and to Eli Lilly and Co., Indianapolis, for generously supplying the acetyl-
strophanthidin used in this study.

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Changes in Cyclic Nucleotide Levels and Contractile
Force in the Isolated Hypoxic Rat Heart during
Perfusion with Glucagon

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WILLIAM J. GEORGE, PH.D.

SUMMARY Isolated rat hearts were perfused with hormonal
concentrations of glucagon during a hypoxic perfusion to determine
whether it would enhance recovery after reoxygenation. Rat hearts
were divided into two groups: (1) those perfused with glucose-free
Tyrode's solution and (2) those perfused with Tyrode's solution
containing glucose. During 3 minutes of exposure to hypoxia both
untreated hearts and hearts perfused with glucagon demonstrated a
decrease in contractile force to 10-20% of control. When glucose
was present in the perfusion medium, cardiac performance was better
during both the periods of hypoxia and reoxygenation. During
reoxygenation, recovery of contractile force was significantly better
(P < 0.05) in glucagon-perfused hearts than in untreated hearts;
this improved recovery occurred regardless of whether glucose was
included in the medium. The enhanced recovery of the glucagon-
perfused hearts was associated with decreases in myocardial levels
of guanosine 3',5'-monophosphate (cyclic GMP) both during the
periods of hypoxia and reoxygenation. At the end of the hypoxic period,
cyclic GMP levels in the glucagon-perfused hearts were 20-64% of the levels in untreated hearts.
Similarly, after 5 minutes of reoxygenation cyclic GMP levels in the glucagon-perfused hearts were
21% of the levels in untreated hearts. The effect of glucagon on
adeno-3',5'-monophosphate (cyclic AMP) concentrations in untreated hearts and in hearts receiving glucagon was not signifi-
cantly different either after 3 minutes of hypoxia or during reoxy-
genation. The rate of anaerobic glycolysis after 3 minutes of hypoxia was higher in untreated hearts than in glucagon-perfused
hearts, as determined by the lactate content of coronary perfusates.
These studies suggest that hormonal concentrations of glucagon exert
a protective effect on the hypoxic rat heart which involves a
modulation of cardiac cyclic GMP accumulation.

ISCHEMIC and hypoxic hypoxia severely impair cardiac
contractility.\textsuperscript{1,2} It has been suggested\textsuperscript{3-4} that the hypoxic
insult depletes cardiac function by depleting the myocar-
dium of utilizable energy substrates, such as adenosine

\textsuperscript{*}Postdoctoral Surgical Research Fellow supported by U.S. Public Health
Service Grant GM-1559-08.

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and Strecoski for hearts isolated from rats pretreated with reserpine. The hearts, which contained higher levels of glycogen, demonstrated a greater glycolytic production of ATP and a better function during hypoxia than did controls. In other studies, hearts of dogs that had been maintained on a high fat diet exhibited better left ventricular performance after 30 minutes of ischemic hypoxia than the hearts of dogs fed normal laboratory chow. This enhanced performance was associated with a greater rate of myocardial glycogen utilization.

It has been reported that the hormone glucagon stimulates glycolgenolysis by activation of phosphorylase, and this is secondary to an increase in the intracellular concentration of the nucleotide, adenosine 3',5'-monophosphate (cyclic AMP). More recently another cyclic nucleotide, guanosine 3',5'-monophosphate (cyclic GMP) has been implicated as the chemical mediator of the negative inotropic effect of cholinergic agents and other cardiac depressants.

Both physiological and pathological changes in cardiac function may be mediated by the relative intracellular concentrations of cyclic AMP and cyclic GMP. In light of these findings, we undertook to determine whether the glycolgenolytic action of glucagon was associated with both a protective effect on the hypoxic rat heart and a modulation of the myocardial levels of these two cyclic nucleotides.

Methods

Male Sprague-Dawley rats (250-300 g) were decapitated; the heart was excised quickly and the aorta attached to the outflow cannula of an Anderson perfusion apparatus. Modified Tyrode's solution was used for coronary perfusion. The iodic composition of the Tyrode's solution in millimoles per liter was: NaCl, 120; KCl, 5; CaCl2, 4; MgSO4, 0.6; NaHCO3, 30; and KH2PO4, 0.6. The hearts were perfused with Tyrode's solution either gassed with 95% O2 and 5% CO2 (PO2 = 450-500 mm Hg) or with 95% N2 and 5% CO2 (PO2 = 10-20 mm Hg). The oxygenated and hypoxic media were kept in parallel systems so that either could be used immediately for coronary perfusion. Aortic filling pressure was maintained at 70 cm H2O. The pH of the perfusate, which was 7.4, was continually monitored during the periods of hypoxia and reoxygenation and remained unchanged throughout the perfusion. To rule out the effect of changes in heart rate on cardiac output and coronary flow, heart rate was maintained constant by electrical stimulation through electrodes attached to the right atrium and the ventricular apex. A stimulus of 4-8 V and a duration of 4 msec (Electronics for Medicine stimulator) was applied at a frequency 20% above the intrinsic rate; this provided a constant rate for each heart in the range of 250-300 beats/min. Force of contraction was measured with a calibrated Grass FT 03 force displacement transducer which was mounted on a movable assembly and connected to the apex of the heart in such a way that tension could be applied by movement of the transducer. In this manner the contraction of each heart was placed at the peak of its length-tension curve. Force and rate of contraction were recorded on a Grass model 7 polygraph. The rate of coronary perfusion was measured for all time intervals by collecting the effluent. Untreated hearts were divided into two major groups: (1) those perfused with glucose-free Tyrode's solution and (2) those perfused with Tyrode's solution containing 5 mM glucose. In both groups, hearts were equilibrated for 10 minutes with oxygenated Tyrode's solution, then perfused for 3 minutes with hypoxic medium, and finally reperfused for 10 minutes with oxygenated Tyrode's solution. Experimental hearts were studied by the same protocol except that during the period of hypoxia, the perfusion fluid contained a subinotropic concentration of glucagon (8.7 x 10^-7 M). Glucagon was present only in the hypoxic perfusion medium. Each heart was exposed to only one dose of glucagon or to one period of hypoxia or to one combined treatment of glucagon plus hypoxia.

In a parallel series of experiments, the procedure was terminated both during the hypoxic period and after reoxygenation. In these studies, the hearts were quickly frozen after 15 seconds, 60 seconds and 3 minutes of hypoxic perfusion and after 5 minutes of reoxygenation. This was done with Wollenberger clamps that had been precooled in liquid nitrogen. The hearts were then stored at -80°C until assayed for their content of cyclic AMP and cyclic GMP. The analyses for cyclic AMP and cyclic GMP were made according to methods previously described. Cyclic AMP concentrations were determined according to the competitive binding assay of Gilman and cyclic GMP levels were measured by the method of Steinier et al. All values are expressed as nanomoles of cyclic nucleotide per kilogram of cardiac tissue. During 0, 15, 60, 120, 180 and 300 seconds of hypoxia lactate concentrations in the coronary effluent were measured by spectrophotometric analyses. The significance of differences between data for untreated and glucagon-perfused hearts was determined by Students t-test.

Results

Figure 1 shows the change in force of contraction of hearts perfused with glucose-free medium during periods of hypoxia and reoxygenation. Within 3 minutes of hypoxic perfusion, force of contraction decreased to approximately 10% of control for both untreated and glucagon-perfused hearts. The most rapid decline occurred within the first 30 seconds, with a less marked but progressive decrement between 30 seconds to 3 minutes. There was no significant difference between the untreated and treated groups during the hypoxic period. During reoxygenation, hearts that had been perfused with glucagon (8.7 x 10^-7 M) during the hypoxic period, exhibited a significantly enhanced recovery at all times (P < 0.05). Glucagon-perfused hearts regained 68% of the control force of contraction after 3 minutes of reoxygenation, whereas untreated hearts attained only 48% of the control value at this same time.

The effect of glucose on contractile force during hypoxia and reoxygenation is shown in Figure 2. Both untreated and glucagon-perfused (8.7 x 10^-7 M) hearts were perfused with Tyrode's solution containing 5 mM glucose. The depression in contractile force during hypoxia was characterized by rapid and slow phases similar to those recorded for hearts perfused with glucose-free solution (Fig. 1), but the depres-

* Subinotropic is used in this manuscript specifically to define concentrations of glucagon equal to or less than 8.7 x 10^-7 M, which exert no observable direct effect on force of contraction in this heart preparation.
The effects of hypoxia lasting 3 minutes and glucagon (8.7 x 10^{-8} M) on cyclic nucleotide levels are shown in Table 2. Cyclic AMP levels were not significantly different between hearts perfused with glucose-containing and glucose-free solution. However, in hearts perfused with Tyrode’s solution containing glucose, cyclic GMP concentration (372 ± 29 nmol/kg) was significantly lower than in control hearts (123 ± 10 nmol/kg) perfused with Tyrode’s solution containing no glucose (P < 0.05). On the other hand, when glucagon was added to the hypoxic perfusion medium there was no significant difference (P > 0.05) in cyclic GMP content between hearts perfused with either glucose-free or glucose-containing medium. In addition, when glucagon was present during the hypoxic perfusion, cardiac cyclic GMP accumulation was significantly less (P < 0.05) than that seen with hypoxia alone. This finding was the same whether glucose was present or not. The concentration of cyclic AMP was not different from control after 3 minutes of hypoxia, regardless of the presence of glucose, of glucagon, or of both. It was observed also that hearts perfused with glucagon during the period of hypoxia contained levels of cyclic GMP and cyclic AMP that were not different from...
TABLE 1  Levels of Cyclic Nucleotides in Cardiac Tissue Perfused with and without Glucose

<table>
<thead>
<tr>
<th>Experimental conditions</th>
<th>Force of cardiac contraction (g tension)</th>
<th>Cyclic AMP (nmol/kg)</th>
<th>Cyclic GMP (nmol/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose-free perfusion</td>
<td>5</td>
<td>12.6 ± 1.2</td>
<td>497 ± 31</td>
</tr>
<tr>
<td>Glucose perfusion</td>
<td>6</td>
<td>16.8 ± 1.7*</td>
<td>480 ± 52</td>
</tr>
</tbody>
</table>

Hearts were frozen after 15 minutes of perfusion with oxygenated Tyrode’s solution. 5 mM glucose was added to medium where indicated.

* P < 0.05, significantly different when compared to glucose-free perfusion.

Each value represents the mean ± SEM; n = number of experiments.

TABLE 2  Levels of Cyclic Nucleotides in Cardiac Tissue after Perfusions with and without Glucose and Glucagon

<table>
<thead>
<tr>
<th>Experimental conditions</th>
<th>Cyclic AMP (nmol/kg)</th>
<th>Cyclic GMP (nmol/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxia 3 min; no glucose</td>
<td>5 503 ± 20</td>
<td>372 ± 29*</td>
</tr>
<tr>
<td>Hypoxia 3 min; glucose 5 mM</td>
<td>6 481 ± 73</td>
<td>123 ± 10*</td>
</tr>
<tr>
<td>Hypoxia 3 min; no glucose; glucagon 8.7 X 10^{-9} M</td>
<td>5 470 ± 13</td>
<td>70 ± 7*</td>
</tr>
<tr>
<td>Hypoxia 3 min; glucose 5 mM; glucagon 8.7 X 10^{-9} M</td>
<td>5 530 ± 36</td>
<td>79 ± 7*</td>
</tr>
<tr>
<td>Hypoxia 3 min + reoxygenation 5 min; no glucose</td>
<td>5 582 ± 30</td>
<td>314 ± 40*</td>
</tr>
<tr>
<td>Hypoxia 3 min + reoxygenation 5 min; glucagon 8.7 X 10^{-9} M; no glucose</td>
<td>5 427 ± 90</td>
<td>67 ± 4*</td>
</tr>
</tbody>
</table>

Hearts were frozen after 3 minutes of perfusion with hypoxic Tyrode’s solution or after 5 minutes of reoxygenation following the hypoxic period.

Superscript letters (a,b,c) indicate significant difference (P < 0.05) when compared to group with same letter.

Each value represents the mean ± SEM; n = number of experiments.

TABLE 3  Cyclic Nucleotide Levels in Hypoxic Cardiac Tissue Perfused with and without Glucagon

<table>
<thead>
<tr>
<th>Experimental conditions</th>
<th>Cyclic AMP* (nmol/kg tissue)</th>
<th>Cyclic GMP* (nmol/kg tissue)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>8 480 ± 52*</td>
<td>84 ± 5*</td>
</tr>
<tr>
<td>Hypoxia 15 sec</td>
<td>8 884 ± 106*</td>
<td>125 ± 6*</td>
</tr>
<tr>
<td>Hypoxia 60 sec</td>
<td>7 899 ± 92*</td>
<td>198 ± 27*</td>
</tr>
<tr>
<td>Hypoxia 60 sec, with glucagon 8.7 x 10^{-9} M</td>
<td>6 630 ± 111</td>
<td>88 ± 6*</td>
</tr>
<tr>
<td>Hypoxia 60 sec, with glucagon 8.7 x 10^{-9} M</td>
<td>6 538 ± 46*</td>
<td>82 ± 13*</td>
</tr>
</tbody>
</table>

Control hearts were frozen after equilibration with oxygenated Tyrode’s solution containing 5 mM glucose. Hypoxic hearts were frozen after a period of hypoxic perfusion with glucose medium as indicated.

Superscript letters (a,b,c) indicate significant difference (P < 0.05) when compared to group with the same letter.

Each value represents the mean ± SEM; n = number of experiments.

TABLE 4  Lactate Concentration in the Coronary Effluent of Isolated Rat Hearts Perfused with Glucagon during Hypoxia

<table>
<thead>
<tr>
<th>Experimental conditions</th>
<th>Lactate (µmol/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>17 531 ± 44</td>
</tr>
<tr>
<td>Hypoxia 15 sec</td>
<td>10 885 ± 93*</td>
</tr>
<tr>
<td>Hypoxia 60 sec</td>
<td>10 2402 ± 239*</td>
</tr>
<tr>
<td>Hypoxia 120 sec</td>
<td>10 4651 ± 301**</td>
</tr>
<tr>
<td>Hypoxia 180 sec</td>
<td>10 4973 ± 169**</td>
</tr>
<tr>
<td>Hypoxia 300 sec</td>
<td>10 3952 ± 220*</td>
</tr>
<tr>
<td>Hypoxia 15 sec with (G)</td>
<td>8 1007 ± 122*</td>
</tr>
<tr>
<td>Hypoxia 60 sec with (G)</td>
<td>10 2235 ± 55</td>
</tr>
<tr>
<td>Hypoxia 120 sec with (G)</td>
<td>10 5421 ± 167**</td>
</tr>
<tr>
<td>Hypoxia 180 sec with (G)</td>
<td>10 5830 ± 276**</td>
</tr>
<tr>
<td>Hypoxia 300 sec with (G)</td>
<td>10 3861 ± 169*</td>
</tr>
</tbody>
</table>

Control hearts were equilibrated with oxygenated Tyrode’s solution for 10 minutes.

(G) = glucagon, 8.7 x 10^{-9} M, included in hypoxic perfusion medium.

* Indicates significant difference (P < 0.05) when compared to control equilibration.

** and *** indicate significant difference (P < 0.05) when compared to group with same letter.

Each value represents the mean ± SEM; n = number of experiments.
Discussion

These studies demonstrate that perfusion of the isolated rat heart with glucagon during hypoxia improves cardiac performance during reoxygenation. The precise mechanism by which glucagon enhances recovery during reoxygenation is unclear. Glucagon produces positive inotropic and chronotropic effects in isolated papillary muscle, closed-chest dog preparations, and cats with chronic heart failure. Since we have demonstrated an enhanced recovery of contractile force after hypoxia with a concentration of glucagon that does not produce a direct positive inotropic effect in our preparation, our studies suggest that the protective effect of this hormone may be unrelated to its known direct inotropic action.

Although glucagon improved recovery during reoxygenation of hearts that were perfused with or without glucose, the performance of the former group was significantly better. Perhaps an explanation of this is that the only source of energy production available to glucose-free hearts during hypoxia was endogenous glycogen which rapidly became depleted. It has been clearly shown that supplying isolated hearts with exogenous carbohydrate maintains myocardial levels of high energy phosphates. Since glucose is the primary energy source for the hypoxic myocardium, increasing glucose supply to the isolated rat heart would be expected to enhance glycolytic production of ATP and therefore improve cardiac performance during hypoxia and reoxygenation. Indeed, although ATP levels were not monitored, the finding of enhanced performance was observed in all of the present experiments.

Our data support the conclusion that there was an acceleration of glycolysis by glucagon during a portion of the hypoxic period. From 2–3 minutes of hypoxia, glucagon-perfused hearts produced more lactate per minute than did control hearts. This increased lactate production caused by glucagon is a measure of the enhanced glycolytic flux and presumably is secondary to the enhanced supply of glucose 1-phosphate from accelerated glycogenolysis. However, the increase in lactate production was not maintained throughout the hypoxic period. In fact, by 300 seconds of hypoxia glucagon-perfused hearts produced approximately the same amount of lactate as did untreated hearts. This failure of glucagon to sustain increased glycolysis during hypoxia may be related to the accumulation of lactate which results in a decrease in intracellular pH and thus inhibits phosphofructokinase activity. Thus, the enhanced rate of glycolysis seen during the initial part of the hypoxic period subsequently would be blocked by lactate accumulation. Nevertheless, the interval during which the rate of glycolysis was increased may have been sufficient for the heart to be resupplied with additional high energy substrates that could be utilized to maintain cellular integrity during hypoxia.

On the other hand, alterations in myocardial concentrations of the cyclic nucleotides may be associated with the protective effect of glucagon. It has been suggested that cyclic AMP mediates the positive inotropic effect of catecholamines and glucagon, whereas cyclic GMP has been associated with the actions of negative inotropic agents. A number of studies has indicated that reciprocal changes in the levels of cyclic AMP and cyclic GMP may be responsible for the physiological effects of adrenergic and cholinergic agents on the heart. Moreover, it has been shown recently that cyclic AMP levels are elevated during the systolic phase of the cardiac cycle, whereas cyclic GMP levels are lowered during this period. Thus, it is possible that the relative concentration of cyclic AMP and cyclic GMP influence the response of the myocardium to various pathological stimuli such as ischemia and hypoxia. Our data strongly support this hypothesis in that the improved recovery of glucagon-perfused hearts during reoxygenation was consistently associated with a higher ratio in the relative concentrations of cyclic AMP to cyclic GMP during the hypoxic insult. Both untreated and glucagon-perfused hearts had a cyclic nucleotide ratio of about 7:1 at the beginning of the hypoxic insult. After 3 minutes of hypoxic perfusion, the ratio of cyclic AMP to cyclic GMP in untreated hearts decreased to 4:1. This finding is in contrast to glucagon-perfused hearts, which maintained a ratio of 7:1. Furthermore, although the concentrations of both cyclic nucleotides changed in response to hypoxia, it is apparent that glucagon-perfused hearts primarily failed to show an increase in cyclic GMP levels in response to hypoxia, as did the untreated hearts. It appears to be this reduction in cyclic GMP accumulation which maintained the cyclic AMP:cyclic GMP ratio of 7:1 in glucagon-perfused hearts. This reduction in cyclic GMP content also was observed in experimental controls in which the only variable was the presence or absence of glucose in the perfusion medium. The absence of glucose from the perfusion medium of control hearts was associated with significant increases in myocardial cyclic GMP content, and decreases in contractile force, but no changes in cyclic AMP levels (Tables 1 and 2). Thus, glucose availability to the myocardium is in some way associated with cyclic GMP accumulation. Perhaps the protective effect of glucagon itself is related to an inhibition in the accumulation of cyclic GMP, since the addition of glucagon to both glucose-containing and glucose-free perfusion media resulted in enhanced contractile force and decreased cyclic GMP levels. Such a regulation of cardiac contraction by cyclic GMP is further supported by preliminary data from this laboratory which show that glucocorticoids appear to provide a protective effect to the heart and decrease cyclic GMP levels.

The results of these studies are in agreement with the "Yin-Yang" theory of Goldberg in which it has been suggested that a "dualism" between the two cyclic nucleotides occurs following cellular events induced by drugs or conditions which, in a broad sense, modulate the tissue accumulation of cyclic GMP or cyclic AMP. The glucagon administration and hypoxic perfusion may indeed represent two interacting stimuli that exert their effects via such a modulation of levels of cardiac cyclic nucleotide. Further studies will be necessary to clarify the precise biochemical mechanism by which this modulation of the intracellular levels of cyclic AMP and cyclic GMP occurs.

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VASCULAR EFFECTS OF ARACHIDONATE IN LUNGS/Wicks et al.

THOMAS C. WICKS, PH.D., JOHN C. ROSE, M.D., MALCOLM JOHNSON, PH.D.,
PETER W. RAMWELL, PH.D., AND PETER A. KOT, M.D.

SUMMARY We compared the effects of arachidonic acid (AA), the biseenoic prostaglandin precursor, with those of prostaglandin F₁₃ (PGF₁₃) and norepinephrine (NE) on pulmonary vascular resistance in the isolated (in situ), perfused canine lung lobe. The isolated lobe was perfused with autologous blood or an artificial perfusate free of cellular elements. The times to onset of action of the three agents were similar, and short. These results suggest that AA is converted into vasoactive intermediates or the prostaglandin act directly on precapillary pulmonary vascular smooth muscle rather than through platelet, plasma, adrenergic, or cholinergic mechanisms.

THE CARDIOVASCULAR actions of the biseenoic prostaglandins, prostaglandin E₂ (PGE₂) and F₉ (PGF₉), have been investigated intensively in several species of animals. PGE₂ produces systemic vasodilatation and a depressor response in the dog, whereas PGF₉ is a moderately active peripheral vasoconstricting agent. Both compounds have a direct positive inotropic effect on the heart. The precursor of the biseenoic prostaglandins, arachidonic acid (AA), is released from cell phospholipids and other lipid sources, and is converted into endoperoxide intermediates and eventually into PGE₂ and PGF₉. Recent studies have shown that AA (300 μg/kg) produces a systemic depressor response in dogs which is equivalent to that caused by a dose of 5 μg/kg of PGE₂.

Information about the selective action of AA on different...
Changes in cyclic nucleotide levels and contractile force in the isolated hypoxic rat heart during perfusion with glucagon.
R W Busuttil, R J Paddock, J W Fisher and W J George

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