Control of Cardiac Sarcolemmal Adenylate Cyclase and Sodium, Potassium—Activated Adenosinetransphosphatase Activities

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ABSTRACT

A plasma membrane preparation purified from guinea pig ventricles without the use of high concentrations of detergents or structure-disrupting salts was used to compare the mechanisms controlling sodium, potassium—activated adenosinetransphosphatase (Na, K-ATPase) and adenylate cyclase activities. The basal ATPase activity of 4-6 μ moles Pj/hour mg−1 protein, measured in 120 mM NaCl or KCl, was approximately doubled in 100 mM NaCl plus 20 mM KCl. This increment, the Na, K-ATPase, was abolished by 10−5M ouabain, the Kī for ouabain being approximately 3 × 10−7M. l-Epinephrine had no effect on Na, K-ATPase, but NaF was inhibitory. Adenylate cyclase, which had a basal activity of approximately 200 pmol cyclic AMP/min mg−1 protein, was increased approximately 50% by NaCl or KCl alone at concentrations up to 0.2M. There was no additional stimulation of adenylate cyclase activity when Na+ and K+ were included together. Both l-epinephrine and NaF caused significant stimulation of adenylate cyclase, but neither basal nor activated cyclic AMP production was influenced by ouabain. Half-maximal stimulation was seen at approximately 5 × 10−7M l-epinephrine. Both the catecholamine and NaF increased the Vmax of cardiac plasma membrane adenylate cyclase without significantly influencing Km. Increasing Ca2+ in the range between 10−7 and 10−5M inhibited basal, l-epinephrine-stimulated, and NaF-stimulated activities. Basal rates of cyclic AMP production were more sensitive to Ca2+ than was l-epinephrine-stimulated adenylate cyclase activity, so that l-epinephrine stimulation was increased from approximately 60% in 0.5 mM EGTA to approximately 150% in 10−3M Ca2+ and 400% in 10−5M Ca2+. The inhibitory effect of Ca2+ on adenylate cyclase activity may represent a negative feedback mechanism by which elevation of intracellular Ca2+ concentration lowers cellular levels of cyclic AMP and thus reduces Ca2+ influx into the myocardium.

KEY WORDS  
ouabain  
guinea pig  
epinephrine  
cyclic adenosine-3',5'-monophosphate  
calcium  
negative feedback

In the heart, in which contractile performance is regulated by systems intrinsic to the muscle, a number of stimuli impinge on the myocardial cell that can, ultimately, modify the interactions between the heart's contractile proteins. These stimuli, which arise from physiological, pharmacological, and pathological influences, probably have their initial action on the plasma membrane. The recent availability of a plasma membrane preparation, purified from mammalian hearts without the use of high concentrations of polar (e.g., LiBr, NaI) or nonpolar (e.g., deoxycholate) structure-disrupting agents (1), permits comparison of the mechanisms influencing two such control systems: the sodium, potassium—activated adenosinetransphosphatase (Na, K-ATPase), believed to represent an activity of the sodium pump (2) that has been suggested to mediate the positive inotropic actions of cardiac glycosides (3-5) and the adenylate cyclase system that has been proposed to mediate cellular actions of agents such as catecholamines (6-9), glucagon (8, 10), and thyroxine (11). Although much information has been obtained to define the...
physiological and pharmacological systems that control the activities of Na, K-ATPase and adenylate cyclase, most studies have used different preparative methods to purify these two activities. In the present study, the mechanisms which control Na, K-ATPase and adenylate cyclase activities of myocardial plasma membranes were compared to determine the extent of independence and interdependence of these two control systems, both of which are located at the cell surface.

Methods

Plasma membranes from guinea pig hearts were prepared as described previously (1). Briefly, the method employed homogenization, osmotic shock, and extraction of the contractile proteins with hypertonic KCl, in some cases followed by exposure to changes in ambient pressure. The preparation used in these experiments was that obtained after the extraction step unless otherwise stated.

Adenylate cyclase activity was assayed under the standard conditions described previously (1) within 30 hours after preparation of the membranes, except that 1 mg/ml of creatine phosphokinase and 25 mM di-Tris phosphocreatine were used as the adenosine triphosphate (ATP) regenerating system. In experiments in which the effects of Ca²⁺ on adenylate cyclase activity were studied, assays were performed at 25°C for 210 minutes in a medium containing 5 mM \([\alpha-\text{32P}]\text{ATP}, 5 \text{ mM MgCl}_2, 0.5 \text{ mM unlabeled cyclic adenosine-3', 5'-monophosphate (cyclic AMP), 0.8 mg/ml of plasma membranes, various concentrations of ionized Ca}^{2+}, \text{ and 100 mM imidazole buffer at pH 6.8.}]\) levels of ionized Ca²⁺ were maintained with Ca-ethyleneglycol bis(β-aminoethyl ether)-N, N'-tetraacetic acid (EGTA) buffers (12). The amount of cyclic AMP released was determined by thin-layer chromatography in 0.3M LiCl on polyethyleneimine-impregnated plastic sheets, according to the method of Bar and Hechter (13). ATP levels, determined by thin-layer chromatography of aliquots of the reaction mixtures on polyethyleneimine-impregnated sheets in 2N HCOOH and 0.5M LiCl, remained essentially constant during the incubations; more than 90% of the radioactivity was recovered as ATP. Standard ATPase assay media contained 0.15-0.2 mg/ml of plasma membranes, 5 mM MgATP, 10⁻⁸M Ca²⁺, 40 mM imidazole buffer at pH 6.8 and 37°C, and various concentrations of KCl, NaCl, or both. The amount of inorganic phosphate (P) produced was determined as described previously (1). The Na, K-ATPase activity was estimated by subtracting the ATPase in 0.12M NaCl from that in 0.02M KCl plus 0.10M NaCl.

Tetra (triethylammonium) [\([\alpha-\text{32P}]\text{ATP (5-10 mc/\mu mole) in aqueous solution at pH 7.4 was pur-}]

chased from New England Nuclear Corporation. Creatine phosphokinase and di-Tris phosphocreatine, obtained from Boehringer Mannheim Corporation and Sigma Chemical Company, respectively, were dissolved in cold 5 mM Tris-HCl (pH 7.5) immediately prior to use. ATP, obtained as Na₂ATP from the Sigma Chemical Company, was deionized by chromatography on Dowex 50 and neutralized with Tris as described earlier (14). Ouabain octahydrate, obtained from Sigma Chemical Company, was dissolved in cold distilled water and stored at 0°C in the dark. All chemicals were reagent grade, and distilled water was deionized and redistilled from glass prior to use. \(\beta\)-Epinephrine, obtained from the Sigma Chemical Company, was dissolved in cold distilled water and used within 2 hours.

Results

ATPase activity of the isolated guinea pig sarcolemma showed the pattern of activation by various mixtures of NaCl and KCl that is typical of plasma membrane Na, K-ATPases (Fig. 1). Thus, ATPase activity was stimulated when Na⁺ and K⁺ were present to-
together, maximal activation being attained at 0.02M KCl and 0.01M NaCl. The specific activity of Na, K-ATPase, estimated by subtracting the ATPase activity in 0.12M NaCl from that in 0.02M KCl plus 0.10M NaCl, was usually within the range of 4.5 to 6.5 μmoles Pi/hour mg⁻¹ protein; that for ATPase in the presence of either NaCl or KCl alone (basal ATPase) was 4-6 μmoles Pi/hour mg⁻¹ protein.

Ouabain (10⁻⁵M) completely abolished the activation by KCl plus NaCl, reducing ATPase activity to the basal level seen with 0.12M NaCl or KCl alone (Fig. 1). Ouabain had no effect on the basal ATPase activity measured in either 0.12M KCl or NaCl alone. As shown in Figure 2, half-maximal inhibition of the ATPase activity by ouabain, determined in 0.02M KCl and 0.10M NaCl, was seen at approximately 3 x 10⁻⁷M ouabain. The ATPase activity in 0.02M KCl plus 0.10M NaCl was inhibited by NaF at concentrations greater than 1 mM. Slight inhibition of basal ATPase in 0.12M NaCl was also seen (Fig. 3). The Na,K-ATPase was inhibited by 50% at approximately 20 mM NaF (Fig. 3). At concentrations as high as 10⁻⁴M, l-epinephrine had no effect on Na,K-ATPase activity.

KCl caused marked stimulation of the adenylate cyclase activities of both the purified plasma membranes and the crude homogenate (Fig. 4). The rate of cyclic AMP production increased almost linearly with increasing KCl concentrations up to 0.2M. Similarly, NaCl at concentrations up to 0.2M caused activation of adenylate cyclase; the extent of activation by KCl and NaCl was indistinguishable (Table 1). In contrast to the ATPase activity, sarcolemmal adenylate cyclase activity was not stimulated by various combinations of NaCl and KCl as long as the total cation concentration remained constant (Fig. 5a). Furthermore, ouabain (10⁻⁵M) had no effect on either basal cyclic AMP production (Fig. 5b) or on adenylate cyclase activity in the presence of various combinations of Na⁺ and K⁺ (Fig. 5a). This lack of a cardiac glycoside effect was apparent over a wide range of ouabain concentrations (Table 2).
Plasma membrane adenylate cyclase activity was stimulated by NaF and l-epinephrine, maximal stimulation under the standard assay conditions being within the range of 100% to 150% for 8 mM NaF and 30% to 50% for 10^{-4}M l-epinephrine. Typical examples of stimulation are shown in Figure 6. NaF at 8 mM gave maximal stimulation; higher concentrations were inhibitory. Maximal stimulation by l-epinephrine was obtained at 10^{-4}M, half-maximal stimulation being seen at approximately 5 \times 10^{-6}M. Propranolol abolished the stimulation by l-epinephrine, and d-epinephrine failed to activate adenylate cyclase activity (Table 3). The stimulatory effects of l-epinephrine and NaF on the adenylate cyclase activity were examined as functions of ATP concentrations up to 0.5 mM at the fixed MgCl2 concentration of 10 mM. Lineweaver-Burk plots showed that the maximal velocity ($V_{\text{max}}$) of the basal activity was increased 21% and 89% by l-epinephrine and NaF, respectively, whereas the $K_m$ for ATP of 0.06 mM was not significantly altered by either l-epinephrine or NaF (Fig. 7).

The activities of basal, l-epinephrine-stimulated, and NaF-stimulated adenylate cyclase depended on ionized Ca^{2+} concentration. The absolute levels of basal and l-epinephrine-stimulated adenylate cyclase activities both decreased as Ca^{2+} concentration was increased, but the extent of stimulation...
by \(l\)-epinephrine was greater at higher \(Ca^{2+}\) concentrations (Fig. 8). The extent of stimulation of adenylate cyclase activity by 8 mM NaF similarly increased with increasing \(Ca^{2+}\) concentration (Table 4). The \(l\)-epinephrine sensitivity of adenylate cyclase activity was examined in the presence of \(10^{-7}\)M and \(10^{-5}\)M \(Ca^{2+}\) (Fig. 9). Increasing \(Ca^{2+}\) concentration caused very little shift in the \(l\)-epinephrine concentration needed for half-maximal stimulation, from \(2 \times 10^{-6}\)M in \(10^{-7}\)M \(Ca^{2+}\) to \(5 \times 10^{-6}\)M in \(10^{-5}\)M \(Ca^{2+}\) (both of which are similar to the value of \(5 \times 10^{-6}\)M measured in 0.5 mM EGTA under slightly different conditions, Fig. 6, bottom), suggesting that \(Ca^{2+}\) may inhibit only an \(l\)-epinephrine-insensitive component of adenylate cyclase. It should be noted that adenylate cyclase activity was much less when reactions were carried out at pH 6.8 and 25°C, in contrast to the other studies reported in the present paper, in which pH was 7.4 and temperature was 37°C. However, the pH dependency of the Ca-EGTA buffers made it necessary to work away from the optimal conditions.

**Discussion**

Two different control systems can be identified in purified guinea pig myocardial plasma membranes. One of these modifies the ATPase activity that is generally attributed to the sodium pump; the other modulates adenylate cyclase activity, which controls cyclic AMP production in the heart. The present findings indicate that the plasma membrane Na, K-ATPase and adenylate cyclase activities are regulated independently in that factors which modify the activity of one enzyme do not cause parallel changes in the other (Table 5). Thus, plasma membrane ATPase is stimulated by the combination of Na\(^+\) and K\(^+\), inhibited by ouabain, and insensitive to epinephrine, whereas adenylate cyclase activity, although enhanced by either

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**TABLE 2**

<table>
<thead>
<tr>
<th>Concentration of ouabain (M)</th>
<th>Adenylate cyclase activity (pmoles cyclic AMP/mg min(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>195 ± 8</td>
</tr>
<tr>
<td>(10^{-9})</td>
<td>207 ± 4</td>
</tr>
<tr>
<td>(10^{-8})</td>
<td>208 ± 11</td>
</tr>
<tr>
<td>(10^{-7})</td>
<td>193 ± 9</td>
</tr>
<tr>
<td>(10^{-6})</td>
<td>197 ± 8</td>
</tr>
<tr>
<td>(10^{-5})</td>
<td>198 ± 8</td>
</tr>
<tr>
<td>(10^{-4})</td>
<td>207 ± 9</td>
</tr>
</tbody>
</table>

Measurements were carried out with 0.4 mg/ml of plasma membranes under standard conditions as described in Methods. The values of adenylate cyclase activity are averages ± SE based on six determinations.
TABLE 3
Effects of l- and d-Epinephrine and of d, l-Propranolol on Cardiac Sarcolemmal Adenylate Cyclase Activity

<table>
<thead>
<tr>
<th>Addition</th>
<th>Adenylate cyclase activity (pmoles cyclic AMP/mg min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>2.27 ± 1.83</td>
</tr>
<tr>
<td>10⁻⁶M l-epinephrine</td>
<td>9.54 ± 1.81*</td>
</tr>
<tr>
<td>10⁻⁴M d-epinephrine</td>
<td>2.27 ± 3.14</td>
</tr>
<tr>
<td>10⁻⁴M l-epinephrine + 5 × 10⁻⁴M d, l-propranolol</td>
<td>3.20 ± 0.91+</td>
</tr>
</tbody>
</table>

The values of adenylate cyclase activity are means ± SE of six determinations. Assays were performed at 25°C and pH 6.8 as described in Methods for studies with Ca²⁺-buffers, except that ATP and protein concentrations were 2 mM and 2.5 mg/ml, respectively. Ca²⁺ concentration was 10⁻⁵M.

* t = 2.815, P < 0.01 compared with control.
+ t = 2.782, P < 0.01 compared with 10⁻⁴M l-epinephrine.

K⁺ or Na⁺ alone, is not affected by Na⁺ and K⁺ together, is insensitive to ouabain, and is stimulated by epinephrine. Both enzymes are inhibited by Ca²⁺, but the percent stimulation of adenylate cyclase that is produced by epinephrine is greater at higher Ca²⁺ concentrations.

The sensitivity of Mg²⁺-dependent ATPase to K⁺ and Na⁺ and that of Na⁺, K-ATPase to ouabain exhibited by the present plasma membrane preparation were similar to those reported by Stam et al. (15) and Matsui and Schwartz (16). The observed kinetic parameters of ouabain-induced inhibition of Na⁺, K-ATPase activity are in good agreement with those reported previously (15, 16). The specific activity of Na⁺, K-ATPase, 4.5–6.5 μmoles P₆/hour mg⁻¹ protein is comparable to that of dog heart Na⁺, K-ATPase (15) but is about one fifth of that of a calf heart microsomal preparation (16). In the latter preparations, however, the membranes were treated with detergent (deoxycholate) and concentrated salt (NaI), which may activate this enzyme. These substances were avoided in our preparation to preserve the labile hormone receptors of the adenylate cyclase system.

The basal adenylate cyclase activity of myocardial plasma membranes in the present investigation was over 200 pmoles cyclic AMP/min mg⁻¹ protein under standard conditions in which ATP concentration was submaximal (0.2 mM). The maximal rates of basal, epinephrine-stimulated, and NaF-stimulated myocardial adenylate cyclase were estimated from the Lineweaver-Burk plots to be about 330, 400, and 630 pmoles/min mg⁻¹ protein, respectively (Fig. 7). These specific activities are higher than those reported previously (6–10) and may reflect the extraction of contractile proteins during the
table 4

<table>
<thead>
<tr>
<th>Ca²⁺ Concentration (M)</th>
<th>Adenylate cyclase activity (pmoles cyclic AMP/mg min⁻¹)</th>
<th>Stimulation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>27.8 ± 1.8</td>
<td>127</td>
</tr>
<tr>
<td>8 mM NaF</td>
<td>63.1 ± 1.8</td>
<td>127</td>
</tr>
<tr>
<td>10⁻⁷</td>
<td>26.3 ± 1.0</td>
<td>182</td>
</tr>
<tr>
<td>10⁻⁶</td>
<td>21.2 ± 1.9</td>
<td>215</td>
</tr>
<tr>
<td>10⁻⁵</td>
<td>12.2 ± 1.2</td>
<td>233</td>
</tr>
<tr>
<td>10⁻⁴</td>
<td>5.1 ± 0.7</td>
<td>391</td>
</tr>
</tbody>
</table>

Measurements were carried out with Ca²⁺ buffers as described in methods. The values of adenylate cyclase activity are means ± se based on six determinations. These studies were carried out at pH 6.8 and 25°C.

Preparation and the inclusion of EGTA, a Ca²⁺ chelator, in the assay media.

Adenylate cyclase activity of the cardiac plasma membranes was stimulated by KCl or NaCl, but unlike ATPase activity adenylate cyclase activity was not stimulated further when KCl and NaCl were present together. In intact tissues there is evidence that K⁺ may participate in the physiological control of cyclic AMP production. Thus, elevation of K⁺ concentration in the perfused rat heart, which leads to membrane depolarization, has been reported to abolish epinephrine-induced cyclic AMP production (17). Similarly, in slices of guinea pig cerebral cortex, incubation with elevated K⁺ concentration or with depolarizing agents such as veratridine and batrachotoxin increases cyclic AMP levels (18, 19). Electrical stimulation of brain slices also has been found to increase cyclic AMP production (20). These observations could be explained if altered K⁺ levels at the cell surface act to modify the adenylate cyclase activity which is located on the plasma membrane. However, the present investigation demonstrates that the adenylate cyclase activity of the isolated myocardial plasma membrane is not influenced when KCl is partially substituted for NaCl, although cyclic AMP production is enhanced when ionic strength is raised with either KCl or NaCl. These apparent discrepancies may be attributed to the fact that isolated plasma membranes are probably not polarized electrically, unlike the plasma membranes of the intact heart. Although the physiological implication of the stimulation of myocardial plasma membrane adenylate cyclase activity by increasing ionic strength is not clear, observations analogous to the present findings have been reported by Dousa and Hechter (21) and Dousa (22) in a vasopressin-sensitive adenylate cyclase preparation from the renal medulla. In these studies, comparison of the effects of polar (KCl and NaCl) and nonpolar (glucose and urea) solutes indicated that it was the polarity of the solute rather than its osmolarity that modified the adenylate cyclase activity.

Ouabain at concentrations as high as 10⁻³M was without effect on adenylate cyclase activity in the presence and the absence of various combinations of NaCl and KCl. Previous reports disagree as to whether cardiac glycosides inhibit adenylate cyclase activity. Cardiac glycosides, like omission of K⁺ from the medium, have been found to inhibit lipolysis (23, 24) possibly by inhibiting the effect of catecholamines (25). Inhibition of epinephrine-induced stimulation of lipolysis and glu-
Table 5
Control of Plasma Membrane Sodium, Potassium-Activated Adenosinetriphosphatase and Adenylate Cyclase Activities

<table>
<thead>
<tr>
<th>Modifier</th>
<th>Na, K-ATPase</th>
<th>Adenylate cyclase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na&lt;sup&gt;+&lt;/sup&gt; + K&lt;sup&gt;-&lt;/sup&gt; together</td>
<td>Increase</td>
<td>No effect</td>
</tr>
<tr>
<td>Cardiac glycosides</td>
<td>Decrease</td>
<td>No Effect</td>
</tr>
<tr>
<td>NaF</td>
<td>Decrease</td>
<td>Increase</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>No effect</td>
<td>Increase</td>
</tr>
<tr>
<td>Ca&lt;sup&gt;2+&lt;/sup&gt;</td>
<td>Decrease</td>
<td>Decrease in basal activity increase in epinephrine and NaF stimulation</td>
</tr>
</tbody>
</table>

Coneogenesis of rat epididymal fat pads by ouabain has been suggested to be due to interference with activation of adenylate cyclase (26). However, in brown fat cells (27) and in guinea pig brain (19) ouabain has been reported to enhance cyclic AMP formation.

Cardiac plasma membrane Na, K-ATPase activity was inhibited by NaF, whereas adenylate cyclase activity was stimulated by low concentrations of NaF. At concentrations above 10 mM, NaF caused inhibition of adenylate cyclase. Stimulation of adenylate cyclase activity by NaF is not, however, attributable to the ability of NaF to inhibit ATPase activity, because the ATP regenerating system in the adenylate cyclase assay medium kept ATP concentrations constant throughout the incubation period, as monitored by thin-layer chromatography (see Methods). Epinephrine, which stimulated adenylate cyclase activity, is without effect on Na, K-ATPase activity (28).

The role of Ca<sup>2+</sup> in the control of adenylate cyclase activity remains controversial. An inhibitory effect of Ca<sup>2+</sup> or a stimulatory effect of EGTA on the basal and the total level of hormone-stimulated cyclic AMP production similar to that found in the present study has also been seen in other tissues (29-32). Similarly, inhibition of basal adenylate cyclase has been found in previous studies of cardiac muscle preparations (33, 34). Sulakhe and Dhalla (34), who studied the effects of increasing Ca<sup>2+</sup> concentration in the millimolar range, did not demonstrate an increase in the stimulation by epinephrine such as was seen in the present study when Ca<sup>2+</sup> concentrations were increased in the micromolar range (Fig. 8). In contrast, other studies with noncardiac preparations indicate that EGTA can inhibit basal or polypeptide hormone-stimulated adenylate cyclase activity, or both (35-39); however, Lefkowitz et al. (35), Bockaert et al. (38), and Bär and Hechter (39) have presented evidence that Ca<sup>2+</sup> has a stimulatory action at low concentration, although higher Ca<sup>2+</sup> concentrations inhibit these activities. These discrepancies may be partly due to the reported Ca<sup>2+</sup> dependence of phosphodiesterase activity (40, 41), since this enzyme, which degrades cyclic AMP, is activated when Ca<sup>2+</sup> is raised from 10<sup>-8</sup>M to 10<sup>-5</sup>M. Thus, the inhibition of basal adenylate cyclase activity by Ca<sup>2+</sup> shown in Figure 8 may be partly explained by enhanced cyclic AMP breakdown at the higher Ca<sup>2+</sup> concentrations. Under the present assay conditions, in which 0.5 mM unlabeled cyclic AMP was included, effects of phosphodiesterase would be minimized.

The present finding that Ca<sup>2+</sup> inhibits cardiac sarcolemmal adenylate cyclase activity indicates that Ca<sup>2+</sup> may participate in the control of cyclic AMP levels in the myocardial cell. This putative control mechanism appears to operate within the range of Ca<sup>2+</sup> concentrations that is found intracellularly. At 10<sup>-7</sup>M Ca<sup>2+</sup>, which approximates the Ca<sup>2+</sup> concentration in the myocardium during diastole (42), basal levels of adenylate cyclase activity are almost twice the level measured in 10<sup>-5</sup>M Ca<sup>2+</sup>, the systolic level of this cation. Inhibition of cyclic AMP production when Ca<sup>2+</sup> levels are increased may represent part of a control mechanism by which increasing intracellular Ca<sup>2+</sup> lowers cyclic AMP concent-

**Proposed interrelationships between Ca<sup>2+</sup> and cyclic AMP levels in the myocardium.**
tration. Such a mechanism may also be manifest by the reported stimulatory effects of Ca\(^{2+}\) on phosphodiesterase, the enzyme responsible for cyclic AMP breakdown. The levels of Ca\(^{2+}\) needed for activation of phosphodiesterase, like those that inhibit adenylate cyclase, are extremely low, half-maximal activation of the former being seen in the micromolar range of Ca\(^{2+}\) concentration (40, 43). Lowering of the cyclic AMP level, the net result of these effects of Ca\(^{2+}\) on adenylate cyclase and phosphodiesterase, appears to represent one limb of a negative feedback control mechanism. The primary limb of this control mechanism involves the effect of both adrenergic agonists (44) and dibutyryl cyclic AMP (45) to increase the influx of Ca\(^{2+}\) into the myocardium, thereby raising intracellular Ca\(^{2+}\) concentration (Fig. 10).

Acknowledgment

The authors gratefully acknowledge the assistance of Mr. David Reiss in obtaining the data presented in Table 3.

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*Circ Res.* 1975;36:8-17
doi: 10.1161/01.RES.36.1.8

*Circulation Research* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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