Effects of Compound 48/80 on Cardiac Function and Histamine Release in Isolated Guinea Pig Hearts

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Compound 48/80에 레나나가 심장의 기능과 히스타민 생성에 미치는 영향

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= 국문초록 =

이 연구는 Langendorff 형식을 도입한 guinea pig 심장에서, compound 48/80이 심장의 기능, 관상동맥 순환과 히스타민 생성에 미치는 영향을 조사하였다. 심장은 95% 산소와 5% 이산화탄소로 산소화시키고 에너지 급원으로 5.5mM 포도당과 2.0mM 피로르산을 넣어준 Krebs-Ringer bicarbonate 용액으로 관류시켰다. 관상동맥 관류량, 심박동수, 좌심실 수축기압력과 그것의 수축력을 조사하기 위하여 여러 농도의 compound 48/80을 bolus injection 또는 continuous infusion 형식으로 주입시켰다. 10에서 200μg의 compound 48/80을 bolus injection시켰음때, compound 48/80은 초기의 일시적인 심실수축력의 증가를 나타낸 후 이어서, 장기간의 점진적인 dose-dependent response 형식으로 심실수축력의 감소현상을 초래하였다. 관상관류량과 심근 산소소비량도 감소하였다. compound 48/80으로 인한 심실수축력의 감소현상은 심박동수의 변화가 일어나지 않았음에도 불구하고 초래되었다.

한편, compound 48/80을 continuous infusion 방식으로 주입시켰을 때에는 dose-dependent response 형태로 단지 심실수축력이 감소되었다. 그리고 관상동맥 관류량과 심근 산소소비량은 심근 산소추출량이 증가하면서 감소되었다. 무변희 발현적인 100μg bolus injection 또는 50 μg/min/g continuous infusion 농도로 compound 48/80을 주입시켰음때 나타나는 반응들은 각각의 첫번째 주입에서 초래되었던 여리가지 기능변화들과 유의한 차이가 없었다. 심장으로부터 히스타민 유출은 100μg의 compound 48/80의 주입시, 10 내지 15초 지난후에 최대의 효과가 발생했다. 이것은 그 이후 점진적으로 감소하면서 주기후 60내지 70초에 도달하면, 주입 이전의 수준으로 되었다. 이상의 연구 결과들을 비추어 보면, compound 48/80로 유발된 심실수축력 감소현상은 부분적으로나마 compound 48/80 자체의 관상동맥 수축에 의한 것으로 추정되고, 또한 compound 48/80에 의하여 관상동맥 혈관에서 유리되어 나온 여리가지 관상동맥 혈관을 수축시키는 물질들이 간접적으로 연관 되었을 가능성이 있다.
Introduction

Compound 48/80 is widely employed in vivo and in vitro experimental studies to simulate the response of antigen-sensitized tissues. Its utility reflects powerful histamine releasing activity secondary to mast cell degranulation\(^1-4\). Histamine is present in large quantities in the guinea pig heart, with most of the amine existing in cardiac mast cells\(^5-7\). However, the amount of histamine that can be released by compound 48/80 is only a small fraction of the total histamine content\(^6-8\). The effects of compound 48/80 on cardiac function are reported to be similar to those caused by exogenous histamine\(^3\).

Little information is available, however, concerning the physiological effects of circulating compound 48/80 on coronary circulation and myocardial oxygen metabolism associated with coronary histamine release. Accordingly, the present study was undertaken to investigate the effects of compound 48/80 on these variables in the isolated, perfused guinea pig heart under conditions of constant coronary perfusion pressure.

Method and Materials

1. Perfusion of the isolated heart

The isolated, perfused guinea pig heart preparation described previously was used in the present study\(^11-13\). Adult guinea pigs of either sex weighing 400–500g were sacrificed. The hearts were quickly excised and mounted on a Langendorff perfusion apparatus within 2–3 minutes. Hearts were cannulated in situ with a polyethylene catheter (PE240, ID. 0.06 inches) via the ascending aorta and retrogradely perfused at a constant pressure of 65 cmH\(_2\)O with oxygenated (95% O\(_2\), 5% CO\(_2\), 295 mOsm, pH 7.40-7.45) Krebs-Ringer bicarbonate solution containing (mM): glucose 5.5; pyruvate 2.0; NaCl 127.5; KCl 4.7; CaCl\(_2\) 2.5; KH\(_2\)PO\(_4\) 1.2; MgSO\(_4\) 7H\(_2\)O 1.2; and NaHCO\(_3\) 24.9. Gentle squeezing of hearts prior to suspending from a non-recirculating extracorporeal perfusion circuit prevented air from entering the aorta upon cannulation. Retrograde aortic inflow was monitored both electromagnetically (Empco Bloodflow Transducer 300 AP, connected to a Carolina Medical Electronics, Model 501 Flowmeter, King, North Carolina, U.S.A., placed in the perfusion circuit 4–5 cm above the heart) and manually with a graduated cylinder and stopwatch. Global left ventricular performance (left ventricular dP/dt\(_{max}\)) was measured with a pressure-probe tipped intraventricular catheter (Millar, Model TC 500, Houston, Texas, U.S.A.) by passing the catheter across the mitral valve and into the left ventricle. Coronary perfusion pressure was continuously monitored by connecting a pressure transducer (Gould/Statham, Model P23Db, Oxnard, California, U.S.A.) to the perfusion circuit just proximal to the heart.

To measure global myocardial oxygen consumption (MVO\(_2\)), pulmonary artery was cannulated with a short, wide-bore polyethylene catheter (PE 240). Perfusate (arterial and venous) PO\(_2\) was recorded with standard electrodes (Blood Gases/pH Analyzer, Corning Medical Instruments, Model 165, Medfield, Massachusetts, U.S.A.) by collecting samples anaerobically (1ml) at selected time intervals as indicated below. Perfusate oxygen contents were calculated as the product of the partial pressure of O\(_2\) and the solubility of oxygen in the perfusate (both arterial and coronary venous) at 37°C. Myocardial oxygen consumption expressed in μL/min/g wet weight of myocardium, was calculated as the product of coronary perfusate flow (CF, ml/min/g) times the arterio-venous difference in O\(_2\) contents. [(a-v)O\(_2\), μL/ml].

Pre-and post-experimental preparation usefulness was tested in order to include only physiologically intact hearts in the final data analysis\(^12,13\). This test consisted of administering 100–200μg of adenosine which produced transient cardiac arrest in diastole accompanied by a 3–4 fold increase in
peak coronary perfusate flow. Hearts not displaying post-experimental responses which were quantitatively similar to the pre-experimental responses were discarded.

2. Drugs

Heparin sodium, adenosine, and compound 48/80 all of which were purchased from Sigma Chemical Company (St. Louis, Missouri, U.S.A.). All stock solutions were freshly prepared in 0.9% w/v saline solution and each solution was administered at selected time intervals as indicated below.

3. Bolus injections of compound 48/80

This heart preparation is stable for at least 60~90 minutes\textsuperscript{[1-13]}, and is suitable for the study of 2~3 repeated bolus injections (or continuous intracoronary infusions) of compound 48/80 on CF, heart rate (HR), left ventricular systolic pressure (LVSP), dP/dt\textsubscript{max}, (a-v)O\textsubscript{2} and MVO\textsubscript{2}. At the end of the stabilization period, hearts were examined for preparation usefulness. After hearts achieved the steady state, control measurements were made and designated control. Compound 48/80 (10~200μg) was then injected through the cannulated aorta in a volume not exceeding 0.2ml. All hemodynamic variables were continuously monitored. One minute after administration of compound 48/80, when hearts were in the steady state, arterial and venous effluent samples were collected. All collected data were designated 48/80. Hearts were then allowed 20~25 minutes to reacquire a new control state, and another bolus injection of compound 48/80 to be washed out. A second set of control data was collected. Thereafter, a second bolus injection of compound 48/80 was repeated as above with a dose (10~200μg) randomly selected. Monitored physiological variables, and arterial and venous effluent perfusate samples were collected in the same period of time as above. Hearts were allowed to restabilize before repeating tests of post-experimental preparation usefulness\textsuperscript{[12,13]}.

A separate group of hearts (n=8) was employed to measure histamine release following treatment with compound 48/80 (100μg). The overall experimental procedure was the same as described above. A bolus injection of 0.1ml of compound 48/80 was given when CF was in the steady state. Subsequently, serial samples (2ml) of venous effluent perfusate were collected at 10~15, 30~40, and 60~70 seconds after administration of compound 48/80. Coronary perfusate flow was continuously measured. The content of histamine in samples was determined by using high performance liquid chromatography (HPLC) technique\textsuperscript{[14]}. Histamine release was estimated as the product of the venous concentration of histamine times the coronary perfusate flow rate.


An experimental protocol similar to that described above for bolus injections was employed in a separate group of hearts during continuous infusion of compound 48/80 (5~100μg/min/g) for 3 minutes in a volume not exceeding 0.1 ml/min. At the end of the 3 minute infusion period, perfusate samples and recorded variables were collected and designated 48/80. After termination of the infusion, hearts were allowed 20~25 minutes for compound 48/80 to be washed out and to restabilize. A second set of control data was then recorded. Subsequently, intracoronary infusion of compound 48/80 was repeated with an infusion rate (5~100μg/min/g) randomly selected. A second set of compound 48/80 data was collected at the end of the infusion period. Tests of preparation usefulness were performed at the end of each experiment\textsuperscript{[12,13]}.

5. Statistical analysis.

All values were expressed as means±S.E. Data obtained at different times and from different groups of hearts were compared for significant differences using Analysis of Variance in the appropriate modification for either paired or non-paired data\textsuperscript{[15]}. Significance was established at p<0.05.
Table 1. Effects of the bolus injections of compound 48/80 on cardiac function and coronary circulation

<table>
<thead>
<tr>
<th>compound 48/80 (μg)</th>
<th>CF (ml/min/g)</th>
<th>HR (bpm)</th>
<th>dP/dt max (mmHg/sec)</th>
<th>(a-v)O2 (μl/ml)</th>
<th>MVO2 (μl/min/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>control</td>
<td>7.2±0.2</td>
<td>210±6</td>
<td>779±55</td>
<td>7.6±0.5</td>
<td>55±4</td>
</tr>
<tr>
<td>10 (n=12)</td>
<td>6.7±0.2*</td>
<td>207±6</td>
<td>752±55</td>
<td>7.6±0.2</td>
<td>50±4*</td>
</tr>
<tr>
<td>control</td>
<td>7.6±0.2</td>
<td>216±6</td>
<td>780±28</td>
<td>7.1±0.4</td>
<td>54±3</td>
</tr>
<tr>
<td>50 (n=15)</td>
<td>6.5±0.2*</td>
<td>212±6</td>
<td>706±27*</td>
<td>7.4±0.4*</td>
<td>49±3*</td>
</tr>
<tr>
<td>control</td>
<td>7.4±0.4</td>
<td>208±9</td>
<td>786±35</td>
<td>7.3±0.4</td>
<td>58±3</td>
</tr>
<tr>
<td>100 (n=15)</td>
<td>5.8±0.4*</td>
<td>203±6</td>
<td>632±53*</td>
<td>7.9±0.4*</td>
<td>46±3*</td>
</tr>
<tr>
<td>control</td>
<td>7.4±0.2</td>
<td>205±6</td>
<td>767±35</td>
<td>7.1±0.2</td>
<td>52±2</td>
</tr>
<tr>
<td>200 (n=11)</td>
<td>5.5±0.2*</td>
<td>200±7</td>
<td>580±34*</td>
<td>7.4±0.2*</td>
<td>41±2*</td>
</tr>
</tbody>
</table>

Data are means± SE. CF, coronary flow; HR, heart rate; dP/dt max, left ventricular rate of pressure development; (a-v)O2, arterio-venous oxygen content difference; MVO2, global myocardial oxygen consumption. *p<0.05, relative to corresponding control value (no compound 48/80) in same column.

Table 2. Effects of the repeated bolus injections of compound 48/80 (100μg) on coronary flow and cardiac function in isolated guinea pig hearts

<table>
<thead>
<tr>
<th></th>
<th>CF (ml/min/g)</th>
<th>HR (bpm)</th>
<th>dP/dt max (mmHg/sec)</th>
<th>(a-v)O2 (μl/ml)</th>
<th>MVO2 (μl/min/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st injection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>control</td>
<td>7.6±0.7</td>
<td>212±8</td>
<td>763±19</td>
<td>7.0±0.3</td>
<td>53±5</td>
</tr>
<tr>
<td>48/80</td>
<td>5.9±0.4*</td>
<td>207±9</td>
<td>640±37*</td>
<td>7.8±0.1*</td>
<td>45±4*</td>
</tr>
<tr>
<td>2nd injection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>control</td>
<td>7.3±0.5</td>
<td>204±6</td>
<td>750±22</td>
<td>7.4±0.4</td>
<td>54±4</td>
</tr>
<tr>
<td>48/80</td>
<td>6.1±0.5*</td>
<td>201±6</td>
<td>661±29*</td>
<td>7.9±0.5*</td>
<td>48±4*</td>
</tr>
</tbody>
</table>

Data are means± SE (n=10). CF, coronary flow; HR, heart rate; dP/dt max, left ventricular pressure development; (a-v)O2, arterio-venous oxygen content difference; MVO2, global myocardial oxygen consumption. *p<0.05, relative to corresponding control value in same column.

Table 3. Effects of the bolus injections of compound 48/80(100μg) on histamine release

<table>
<thead>
<tr>
<th>Time(seconds)</th>
<th>Histamine release (ng/min/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>control</td>
<td>209±13</td>
</tr>
<tr>
<td>10~15</td>
<td>514±24*</td>
</tr>
<tr>
<td>30~40</td>
<td>265±16*</td>
</tr>
<tr>
<td>60~70</td>
<td>215±9</td>
</tr>
</tbody>
</table>

Data are mean± SE (n=8). Perfusate samples were collected during each time period after the administration of compound 48/80. *p<0.05, relative to control value.

Results

1. Effects of bolus injections of compound 48/80 on cardiac function

Table 1 summarizes the effects of bolus injection of compound 48/80 on cardiac function and coronary circulation. Compound 48/80 in a range of 10~20μg produced initial and transient positive inotropic responses rapidly (for 10~15 seconds after injections) followed by late and prolonged negative inotropism (data not shown). These responses were dose-dependent. Heart rate was unaffected by compound 48/80 even at high doses (200μg). One minute after bolus injection, CF and global MVO2 decreased in a dose-dependent fashion, while myocardial oxygen extraction increased significantly at all but the lowest dose of compound 48/80.

Table 2 shows the effect of repeated injections of 100μg of compound 48/80 on contractility, CF and MVO2. The cardiac and vascular responses to the second injection of compound 48/80 were
Table 4. Effects of the continuous infusions of compound 48/80 on cardiac function and coronary circulation

<table>
<thead>
<tr>
<th>48/80 (µg/min/g)</th>
<th>CF (ml/min/g)</th>
<th>HR (bpm)</th>
<th>dP/dt max (mmHg/sec)</th>
<th>(a-v)O₂ (µl/ml)</th>
<th>MVO₂ (µl/min/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>control</td>
<td>7.5 ± 0.5</td>
<td>208 ± 12</td>
<td>745 ± 22</td>
<td>7.0 ± 1.1</td>
<td>53 ± 6</td>
</tr>
<tr>
<td>5 (n=6)</td>
<td>7.2 ± 0.4</td>
<td>206 ± 9</td>
<td>731 ± 21</td>
<td>7.3 ± 1.0</td>
<td>52 ± 5</td>
</tr>
<tr>
<td>control</td>
<td>7.9 ± 0.5</td>
<td>210 ± 10</td>
<td>735 ± 29</td>
<td>6.9 ± 0.6</td>
<td>54 ± 5</td>
</tr>
<tr>
<td>25 (n=8)</td>
<td>7.0 ± 0.4*</td>
<td>205 ± 7</td>
<td>659 ± 13*</td>
<td>7.4 ± 0.6*</td>
<td>51 ± 5</td>
</tr>
<tr>
<td>control</td>
<td>7.6 ± 0.4</td>
<td>207 ± 8</td>
<td>765 ± 20</td>
<td>7.4 ± 0.4</td>
<td>55 ± 5</td>
</tr>
<tr>
<td>50 (n=11)</td>
<td>6.3 ± 0.3*</td>
<td>201 ± 6</td>
<td>631 ± 31*</td>
<td>8.1 ± 0.3*</td>
<td>51 ± 3*</td>
</tr>
<tr>
<td>control</td>
<td>7.3 ± 0.5</td>
<td>207 ± 8</td>
<td>715 ± 43</td>
<td>7.4 ± 0.3</td>
<td>53 ± 5</td>
</tr>
<tr>
<td>100 (n=7)</td>
<td>4.4 ± 0.4*</td>
<td>200 ± 4*</td>
<td>379 ± 67*</td>
<td>8.5 ± 0.3*</td>
<td>37 ± 4*</td>
</tr>
</tbody>
</table>

Data are means ± SE. CF, coronary flow; HR, heart rate; dP/dt max, left ventricular rate of pressure development; (a-v)O₂, arterio-venous oxygen content difference; MVO₂, global myocardial oxygen consumption. *p<0.05, relative to corresponding control value in same column.

not significantly different from those seen during the first injection.

2. Effects of bolus injections of compound 48/80 on histamine release

The maximum effect of compound 48/80 (100µg) on histamine release occurred at 10~15 seconds after injection. Cardiac histamine release increased by 146 ± 24% during this period (Table 3). Thirty-40 seconds after compound 48/80 treatment, histamine release was still elevated significantly, but lower (p<0.05) than the maximum values obtained at 10~15 seconds. By 60~70 seconds, histamine release did not differ from control.

3. Effects of continuous infusions of compound 48/80 on cardiac function

Only negative inotropism was seen in the group of hearts exposed to continuous intracoronary infusion of compound 48/80. The effect was dose-dependent in the range of 10~100 µg/min/g (Table 4). Unlike bolus injections, infusion of 100 µg/min/g for 3 minutes produced small but significant decreases in HR (p<0.05). Coronary perfusate flow and MVO₂ decreased significantly by 40% and 31%, respectively, at the highest dose of compound 48/80. At this same dose, (a-v)O₂ increased significantly by 15% (p<0.05). Effluent perfusate pH decreased consistently and significantly during the infusion of compound 48/80.

A separate group of hearts (n=4) was employed to examine the effects of repeated infusions of 50 µg/min/g of compound 48/80 on cardiac function and coronary circulation. The responses were not significantly different from those observed during the first infusion of 50 µg/min/g as shown in Table 4 (data not shown).

Discussion

In the current study intracoronary administration of compound 48/80 was employed to explore its effects on cardiac function, coronary circulation, and myocardial oxygen consumption in isolated guinea pig hearts perfused at constant pressure. Several doses of compound 48/80 were employed as bolus injections or continuous infusions in a preparation devoid of neuro-humoral and blood-borne influence(6). Since compound 48/80 is also known to liberate histamine(7), we measured myocardial histamine release in response to bolus injection of compound 48/80.

1. Compound 48/80 and histamine release

The results show that the maximum release of
histamine occurred within 10~15 seconds after bolus injection of compound 48/80. The rate of release was still significantly elevated at forty seconds. However, the rate of release at 70 seconds after the injection was not significantly different from control levels, suggesting complete washout at that time. These results are consistent with the concept that compound 48/80 is a prompt and effective histamine releasing agent. In a related study Gomes and Antonio reported that the releasable cardiac histamine was liberated by 50µg of compound 48/80 in one minute. The remaining releasable histamine pool was liberated by three minutes. This report and the results of the present study indicate that histamine release in the guinea pig heart is an explosive phenomenon.

Histamine release by compound 48/80 is also reported to be dose-dependent in the isolated guinea pig heart. The preparation contains large quantities of histamine (4~7µg/g wet tissue) which are stored predominantly in mast cells. Compound 48/80, in bolus doses as high as 200µg, degranulates mast cells and releases histamine without causing membrane disruption. Gomes et al. have shown that a histamine concentration of 0.5µg in 10ml of effluent perfusate can occur with bolus injection of 50µg of compound 48/80. The maximum effect of compound 48/80 on histamine release occurs at a dose of 100~200µg. According to these data, the maximum rate of histamine release in response to 100µg of compound 48/80 is approximately 0.5µg/min/g. This is probably near maximum for this preparation. Poch and Kukovetz reported no significant histamine release at doses of compound 48/80 less than 50µg.

2. Compound 48/80 and cardiac function

Compound 48/80 and cardiac anaphylaxis produce similarities in their cardiac actions. As with immunologically induced changes in cardiac function, compound 48/80 produces tachycardia, arrhythmias, and positive chronotropic and inotropic effects in isolated, perfused guinea pig hearts. Since compound 48/80-induced changes in cardiac function are attenuated by H1 and H2 histamine antagonists, the pharmacological actions of compound 48/80 are assumed to be due to an effect on histamine release.

As might be expected, bolus injections of compound 48/80 produced an early but transient positive inotropic response (10~15 seconds after injection), which occurred in parallel with the maximum histamine release exhibited at 10~15 seconds. This response was rapidly followed by a more sustained negative inotropic response, even though histamine release was significantly elevated for at least 40 seconds. Conversely, continuous infusion of compound 48/80 produced only negative inotropism, which was dose-dependent. The administration route-dependent effects of compound 48/80 on cardiac inotropic responses might, therefore, be related to histamine release. A suddenly increasing concentration of compound 48/80, e.g., with bolus injection, might release enough histamine to produce positive inotropic responses. Slowly increasing concentrations of compound 48/80, e.g., such as with continuous infusion, might produce little effect on histamine release. Unfortunately, the rate of histamine release was not determined in the present study. Even though the total amount of compound 48/80 infused for three minutes was greater than that injected as a single bolus, the infused compound 48/80 apparently gets washed out prior to causing significant release of histamine.

The present study conducted additional experiments to examine whether the cardiac and vascular actions of compound 48/80 with subsequent injections are conservable. There were no differences in any of the measured cardiac responses to duplicate injections of compound 48/80. These findings indicate that the myocardium after the first injection remained intact. Therefore, we can exclude the possibilities of tachyphyaxis or preparation deteriora-
tion as explanations for the observed responses to the first injection of compound 48/80. This is contrary to a previous report showing considerable differences in the inotropic response to successive injections of compound 48/80. These findings indicate that the myocardium after the first injection remained intact. Therefore, we can exclude the possibilities of tachyphylaxis or preparation deterioration as explanations for the observed responses to the first injection of compound 48/80. This is contrary to a previous report showing considerable differences in the inotropic response to successive injections of compound 48/80. The second injection did not show the transient positive inotropic response, but rather produced a more intense negative inotropic response. This discrepancy might be explained on the basis of incomplete washout of compound 48/80 prior to the second injection. Thus, the cardiac and vascular conditions during the second injection of compound 48/80 would have been different from those during the initial injection.

3. Compound 48/80 and coronary perfusate flow and myocardial oxygen consumption

Compound 48/80 produced a reduction in coronary perfusate flow under conditions of constant coronary perfusion pressure. This is consistent with the findings of Gomes et al. using isolated perfused guinea pig hearts. The decrement in coronary perfusate flow was dose-dependent. The reduction in coronary perfusate flow might be accompanied by a reduction in myocardial oxygen supply. This, in turn, was accompanied by an increment in oxygen extraction. Therefore, MVO₂ remained constant, at least under conditions of constant infusion of 5–25μg/min/g. The increase in oxygen extraction was limited or insufficient at higher doses of compound 48/80, because the myocardial oxygen consumption was still significantly reduced. The latter finding can be explained by the fact that oxygen demand decreased as cardiac performance decreased at higher doses of compound 48/80.

The mechanism of the compound 48/80 induced coronary vasoconstriction cannot be determined with certainty in the present study. Kang et al. have shown that exogenous histamine causes coronary vasoconstriction in this preparation when perfused at a constant pressure. Accordingly, the histamine released by compound 48/80 could have caused active coronary vasoconstriction. Alternatively, the response might have been passive, due to a reduction in oxygen demand. This explanation, based on bolus injections, might not apply to continuous infusion. Compound 48/80 is known to release other endogenous vasoconstrictors, e.g., slow reacting substance and prostaglandins. Bach et al. demonstrated that the release of the slow reacting substance by compound 48/80 was inhibited by a high dose of indomethacin. The more recent data of Gomes and Antonio show that indomethacin inhibits nearly all the effects of compound 48/80. Because of the similarities between the effects of compound 48/80 and cardiac anaphylaxis on the heart, the thromboxanes, which are also known to be released during cardiac anaphylaxis, could have contributed to the coronary vasoconstriction seen in the present study.

In summary, these results have found that bolus injection of compound 48/80 produces rapid but transient histamine release. The accompanying negative inotropism might be due, in part, to the vasoconstrictor actions of compound 48/80. Other, indirect effects such as release of endogenous coronary vasoconstrictors, might also have contributed to the response. Further study is needed to clarify these possibilities.
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References


8) Gomes JC and Antonio A: Histamine release from the isolated guinea pig heart by compound 48/80. Gen Pharmacol 16: 399, 1985


