adrenergic response. J Clin Invest **72**:732–738, 1983.
22. Tamai J, Hori M, Kagiya T, Iwakura K, Iwai K, Kitabatake A, Watanabe Y, Yoshida H, Inoue M, Kamada T. Role of alpha 1-adrenoceptor activity in progression of cardiac hypertrophy in guinea pig hearts with pressure overload. Cardiovasc Res **23**: 315–322, 1989.
23. Overbeck HW. Cardiovascular hypertrophy and waterlogging in coarctation hypertension: Role of sympathoadrenergic influences and pressure. Hypertension **79**:486–492, 1979.
24. Oparil S, Cutilleta AF. Hypertrophy in the denervated heart: A comparison of central sympatholytic treatment with 6-hydroxydopamine and peripheral sympathectomy with nerve growth factor antiserum. Am J Cardiol **44**:970–978, 1979.
25. Tomanek RJ, Bhatnagar RK, Schmid P, Brody MJ. Role of catecholamines in myocardial cell hypertrophy in hypertensive rats. Am J Physiol **242**:H1015-H1021, 1982.
26. Lauva IK, Tomanek J. The effects of beta adrenoceptor blockade with atenolol on myocardial cellular and subcellular hypertrophy in spontaneously hypertensive rats. Anat Rec **207**:615–622, 1983.
27. Tomanek RJ, Carlson DW, Palmer PJ, Bhatnagar RK. Role of sympathetic nerves during developing cardiac hypertrophy in Gnollman hypertensive rats. Am J Physiol **253**:H818-H825, 1987.
28. Vaughn Williams EM, Dukes ID. The absence of effect of chemical sympathectomy on ventricular hypertrophy induced by hypoxia in young rabbits. Cardiovasc Res **17**:379–389, 1983.
29. Dennis P, Vaughn Williams EM. Hypoxic cardiac hypertrophy is not inhibited by cardioselective or non-selective β-adrenoceptor antagonists. J Physiol **324**:365–374, 1982.
30. Reibel DK, O'Rourke B, Foster KA, Hutchinson H, Uboh CE, Kent RL. Altered phospholipid metabolism in pressure-overload hypertrophied hearts. Am J Physiol **250**:H1-H6, 1986.
31. Emilsson A, Gudbjarnason S. Changes in fatty acyl chain composition of rat heart phospholipids induced by noradrenaline. Biochim Biophys Acta **664**:82–88, 1981.
32. Emilsson G, Gudbjarnason S. Reversible alterations in fatty acid profile of glycerophospholipids in rat heart muscle induced by repeated norepinephrine administration. Biochim Biophys Acta **730**:1–6, 1983.
33. Bloj B, Morera RD, Farias RN, Trucca RE. Membrane lipid fatty acids and regulation of membrane-bound enzymes. Biochim Biophys Acta **311**:67–69, 1973.
34. Stubbs CD, Smith AD. The modification of mammalian membrane polyunsaturated fatty acid composition in relation to membrane fluidity and function. Biochim Biophys Acta **799**:89–137, 1984.
35. Morkin E, Ashford TP. Myocardial DNA synthesis in experimental cardiac hypertrophy. Am J Physiol **215**:1409–1413, 1968.
36. Gilfillan AM, Chu AJ, Smart DA, Rooney SA. Single plate separation of lung phospholipids including disaturated phosphatidylcholine. J Lipid Res **24**:1651–1656, 1983.
37. Morrison WR, Smith LM. Preparation of fatty acid methyl esters and dimethylacetals from lipids with boron trifluoride-methanol. J Lipid Res **5**:600–608, 1964.
38. Sordahl LA, McCollum WB, Wood WG, Schwartz A. Mitochondria and sarcoplasmic reticulum function in cardiac hypertrophy and failure. Am J Physiol **224**:497–502, 1973.
39. Hemwall EL, Duthinh V, Houser SR. Comparison of slow response action potentials from normal and hypertrophied myocardium. Am J Physiol **246**:H675-H682, 1984.
40. Foster KA, Hock CE, Reibel DK. Altered responsiveness of hypertrophied rat hearts to alpha- and beta-adrenergic stimulation. J Mol Cell Cardiol **23**:91–101, 1991.
41. Sandler G, Wilson GM. The production of cardiac hypertrophy by thyroxine in the rat. Q J Exp Physiol **44**:282–289, 1959.
42. Cohen J, Aroesty JM, Rosenfeld MG. Determinants of thyroxine-induced cardiac hypertrophy in mice. Circ Res **18**:388–397, 1966.
43. Steffen DG, Platner WS. Subcellular membrane fatty acids of rat heart after cold acclimation or thyroxine. Am J Physiol **231**:650–654, 1976.