The Genesis of Arrhythmias during Myocardial Ischemia

Dissociation between Changes in Cyclic Adenosine Monophosphate and Electrical Instability in the Rat

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SUMMARY. It has been proposed that increases in tissue cyclic adenosine monophosphate during ischemia may be responsible for the induction of arrhythmias that occur during the early minutes of ischemia. We have tested this hypothesis using the isolated perfused rat heart with coronary artery occlusion for 30 minutes. In control hearts, after a transient small rise, cyclic adenosine monophosphate content remained close to its preischemic value (3.0 ± 0.1 nM/g dry weight) throughout the period of occlusion. Eight percent (1/12) of the hearts fibrillated. Ninety-two percent (11/12) of the hearts exhibited ventricular tachycardia, and the mean total number of premature ventricular complexes was 528 ± 121. Inclusion of epinephrine (1.0 μM) in the perfusion fluid elevated cyclic adenosine monophosphate prior to coronary occlusion (to 10.7 ± 0.6 nM/g dry weight) and also throughout the ischemic period. It also increased arrhythmias such that 83% (20/24) of hearts fibrillated, 100% exhibited ventricular tachycardia, and the mean number of premature ventricular complexes increased to 747 ± 86. Inclusion of forskolin (0.2 μM), which stimulates adenylyl cyclase independently of the β-receptor, increased cyclic adenosine monophosphate content to a greater extent than epinephrine, to 14.1 ± 0.9 nM/g dry weight before the onset of ischemia and to 8.2 ± 0.4 nM/g dry weight after 30 minutes of ischemia. Despite the large increase in cyclic adenosine monophosphate, there was no increase in rhythm disturbances which were less than those seen in controls. Thus, no hearts fibrillated, the incidence of ventricular tachycardia was reduced to 58% (7/12), and the mean number of premature ventricular complexes was greatly reduced (79 ± 29, P < 0.001 compared to the number with drug carrier alone). Higher concentrations of both epinephrine and forskolin caused changes that were qualitatively similar to those seen with the lower concentrations. In addition, when hearts were paced at 400 impulses/min, again only epinephrine increased the severity of ischemia-induced arrhythmias. In conclusion, despite its ability to increase cyclic adenosine monophosphate content to a greater extent than epinephrine, forskolin exerts an antiarrhythmic effect. This suggests that increased cyclic adenosine monophosphate content is not necessarily involved in the genesis of ischemia-induced arrhythmias, and that some other facet of adrenoceptor stimulation or catecholamine action may be involved. (Circ Res 57: 668-675, 1985)

IN 1971, Ueda and Okumura suggested a link between the intracellular accumulation of cyclic adenosine monophosphate (cAMP) and the induction of cardiac arrhythmias. Since that time, a number of other investigators (Lubbe et al., 1976, 1978; Podzuweit et al., 1978; Corr et al., 1978) have supported the concept of an association between increased cyclic adenosine monophosphate (cAMP) and the onset of severe ventricular arrhythmias, particularly during ischemia. It has been proposed that within ischemic tissue cAMP increases before the onset of arrhythmias, and that the arrhythmias can be exacerbated by agents such as epinephrine and norepinephrine, which increase cAMP, and can be decreased by agents such as propranolol and other β-blockers, which limit the production of cAMP. Although such associations have been demonstrated, a clear cause-and-effect relationship has not been established.

The diterpene derivative, forskolin, which can be isolated from the plant, Coleus forskohlii (Lindner et al., 1978), has been shown to be capable of inducing substantial increases in the cAMP content of the myocardium and other tissues. It is of particular interest that this is achieved by activation of adenylyl cyclase, independent of the β-receptor (Seamon and Daly, 1981). This contrasts with epinephrine, norepinephrine, and isoprenaline, which increase tissue cAMP content by activating adenylyl cyclase via the β-receptor. Forskolin thus provides a way of dissociating β-receptor-mediated effects from adenylyl cyclase-mediated effects, and we have exploited this property to test the hypothesis that increased cellular cAMP content during ischemia may be responsible for the genesis of "early" ischemia-induced arrhythmias (i.e., in the rat, those arrhythmias that occur during the first 30 minutes of coronary artery occlusion). To achieve this, we compared the effects on
cardiac rhythm of increasing cAMP during ischemia by (1) β-receptor stimulation with epinephrine and (2) adenyl cyclase stimulation with forskolin. We used an isolated rat heart preparation, in order to eliminate any complications of interpretation which might be caused by coincident changes in peripheral tissues.

Methods

Animals

Male Wistar rats (250–300 g body weight) were used for all studies.

Perfusion Technique and Perfusion Fluids

Rats were anesthetized with diethyl ether, the left femoral vein was exposed, and heparin (200 U) was administered intravenously. One minute later, the hearts were excised and placed in ice-cold perfusion fluid (10 mM HEPES, 120 mM NaCl, 4.5 mM KCl, 1.2 mM MgCl2, 1.2 mM CaCl2, and 11.1 mM glucose). The perfusion fluid was made with 10 mM HEPES (pH 7.4 when gassed with 95% O2 and 5% CO2) at 37°C, to which glucose (11.1 mM) had been added.

For studies with epinephrine, the bitartrate salt was dissolved in the Krebs-Henseleit bicarbonate buffer (pH 7.4) and was subjected to perfusion for 10 minutes, during which time a suture was placed around the aorta and perfused in the Langendorff mode (Langendorff, 1895). The Krebs-Henseleit bicarbonate buffer (pH 7.4 when gassed with 95% O2 and 5% CO2) at 37°C, to which glucose (11.1 mM) had been added.

An epicardial electrocardiogram (ECG) was obtained from each heart via bipolar electrodes, and heart rate was calculated from the ECG trace. In the paced-heart studies, hearts were perfused with buffer containing an appropriate amount of drug vehicle (polyethylene glycol). An epicardial electrocardiogram (ECC) was obtained from each heart via bipolar electrodes, and heart rate was calculated from the ECG trace. In the paced-heart studies, hearts were perfused with buffer alone or with buffer containing epinephrine (1 μM) or forskolin (0.2 μM), and were stimulated at a rate of 400 impulses/min throughout the perfusion period. This was achieved by attaching two silver wires to the heart. These wires delivered a 5-msec square wave pulse of 0.5 mA from a standard laboratory stimulator.

Experimental Time Course

Hearts were perfused aerobically for a control period of 10 minutes, during which time a suture was placed around the left anterior descending coronary artery. The artery then was occluded, to generate an area of regional ischemia, for up to 30 minutes. For studies of rhythm disturbance, hearts (n = 12 in each group) were monitored throughout the control period and the 30-minute period of ischemia.

For cAMP studies, hearts (n = 7 in each group) were rendered ischemic for 0, 1, 3, 5, 10, 20, or 30 minutes. After this time, the outline of the ischemic zone was marked on each heart with gentian violet (to aid later identification and tissue separation for the cAMP assay), and the hearts were frozen in liquid nitrogen.

Determination of cAMP

After freezing, hearts were lyophilized, and the ischemic zone was dissected from nonischemic tissue (with the aid of the gentian violet markings). The cAMP content of tissue from the central ischemic zone was determined by means of a standard protein-binding assay (Brown et al., 1971).

Statistical Analysis

We determined the significance of differences by performing a one-way analysis of variance followed by appropriate unpaired t-tests. Since several unpaired t-tests were performed on a given variable, we restricted our attention to comparisons between epinephrine and its control group, and, likewise, to forskolin and the drug-carrier-alone group. To avoid spurious findings, only results giving P values below 0.01 were considered significant.

Distributions of discrete variables were compared, first by modified χ2-test using a 2 × 6 table, and then by a second χ2-test with a Yates correction for 2 × 2 tables comparing individual groups as described above.

Results

To undertake an acceptable comparison between forskolin and epinephrine, it was essential to select approximately "equipotent" concentrations (in terms of cAMP increases and contractile effects). Therefore, the first part of the study was directed at establishing appropriate drug concentrations.

Selection of "Equipotent" Drug Doses

In previous studies (Buschmans et al., 1983), we have established a dose-response relationship for forskolin, and have demonstrated the drug to be active over a wide range (10⁻⁹–10⁻⁵ M). For the present studies, we selected an intermediate concentration (2 × 10⁻⁷ M) which we estimated would increase tissue cAMP content by between 300% and 400%. Hearts (at least eight in each group) were subjected to perfusion for 10 minutes, during which time heart rate and coronary flow were continuously recorded. The hearts then were frozen in liquid nitrogen, freeze-dried, and analyzed for cAMP content. The following groups were studied: (1) hearts perfused with unmodified perfusion fluid, (2) hearts perfused with buffer containing polyethylene glycol, (3) hearts perfused with buffer containing 2 × 10⁻⁷ M forskolin, and (4) hearts perfused with 10⁻⁸, 10⁻⁹, 10⁻¹⁰, or 10⁻¹¹ M epinephrine.

The results indicate that forskolin increased tissue cAMP by 370%, from the placebo-treated group value of 3.0 ± 0.1 nm/g dry weight to 14.1 ± 0.9 nm/g dry weight. It also increased heart rate by 21% from 324 ± 6 to 393 ± 7 beats/min and coronary flow by 26% from 13.8 ± 0.4 to 17.4 ± 0.4 ml/min. Epinephrine caused a dose-dependent increase in cAMP, heart rate, and coronary flow. A concentration of 10⁻⁷ M epinephrine produced effects that were most similar to those produced by the selected forskolin concentration. This concentration of epinephrine increased cAMP to 10.7 ± 0.6 nm/g dry weight, heart rate to 371 ± 3 beats/min, and coronary flow to 16.1 ± 0.3 ml/min. This concentration therefore was selected for future studies. However, to confirm these findings with other concentrations of forskolin and epinephrine, further studies on rhythm disturbances during ischemia were performed with 10 μM epinephrine and 2 μM forskolin.
Studies with Regional Ischemia

Two series of studies were performed, one involving a comparison of the effects of forskolin and epinephrine on cardiac arrhythmias, and the other measuring the effects of selected doses of these agents on tissue cAMP.

Cardiac Rhythm

Hearts (n = 12 in each group) were subjected to 10 minutes of control perfusion followed by a 30-minute period of regional ischemia induced by coronary artery occlusion. Six groups were studied: (1) normal perfusion fluid throughout, (2) 1 μM epinephrine in the perfusion fluid throughout, (3) 10 μM epinephrine in the perfusion fluid throughout, (4) 0.2 μM forskolin in the perfusion fluid throughout, (5) 2 μM forskolin in the perfusion fluid throughout, and (6) forskolin carrier (polyethylene glycol) alone in perfusion fluid throughout. Table 1 shows the results for incidence of ventricular fibrillation, mean duration of ventricular fibrillation, incidence of ventricular tachycardia, mean durations of ventricular fibrillation and tachycardia, and the total number of premature ventricular complexes recorded for each group studied. In control hearts, 8% (1/12) developed ventricular fibrillation, and all hearts exhibited premature ventricular complexes with a mean number of 528 ± 121. As would be expected from the known arrhythmogenic properties of epinephrine, inclusion in the perfusate resulted in a dramatic increase in the incidence of ventricular fibrillation, which increased from its control value of 8% to 83% (10/12 hearts, P < 0.01) with 1 μM epinephrine, and to 100% (12/12 hearts, P < 0.001) with 10 μM epinephrine. The incidence of ventricular tachycardia and the number of premature ventricular complexes also increased, but these changes did not achieve a level of statistical significance.

In hearts perfused with polyethylene glycol (the carrier for forskolin), there was no significant difference from the control group for any of the indices studied. Seventeen percent (2/12) of the hearts exhibited ventricular fibrillation, 100% exhibited ventricular tachycardia, and the mean number of premature ventricular complexes was 561 ± 105.

In hearts perfused with forskolin, a totally unexpected result was obtained. Not only did the drug fail to increase the incidence or severity of arrhythmias, but, in contrast, it exhibited an antiarrhythmic effect. Thus, the incidence of ventricular fibrillation was reduced to zero by 0.2 μM forskolin, and compared with control hearts or hearts perfused with polyethylene carrier, forskolin reduced the incidence of ventricular tachycardia significantly: to 58% by 0.2 μM forskolin (P < 0.05) and to 0% by 2 μM forskolin (P < 0.001) compared with that produced by drug carrier alone. The duration of ventricular tachycardia was also reduced to 10 ± 2 seconds by 0.2 μM forskolin (P < 0.05 compared to drug carrier alone) and to 0 second by 2 μM forskolin. The total number of premature ventricular complexes was reduced to 79 ± 29 (P < 0.001) by 0.2 μM forskolin and to 20 ± 15 by 2 μM forskolin (P < 0.001).

Cardiac Function

Analysis of coronary flow and heart rate in the six groups studied revealed (Table 2) that, before and throughout the 30-minute period of occlusion, both epinephrine and forskolin caused significant (P < 0.001) and similar increases in heart rate (approximately 12% and 14% by epinephrine, and 20% and 22% by forskolin), and also in coronary flow (approximately 12% by both concentrations of epinephrine, and 26% and 37% by forskolin). These increases were sustained throughout the 30-minute period of regional ischemia.

Effect of Pacing

Alteration in heart rate is a well-known factor influencing myocardial electrical instability. For this reason, it was considered necessary to repeat the initial study at exactly the same heart rates in both the forskolin and epinephrine-treated groups. These results are shown in Table 3. A comparison of Tables 1 and 3 shows that in the control untreated hearts, increasing heart rate from approximately 300–400 beats/min did not significantly increase the inci-

### Table 1

<table>
<thead>
<tr>
<th>Control</th>
<th>Epinephrine</th>
<th>Drug-carrier for forskolin</th>
<th>Forskolin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 μM</td>
<td>10 μM</td>
<td>0.2 μM</td>
</tr>
<tr>
<td>n</td>
<td>12</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Incidence of VF</td>
<td>8%</td>
<td>83%†</td>
<td>100%‡</td>
</tr>
<tr>
<td>Incidence of VT</td>
<td>92%</td>
<td>100%</td>
<td>92%</td>
</tr>
<tr>
<td>Duration of VF (sec)</td>
<td>152</td>
<td>26 ± 5</td>
<td>574 ± 220</td>
</tr>
<tr>
<td>Duration of VT (sec)</td>
<td>34 ± 11</td>
<td>37 ± 6</td>
<td>34 ± 9</td>
</tr>
<tr>
<td>Total no. of PVC</td>
<td>528 ± 121</td>
<td>747 ± 6</td>
<td>782 ± 208</td>
</tr>
</tbody>
</table>

VF = ventricular fibrillation, VT = ventricular tachycardia, PVC = premature ventricular complexes. Asterisks indicate a statistical difference from control (or, for forskolin, from the drug-carrier group) at the level of: * P < 0.05, † P < 0.01, ‡ P < 0.001. Values for duration of VF, VT, and PVC are shown as the mean ± sem.
### TABLE 2
Effect of Epinephrine and Forskolin on Heart Rate and Coronary Flow during a 30-Minute Period of Coronary Artery Occlusion in the Isolated Perfused Rat Heart

<table>
<thead>
<tr>
<th>Time of coronary artery occlusion (min)</th>
<th>Heart rate (beats/min)</th>
<th>Coronary flow (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Epinephrine 1 µM</td>
</tr>
<tr>
<td>0</td>
<td>331 ± 7</td>
<td>290 ± 6</td>
</tr>
<tr>
<td>5</td>
<td>283 ± 8</td>
<td>278 ± 7</td>
</tr>
<tr>
<td>10</td>
<td>276 ± 6</td>
<td>276 ± 6</td>
</tr>
<tr>
<td>15</td>
<td>268 ± 6</td>
<td>268 ± 6</td>
</tr>
<tr>
<td>20</td>
<td>262 ± 6</td>
<td>262 ± 6</td>
</tr>
<tr>
<td>25</td>
<td>260 ± 6</td>
<td>260 ± 6</td>
</tr>
<tr>
<td>30</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 3
Comparison of Effects of Epinephrine (1 µM) and Forskolin (0.2 µM) on Ventricular Rhythm Disturbances during a 30-Minute Period of Coronary Artery Occlusion in the Isolated Rat Heart

<table>
<thead>
<tr>
<th></th>
<th>Incidence of VF (%)</th>
<th>Incidence of VT (%)</th>
<th>Duration of VF (sec)</th>
<th>Duration of VT (sec)</th>
<th>Total no. of PVC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>33%</td>
<td>92%</td>
<td>517 ± 249</td>
<td>38 ± 2</td>
<td>568 ± 238</td>
</tr>
<tr>
<td>Epinephrine 1 µM</td>
<td>83%</td>
<td>92%</td>
<td>140 ± 56</td>
<td>49 ± 24</td>
<td>860 ± 291</td>
</tr>
<tr>
<td>Forskolin 0.2 µM</td>
<td>33%</td>
<td>58%</td>
<td>364 ± 247</td>
<td>24 ± 8</td>
<td>218 ± 94</td>
</tr>
</tbody>
</table>

Values are shown as the mean ± SEM. Asterisks indicate a statistical difference of epinephrine from the control or forskolin from the drug carrier at the level of: *P < 0.02; †P < 0.01; ‡P < 0.001.

Effects upon cAMP

Here, the objective was to subject hearts to regional ischemia and to freeze them at various times after the onset of occlusion and, by analysis, to determine the temporal characteristics of tissue cAMP content within the ischemic zone under various perfusion conditions. This was readily accomplished in the drug-free series, and also in the forskolin series (0.2 µM); however, in the epinephrine series (1 µM), the high incidence of ventricular fibrillation made it impossible to obtain multiple groups of nonfibrillating hearts at exact times beyond the first 5 minutes of ischemia. Beyond this time, therefore, all hearts were freeze-clamped as soon as they fibrillated. In this way, an indication of cAMP changes within the ischemic zone in the epinephrine-treated group could be obtained throughout the 30-minute period.

The results (Fig. 1) revealed that, in the control group of hearts (Fig. 1A), cAMP at the onset of ischemia was 3.0 ± 0.1 µM/g dry weight (a value consistent with a number of published values). During the first 1–3 minutes of ischemia, there was a small but significant (P < 0.05) increase (to 3.6 ± 0.2 µM/g dry weight) in tissue cAMP content. This value declined to preischemic values by 5 minutes of ischemia, and then remained relatively constant throughout the remainder of the 30-minute ischemic interval. It is clear that there was no increase in cAMP during the period (5–20 minutes) of maximal
FIGURE 1. cAMP and electrical instability during a 30-minute period of regional myocardial ischemia in the rat. Hearts (n = 7-12 in each group) were subjected to 10 minutes of coronary artery occlusion. The hearts were freeze-clamped at various times and were used for the measurement of tissue cAMP content. In parallel studies (and also up to the time of freeze-clamping in the cAMP studies), cardiac rhythm disturbances were monitored, and the lower panels show the mean number of premature ventricular complexes recorded/min, and the vertical lines indicate the number of hearts that went into ventricular fibrillation and the time of onset. Panel A: control; panel B: 0.2 μM forskolin in the perfusate throughout the experimental period; panel C: 1 μM epinephrine in the perfusate throughout the experimental period. For the cAMP results, the bars represent the standard errors of the mean and the asterisks indicate a significant (P < 0.05) difference from the preocclusion control value.
The cAMP Hypothesis of Arrhythmogenesis

The cAMP hypothesis of arrhythmogenesis was originally formulated to account for the arrhythmogenic properties of catecholamines (Podzuweit et al., 1980), and the mechanism by which cAMP was suggested to increase the severity of ventricular arrhythmias was thought to be related to the formation of slow response action potentials. Action potentials recorded during myocardial ischemia have been suggested to consist of slow response action potentials (Cranesfield et al., 1972; Wit and Bigger, 1975) and/or depressed fast response action potentials (El-Sherif and Lazzara, 1979). A vital difference between these two types of action potentials is that the upstroke of the fast response depends on the fast Na+ channel, while the slow response depends on the slow inward Ca++ channel. The fast response can be diminished by an increase in extracellular potassium concentration, and the slow response can be enhanced by the presence of exogenous catecholamines. Both of these conditions occur during myocardial ischemia (Opie et al., 1979). It has been suggested that slow responses are arrhythmogenic due to their much slower propagation rate, and have been recorded during myocardial ischemia (Myerburg et al., 1977).

Podzuweit et al. (1978), using open-chest baboons, originally demonstrated that cAMP content within the ischemic zone rose significantly, approximately 10 minutes before the onset of ventricular fibrillation. This observation was supported by Corr et al. (1978) who, using the anesthetized cat, showed an association between increased cAMP content and ischemia-induced ventricular arrhythmias. Additional supportive evidence for the cAMP hypothesis came from a study by Lubbe et al. (1976), who suggested that administration of dibutyryl cAMP reduced ventricular fibrillation threshold in isolated rat hearts.

However, other evidence does not support the cAMP hypothesis. Russell and Oliver have shown (1979), in the open-chest dog with coronary artery ligation, that the threshold of the myocardium for the induction of multiple extrasystoles fell, and spontaneous ventricular complexes developed, at a time when cAMP probably did not increase. In addition, recent preliminary evidence (Kane et al., 1984) suggests that, in the in vivo anesthetized rat with acute coronary artery occlusion, although inhibitors of phosphodiesterase are arrhythmogenic, there is no evidence to support the hypothesis of Podzuweit et al. (1980) that an increase in myocardial cAMP content within the myocardium is responsible for this increase in arrhythmias.

Forskolin, cAMP, and Arrhythmias

In our study, both epinephrine and forskolin were used to evoke similar increases in heart rate, coronary flow, and cellular cAMP content; yet, despite this, only epinephrine increased the incidence of ischemia-induced arrhythmias. We have therefore demonstrated that large increases in cAMP content within the ischemic zone cannot necessarily be as-
sociated with an increase in rhythm disturbances. If increases in cellular cAMP content are not involved in the genesis of ischemia-induced ventricular arrhythmias in this preparation, it becomes necessary to consider other, possibly adrenoceptor-independent, mechanisms, by which catecholamines or their degradation products may be arrhythmogenic. Such possibilities include free radicals generated from the oxidation of catecholamines and catecholamine-stimulated increases in calcium influx via the slow inward current that may not involve cAMP increases. The latter process would explain the anti-arrhythmic effects of \( \beta \)-blocking agents without involving cAMP. With regard to the possible involvement of free radicals, catecholamines are highly susceptible to both enzyme-mediated (monooamine oxidase) and autooxidation. In addition to forming potentially toxic products such as adrenochrome (Takeo et al., 1981), oxygen-derived free radicals such as superoxide are produced. We (Manning et al., 1984, Manning and Hearse, 1984) and others (Woodward and Zakaria, 1985) have recently presented evidence that inhibition of free radical production or supplementation of natural scavenging processes can greatly reduce arrhythmias during reperfusion and, to a lesser extent, during ischemia. Although speculative, it may be that the arrhythmogenic properties of catecholamines are at least in part due to their metabolism and their by-products. This phenomenon would be unrelated to the adrenergic receptors or their activity, and would explain why forskolin, for which there is no evidence of free radical production, is not arrhythmogenic.

It is also known that some effects of \( \beta \)-adrenoceptor stimulation are not mediated through adenylyl cyclase, e.g., inhibition of magnesium influx (Maguire and Erdohs, 1980; Erdohs and Maguire, 1983). This may cause alterations in calcium influx that are independent of changes in cAMP and may result in arrhythmias.

Complications and Alternative Interpretations

In seeking to explain the apparent contradictions between our results and those of Podzuweit et al. (1978), a number of possibilities should be considered. First, it is possible that forskolin and epinephrine stimulate the production of cAMP from totally separate compartments of adenylyl cyclase, epinephrine stimulating the pool of cAMP that is arrhythmogenic and forskolin stimulating the pool that is not arrhythmogenic. Although there is no evidence available to support this possibility, there is obviously a clear need to establish the cellular location of elevated cAMP pools. Second, although again no evidence is available, there may be differences between species or cell types (for example, myocytes vs. vascular endothelium or smooth muscle cells) in the extent to which forskolin or catecholamines can stimulate cAMP production. Alternatively, it is possible that the forskolin-mediated rise in cAMP con-
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Advan Myocardiol 2: 133–143
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