Cardiac Actions of Glucagon

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ABSTRACT

Glucagon increased heart rate and contractile force in the anesthetized dog and increased isometric tension in the isolated dog papillary muscle. The positive inotropic and chronotropic responses were not abolished or reduced by previous administration of the beta-receptor blocking agent propranolol, in doses of 0.5 mg/kg. Glucagon increased the force and rate of cardiac contraction even when cardiac-depressant doses of propranolol, 2 mg/kg, had been given. Previous treatment with reserpine (1.0 mg/kg on each of 3 consecutive days) failed to diminish the positive inotropic and chronotropic effects of glucagon. However, previous administration of tyramine, 0.05 mg/kg, which resulted in a positive inotropic response in the dog, significantly reduced the glucagon-induced positive inotropic response. Theophylline, 10 mg/kg, likewise prevented the inotropic action of glucagon without preventing the positive inotropic effect of calcium chloride. The increase in isometric tension produced by glucagon in the isolated dog papillary muscle was prevented during simultaneous exposure of the muscles to acetylcholine. The results of these studies are discussed in reference to the known metabolic actions of glucagon and the catecholamines and the possibility that they both share a common mechanism of action mediated through an increase in the intracellular concentration of cyclic 3',5' AMP.

ADDITIONAL KEY WORDS propranolol tyramine reserpine theophylline heart rate acetylcholine papillary muscle dichloroisoproterenol beta-receptor blockade

The production of hepatic glycogenolysis by both epinephrine and glucagon was demonstrated by Sutherland and Cori (1); this led Farah and Tuttle (2) to study the cardiac actions of glucagon. These initial studies showed glucagon to be without inotropic or chronotropic effects in the intact, anesthetized dog, but to possess positive inotropic and chronotropic actions in the dog heart-lung preparation and on isolated hearts of several species (2). In addition, the cardiotimulatory effects of glucagon were reported to be reduced or abolished by the beta-receptor blocking agent, dichloroisoproterenol. Regan et al. (3) likewise reported the positive inotropic action of glucagon to be inhibited by dichloroisoproterenol and suggested that the hormone acted at beta-receptor sites. Studies by Whitehouse and James (4) suggested that the positive chronotropic effect of glucagon injected into the nutrient artery of the canine sinus node was due in part to the local release of nodal stores of norepinephrine and in part to a direct action of glucagon on the sinus node.

The metabolic effects of glucagon upon the isolated perfused heart are essentially identical to those of epinephrine and Kreisberg and Williamson suggested that their effects are mediated by a common mechanism (5). Both glucagon and epinephrine activate cardiac and hepatic phosphorylase (6, 7) and cyclic 3', 5' AMP levels of adipose tissue are increased by glucagon (8); effects which support the concept that both glucagon

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and epinephrine have similar metabolic actions upon a variety of tissues.

The purposes of this investigation were to determine, in the dog heart, whether the cardiotimulatory effects of glucagon are dependent upon direct activation of myocardial beta-receptors or upon an indirect release of endogenous catecholamines, and to explore possible mechanisms by which to explain the cardiac actions of the pancreatic hyperglycemic factor, glucagon.

**Methods**

**Open-Chest Dog Preparation.**—Dogs weighing between 9 and 17 kg were anesthetized with pentobarbital sodium, 30 mg/kg iv. Positive pressure respiration was maintained by a Harvard respirator pump. Systemic arterial blood pressure was measured from the femoral artery by a Statham pressure transducer. The cervical vagi were severed bilaterally. The chest was entered through the fourth or fifth right interspace, and the pericardium was opened and sutured to the body wall to form a cradle for the heart. A Brodie-Walton strain gauge arch was sutured to the anterior wall of the right ventricle. The segment of ventricular muscle between the feet of the arch was stretched to a length which produced the greatest active tension. Changes in contractile force were expressed either in grams or as percentage change from control which was taken as 100 percent. Cardiac rate was recorded with a Grass cardiotachograph. Recordings were made on a Grass Model 7 polygraph.

The Locke bathing solution was of the following composition expressed as g/liter: NaCl, 9.0; CaCl₂ • 2H₂O, 0.24; KCl, 0.42; Dextrose, 2.0 and NaHCO₃, 0.5. The solution was equilibrated with 95% O₂-5% CO₂ and had a pH of 7.4.

Solutions for in vivo studies were made each day by dissolving the glucagon¹ in 0.9% sodium chloride solution containing 0.1% Tris (hydroxy-methyl) aminomethane (Tris Buffer) adjusted to a pH of 9.5. Solutions were made so as to contain glucagon in a concentration of 50 µg/ml. Drug solutions used for in vitro studies were prepared so as to have a final glucagon concentration of 500 µg/ml dissolved in Locke’s solution containing 0.1% Tris Buffer and adjusted to a pH of 8.5.

The standard t-test as described by Snedecor and Cochran (9) was used for group comparisons;

²The glucagon used in these studies was obtained from the Lilly Research Laboratories as crystalline glucagon (Lot 258-254 B-167-1).

| Table 1 |
|---|---|---|---|---|---|---|---|
| **Dose of glucagon (mg/kg)** | **Mean increase in force (g)** | **P value** | **Mean increase in heart rate (beats/min)** | **P value** |
| **Before** | **After** | **Before** | **After** |
| 0.5 | 3.2 ± 0.4 | 1.6 ± 0.8 | >0.05 | 10.0 ± 1.6 | 6.0 ± 1.6 | >0.05 |
| 2.0 | 12.4 ± 5.4 | 9.2 ± 3.2 | >0.05 | 39.0 ± 8.1 | 29.0 ± 6.9 | >0.05 |
| 4.0 | 19.6 ± 0.2 | 18.8 ± 5.4 | >0.05 | 64.0 ± 8.7 | 63.0 ± 8.9 | >0.05 |
| 8.0 | 25.2 ± 0.2 | 25.2 ± 6.6 | >0.05 | 81.0 ± 7.8 | 94.0 ± 6.8 | >0.05 |
| 10.0 | 23.6 ± 1.0 | 27.6 ± 3.8 | >0.05 | 87.5 ± 5.2 | 106.3 ± 4.7 | >0.05 |

²The glucagon used in these studies was obtained from the Lilly Research Laboratories as crystalline glucagon (Lot 258-254 B-167-1).

Dog Papillary Muscle Preparation.—Papillary muscles were obtained from dogs weighing between 7 and 9 kg, anesthetized with pentobarbital sodium. Right ventricular papillary muscles were removed rapidly and suspended in a 25-ml organ bath by 4-0 silk ties, one end attached to a muscle holder and the other to a Grass FT-03 force displacement transducer. The papillary muscles were placed under a resting tension of 2 g and stimulated through punctate electrodes with a Grass SD-5 stimulator at a rate of 30/min, with square wave stimuli of 1-msec duration at a voltage 25% greater than threshold. Recordings were made on a Grass Model 7 polygraph.

The purposes of this investigation were to determine, in the dog heart, whether the cardiotimulatory effects of glucagon are dependent upon direct activation of myocardial beta-receptors or upon an indirect release of endogenous catecholamines, and to explore possible mechanisms by which to explain the cardiac actions of the pancreatic hyperglycemic factor, glucagon.

²The glucagon used in these studies was obtained from the Lilly Research Laboratories as crystalline glucagon (Lot 258-254 B-167-1).
Effect of propranolol and then glucagon administered to an anesthetized dog. The upper panels show the marked depression of heart rate and myocardial contractile force following the administration of propranolol. These changes are accompanied by a slight decrease in the mean blood pressure. The lower panels show the positive chronotropic and inotropic responses to glucagon. The systemic blood pressure is not altered significantly.

the t-test for paired comparisons was used according to Hill (10). All values are expressed along with their standard errors (±SE).

Results
EFFECTS OF GLUCAGON ON CONTRACTILE FORCE, HEART RATE, AND BLOOD PRESSURE

Glucagon was administered in cumulative doses of 0.5, 2.0, 4.0, 8.0, and 16.0 μg/kg to each of 4 dogs, while a fifth dog received glucagon up to a cumulative dose of 8 μg/kg. Each subsequent dose was administered when the peak inotropic and chronotropic responses to the previous dose had been attained. The interval between injections was never greater than 4 minutes and the responses to glucagon became manifest 10 to 15 seconds after its intravenous administration. There was a progressive increase in both force and rate with each increment in the dose. The average durations of the increases in heart rate and contractile force after a total cumulative dose of 16 μg/kg were 45 and 30 minutes respectively, after which both heart rate and ventricular contractile force gradually returned to control levels. The durations of the increases above control never exceeded 60 minutes. The blood pressure responses to the doses of glucagon used were transient, were seen within 10 to 15 seconds after injection, and consisted of an average decrease of 8 mm Hg. When heart rate and contractile force had returned to control levels for 30 minutes, each of the dogs was given propranolol, 0.5 mg/kg iv, followed in 15 minutes by administration of glucagon in the same manner as before up to a cumulative dose of 16 μg/kg (except in one dog in which 8 μg/kg was the cumulative dose).

The ability of glucagon to produce a positive inotropic and chronotropic response in the presence of beta-receptor blockade was demonstrated in a second group of 5 dogs which received propranolol in a dose of 2 mg/kg. These data are also summarized in

\[ P \text{ value} < 0.05 \]

2Propranolol was supplied by Ayerst Laboratories.

TABLE 2
Effect of Isoproterenol on Contractile Force before and after Propranolol, 0.5 mg/kg

<table>
<thead>
<tr>
<th>Dose of isoproterenol (μg/kg)</th>
<th>Before (g)</th>
<th>After (g)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05</td>
<td>13.2 ± 1.8</td>
<td>0</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>0.10</td>
<td>22.8 ± 3.4</td>
<td>0</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>0.20</td>
<td>34.0 ± 4.4</td>
<td>0</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>0.80</td>
<td>45.6 ± 8.2</td>
<td>6.0 ± 1.6</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>1.60</td>
<td>12.4 ± 1.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.20</td>
<td>30.0 ± 3.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.40</td>
<td>41.6 ± 4.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Force was measured as increase from control. The values are the means of the increase in force ±SE obtained from 5 dogs.
Table 1 and illustrate that, in the presence of much more propranolol than is required to achieve beta-receptor blockade, glucagon is capable of augmenting cardiac contractile force and heart rate. The recordings shown in Figure 1 are typical of the results obtained with glucagon in dogs pretreated with large, myocardial depressant doses of propranolol.

The effectiveness of propranolol, 0.5 mg/kg, in producing beta-receptor blockade was examined in a group of 5 dogs. The positive inotropic responses to geometrically increasing single doses of isoproterenol were compared before and after the administration of propranolol. The results of one such experiment are shown in Figure 2 and the data from all 5 dogs are summarized in Table 2. Examination of the data, as well as the tracings in Figure 2, illustrate the marked increase in the dose of isoproterenol required to produce a positive inotropic response in the dog pretreated with propranolol. Furthermore, after propranolol the large doses (0.8 to 6.4 μg/kg) of isoproterenol required to cause an
increase in myocardial force are associated with increases in systemic blood pressure as illustrated in Figure 2. The results with isoproterenol after beta-receptor blockade are in marked contrast to the observations made with glucagon under similar conditions.

It has been reported previously that dichloroisoproterenol, a beta-receptor blocking agent, prevented the cardiac effects of glucagon (2, 3). This finding was confirmed in 3 dogs each of which failed to exhibit a positive inotropic or chronotropic response to glucagon, 4 μg/kg iv, following pretreatment with dichloroisoproterenol in a dose of 7 mg/kg. The results of one such experiment are illustrated in Figure 3 in which control responses to isoproterenol consisted of an increase in myocardial force and heart rate, both responses being prevented by dichloroisoproterenol. Likewise, glucagon, 4 μg/kg, failed to produce the typical responses previously illustrated in Figure 1. It should be noted that in each of the animals receiving dichloroisoproterenol there was an associated increase in cardiac contractile force which was sustained. The injection of glucagon 15 minutes after dichloroisoproterenol (at a time when force and rate were increased due to dichloroisoproterenol) was not accompanied by a positive inotropic effect and produced a minor increase in heart rate; the mean increases in ventricular force and heart rate were 41.2 (±7.1) and 33.8 (±4.3) % respectively before dichloroisoproterenol as
TABLE 3
Effect of Glucagon on Contractile Force and Heart Rate before and during Theophylline-Induced Stimulation

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Glucagon (4 μg/kg)</th>
<th>Theophylline (10 mg/kg)</th>
<th>Glucagon (4 μg/kg) Plus CaCl₂ (5 mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Force (g)</td>
<td></td>
<td>41.8 ± 2.2</td>
<td>40.0 ± 2.2</td>
<td>78.4 ± 4.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>67.2 ± 2.2</td>
<td>71.8 ± 3.2</td>
<td>92.2 ± 5.2</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>120.7 ± 10.0</td>
<td>207.7 ± 14.4*</td>
<td>119.3 ± 8.1</td>
<td>212.4 ± 11.5*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>164.7 ± 8.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All values are means ± se obtained from 9 dogs.
*The significance of the difference, P, for the two glucagon values is greater than 0.50.

FIGURE 4
Effects of glucagon in the dog pretreated with reserpine before and during cardiac stimulation with theophylline. Upper part of each segment shows right ventricular contractile force with heart rate recorded below. (A) Control response to glucagon showing a positive inotropic and chronotropic effect. (B) Two hours after the initial dose of glucagon, the dog was given theophylline as a slow intravenous infusion which resulted in a sustained increase in force and rate. (C) Glucagon, 4 μg/kg, administered during the theophylline-induced cardiac stimulation, failed to produce a further augmentation in force, although CaCl₂ produced a positive inotropic effect.

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TABLE 4

Effect of Glucagon on Contractile Force before and during Tyramine-Induced Stimulation

<table>
<thead>
<tr>
<th>Control</th>
<th>Glucagon (4 µg/kg)</th>
<th>Tyramine (0.05 mg/kg)</th>
<th>Tyramine plus Glucagon (4 µg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>49.2 ± 7.8</td>
<td>80.0 ± 9.0</td>
<td>37.6 ± 5.2</td>
<td>68.0 ± 6.6</td>
</tr>
</tbody>
</table>

P < 0.05  P < 0.01  P > 0.20

All values are mean contractile force in grams ± se.

compared to no increase in ventricular force and an average chronotropic response of only 8.3 (± 2.1) % after dichloroisoproterenol. In 3 other dogs propranolol was administered in a dose of 1 mg/kg followed by dichloroisoproterenol, 7 mg/kg. In each of these 3 dogs, dichloroisoproterenol now produced a depression in cardiac force and the subsequent administration of glucagon, 4 µg/kg, resulted in positive inotropic and chronotropic effects which averaged 35.7 (± 6.1) and 28.2 (± 2.1) %, respectively. It appears, therefore, that the apparent ability of dichloroisoproterenol to block the cardiac actions of glucagon is in some manner related to the intrinsic sympathomimetic activity of the beta-receptor blocking agent.

EFFECTS OF GLUCAGON BEFORE AND AFTER THEOPHYLLINE IN THE DOG PRETREATED WITH RESERPINE

These studies were conducted on 9 dogs pretreated with reserpine, 1 mg/kg im, on each of 3 days prior to the experimental procedure. The depletion of myocardial stores of catecholamine was shown by the inotropic response to tyramine (0.05 mg/kg) which averaged 5.5% (± 3.1) (determined in 6 of the 9 dogs) as compared to a group of 5 control animals in which the same dose of tyramine produced a mean inotropic response of 101% (± 15.2).

Glucagon, 4 µg/kg, was administered to the 9 dogs pretreated with reserpine and this resulted in an average increase of 25.49 (80.7%) in contractile force and a mean increase of 87.0 (± 11.8) beats/min in the heart rate (Table 3).

Two hours after the initial glucagon injection, each of the animals received theophylline, 10 mg/kg, as a slow infusion for 15 minutes, which produced a gradual increase in contractile force and heart rate (Table 3 and Figure 4). When the response to theophylline had stabilized, glucagon was administered in a dose of 4 µg/kg. As shown in Figure 4 and summarized in Table 3, the administration of glucagon then failed to elicit its typical inotropic response. The combined administration of theophylline and glucagon had not produced a maximal inotropic response because the administration of CaCl₂, 5 mg/kg, resulted in a further augmentation in contractile force.

Effect of a cumulative increase in the concentration of glucagon upon the development of isometric tension in the isolated dog papillary muscle. Line above bar is 1 SEM.
EFFECT OF TYRAMINE ON THE INOTROPIC RESPONSE TO GLUCAGON

Glucagon, 4 μg/kg, was administered to 5 dogs before and during myocardial stimulation with tyramine, 0.05 mg/kg. Tyramine, an indirectly acting sympathomimetic amine, was used to produce a sustained increase in myocardial force. The data summarized in Table 4 show the absolute mean values for contractile force during the control states and following drug administrations. During the augmentation of contractile force by tyramine, the inotropic response to glucagon could not be elicited as in the control period prior to tyramine.

EFFECT OF GLUCAGON ON THE DOG PAPILLARY MUSCLE PREPARATION

In eight papillary muscles exposed to cumulative concentrations of glucagon: 0.1, 0.5, 2.0, and 8.0 μg/ml, isometric tension increased progressively as the concentration of glucagon was increased (Fig. 5). The inotropic response was sustained but it could be reversed by washing the papillary muscles with a glucagon-free medium. The isometric tension of the muscles increased repeatedly upon subsequent exposures to glucagon.

The positive inotropic response to glucagon in 6 papillary muscles could be prevented or significantly reduced by previous exposure to acetylcholine in a concentration of 16 μg/ml. Acetylcholine itself had a transient effect, which consisted of a brief increase in tension. Figure 6 was taken from a representative experiment showing the responses to glucagon before the addition of acetylcholine and again during exposure of the muscle to acetylcholine. The difference between the responses was significant (P < 0.01, paired comparison) and the response of the muscle to glucagon could be restored by washing the preparation in a drug-free medium. Following the removal of acetylcholine from the bathing solution, the subsequent addition of glucagon, 8 μg/ml, resulted in a marked increase in tension which was greater than that obtained in each of the muscles during their initial exposure to glucagon.

Discussion

Previous studies with glucagon (2-4) have demonstrated its cardio-stimulatory actions.
and have suggested a similarity between glucagon and the catecholamines with respect to their positive inotropic and chronotropic effects. Farah and Tuttle (2) and Regan et al. (3) suggested that the cardiac actions of glucagon are mediated through a stimulation of beta-receptors since the beta-receptor blocking agent, dichloroisoproterenol, could prevent the cardiac actions of glucagon. A similar conclusion was reached by Whitehouse and James (4), who reported that the positive chronotropic action of glucagon could be reduced by the administration of pronethalol. The results of the present investigation are in disagreement with these earlier observations regarding the effectiveness of beta-receptor blockade in preventing the actions of glucagon. A possible explanation for the discrepancy may be the dose of dichloroisoproterenol used in the study by Farah and Tuttle (2); they stated that 24 to 48 mg of dichloroisoproterenol/liter of blood was required to prevent or reduce the action of 100 to 200 µg of glucagon on cardiac contractility in the dog heart-lung preparation. This dose of dichloroisoproterenol given to the dog heart-lung preparation might be considered to be excessive, since Moran and Perkins (11) demonstrated that 7 mg/kg of dichloroisoproterenol/liter of blood was required to prevent or reduce the action of 100 to 200 µg of glucagon on cardiac contractility in the dog heart-lung preparation. This dose of dichloroisoproterenol given to the open-chest dog was sufficient to achieve beta-receptor blockade. In the present study, propranolol was used to produce beta-receptor blockade in doses of 0.5 mg/kg and 2.0 mg/kg. Previous studies (12, 13), as well as the present investigation, have shown that propranolol in a dose of 0.5 mg/kg produces a significant degree of beta-receptor blockade. However, the chronotropic and inotropic responses to glucagon were not blocked or reduced with either of these doses of propranolol. The evidence suggests that the cardiac actions of glucagon are not dependent upon beta-receptor stimulation as reported in previous studies (2, 3) in which dichloroisoproterenol was used to achieve specific beta-receptor blockade.

Dichloroisoproterenol, as shown by Fleming and Hawkins (14), acts as a "competitive dualist" and, as first demonstrated by Moran and Perkins (11), is capable of inducing myocardial augmentation of rate and force in addition to producing beta-receptor blockade. After dichloroisoproterenol glucagon failed to elicit its usual positive inotropic and chronotropic responses, as shown in the present study. However, prevention of the intrinsic sympathomimetic action of dichloroisoproterenol by previous beta-receptor blockade with propranolol now made it possible to elicit the positive chronotropic and inotropic responses to glucagon even though dichloroisoproterenol had been administered previously. Thus, it appears that the intrinsic sympathomimetic activity and not the beta-receptor blocking activity of dichloroisoproterenol may account for its ability to interfere with the cardiac actions of glucagon. This suggestion is supported by the observations made following theophylline or tyramine in which both agents effectively reduced the myocardial responses to the subsequent administration of glucagon. Although theophylline interfered with the cardiac actions of glucagon, it did not produce a maximum inotropic effect since it did not prevent a further augmentation in force by calcium chloride.

The ability of glucagon to elicit a positive inotropic and chronotropic response after beta-receptor blockade should be of interest in view of the potential clinical use of propranolol. It is possible, although further studies are required, that augmentation of myocardial contractility and heart rate brought about by glucagon might serve as a therapeutic approach to counteracting the myocardial depression and heart failure which may occur in the clinical use of propranolol (15, 16).

Pretreatment with reserpine failed to reduce the positive inotropic and chronotropic responses to glucagon even though the cardiac response to tyramine had been markedly reduced. These results are in agreement with previous reports (2, 3) and suggest that the cardiac actions of glucagon do not require a release of endogenous catecholamines.
Most of the metabolic actions of the catecholamines and glucagon upon the heart are qualitatively similar, with cyclic 3', 5' AMP as the most likely mediator (3, 5, 6). Cornblath et al. (6), using the isolated, perfused rat heart, demonstrated an increase in cardiac muscle phosphorylase when glucagon was added to the perfusion medium. Murad et al. (17) have reported the formation of cyclic 3', 5' AMP by catecholamines added to adenyl cyclase preparations from dog hearts. Although direct evidence is lacking for a stimulatory effect of glucagon upon cyclic 3', 5' AMP formation in cardiac muscle, there are sufficient data from studies in liver (18) and adipose tissue (8) to show that glucagon is capable of increasing the activity of this nucleotide. Indirect data suggest that a similar event occurs in cardiac muscle (5, 6).

Using isolated guinea pig hearts, Vincent and Ellis (19) demonstrated that acetylcholine inhibited the glycogenolytic actions of epinephrine and of theophylline. Recently, Meester and Hardman (20) reported that acetylcholine prevented the positive inotropic action of epinephrine and of theophylline in rabbit and turtle ventricular muscle, observations that support the earlier findings reported by Hollenberg et al. (21) who found that acetylcholine prevented the positive inotropic actions of epinephrine and norepinephrine when administered into the coronary arterial blood supply. The observations with glucagon provide further evidence for the similarity between it and epinephrine upon the myocardium. The ability of acetylcholine to prevent the positive inotropic responses to glucagon could be related to the effects of these agents on cyclic 3', 5' AMP formation. This interpretation is supported by the observations of Murad et al. (17) who demonstrated that the formation of cyclic 3', 5' AMP upon the addition of catecholamines to adenyl cyclase preparations from dog hearts could be reduced by the presence of acetylcholine. Sutherland et al. (22) have proposed a hypothesis which emphasizes the importance of cyclic 3', 5' AMP in the positive inotropic response to epinephrine. Whether glucagon acts similarly remains to be determined by direct biochemical studies.

References


