PULMONARY VASCULAR AND CARDIAC EFFECTS OF GLUCAGON BEFORE AND AFTER ADRENERGIC BETA-RECEPTOR BLOCKADE.

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Summary: In dogs, glucagon exerts a local pulmonary vasodilator action as indicated by a fall of arterial pressure in the perfused left lower lobe of the lung. It elevates pulmonary arterial blood pressure in the intact preparation as a result of its cardio-stimulatory actions. It augments cardiac contractility and rate and lowers systemic arterial blood pressure. Similar but more pronounced effects are produced by isoprenaline. Since the cardiopulmonary responses to isoprenaline are blocked by propranolol while those to glucagon remain unaffected, it is suggested that the basic receptor mechanisms underlying the actions of two compounds are not identical. Further, glucagon may be of therapeutic usefulness in propranolol-induced myocardial depression.

Key Words: cardiopulmonary effects of glucagon propranolol isoprenaline and glucagon

INTRODUCTION

Glucagon has been recently investigated for the cardiovascular actions both in animals and man (8, 9, 11, 21, 25). It shares the properties of catecholamines in exerting powerful positive inotropic and chronotropic actions on the heart resulting in an increase in cardiac output. However, its pulmonary vascular effects have not been elucidated. Further, there is disagreement on the ability of adrenergic beta-receptor antagonists to modify its cardiac actions. While dichloroisoprenaline blocks both the inotropic and chronotropic responses to glucagon (4), propranolol antagonizes only the cardioaccelerator action (6). Hence the present work has been undertaken with the purpose of investigating the cardiopulmonary actions of glucagon and comparing them with isoprenaline before and after beta-adrenergic receptor blockade induced by propranolol.

MATERIALS AND METHODS

Adult mongrel dogs of either sex, weighing 11-19 kg were anaesthetized with chloralose (80 mg/kg iv) and pentobarbitone sodium (10 mg/kg iv). Heparin sodium (5 mg/kg iv) was routinely used as an anticoagulant. Systemic arterial blood pressure was recorded from a carotid artery by a mercury manometer and heart rate was measured with lead II from a Galileo electrocardiograph. After instituting artificial ventilation under positive pressure, the chest was opened in the left fifth intercostal space to measure one or more of the following...
in the same animal according to methods described earlier (10, 12): (i) pulmonary arterial blood pressure of the intact lung; (ii) pulmonary perfusion pressure of the left lower lobe of the lung; and (iii) cardiac contractility.

Drugs, doses and route of administration: The following drugs and doses were used: 0.1% solution of crystalline glucagon (Lot number 258-234 B-167-1 of Lilly Research Laboratories) in sterile normal saline in a dose of 50 μg/kg; propranolol hydrochloride, 0.5 mg/kg; and isoprenaline sulphate, 2 μg/kg. All drugs were administered intra-arterially by injecting into the rubber tubing close to the cannulated pulmonary artery.

Conduct of the experiment: Isoprenaline and glucagon were administered at 20 to 30 min interval. This was followed by propranolol, 10 min after which injections of isoprenaline and glucagon was repeated. In some experiments, the sequence of administration of isoprenaline and glucagon was reversed.

RESULTS

Glucagon (Table I) caused an increase in pulmonary arterial blood pressure of the intact lung by 25%, a decrease in enhancement of cardiac contractility by 11%, and a decrease in pulmonary perfusion pressure by 11%. These effects are maximal at 5 to 10 min after injection. Isoprenaline responses to isoprenaline but the hypotensive and pulmonary perfusion parameters were statistically significant, thus confirming the do

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Number of observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary arterial blood pressure (cm H₂O)</td>
<td>7</td>
</tr>
<tr>
<td>Pulmonary perfusion pressure (mm Hg)</td>
<td>7</td>
</tr>
<tr>
<td>Systemic arterial blood pressure (mm Hg)</td>
<td>18</td>
</tr>
<tr>
<td>Cardiac contractility (mm)</td>
<td>7</td>
</tr>
<tr>
<td>Heart rate/min</td>
<td>18</td>
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</tbody>
</table>

*Statistical analysis was performed

**Pulmonary vascular effects**: The reduction of pulmonary vascular resistance of their local pulmonary vascular resistance of both the compounds produced an increase in cardiac contractility from their cardiostimulatory component of action and left ventricular end-diastolic pressure. This confirms the data that glucagon and isoprenaline were beneficial in the treatment of hypotension and pulmonary hypertension.
Cardiopulmonary Responses to Glucagon

Note that while

**Table 1:** Cardiopulmonary actions of glucagon and isoprenaline.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Number of observations</th>
<th>Before glucagon</th>
<th>After glucagon</th>
<th>Before isoprenaline</th>
<th>After isoprenaline</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary arterial blood pressure (cm H₂O)</td>
<td>7</td>
<td>22.3±1.2</td>
<td>28.0±1.3</td>
<td>21.1±1.0</td>
<td>28.3±1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulmonary perfusion pressure (mm Hg.)</td>
<td>7</td>
<td>27.6±1.04</td>
<td>24.6±1.3</td>
<td>27.5±1.2</td>
<td>23.8±1.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Systemic arterial blood pressure (mm Hg.)</td>
<td>18</td>
<td>121.7±8.7</td>
<td>108.0±9.5</td>
<td>122.7±3.7</td>
<td>67.5±7.07</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiac contractility (mm)</td>
<td>7</td>
<td>105.5±5.4</td>
<td>142.0±5.5</td>
<td>91.8±10.9</td>
<td>138.3±16.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate/min</td>
<td>18</td>
<td>212.5±9.3</td>
<td>262.8±6.1</td>
<td>210.5±9.3</td>
<td>291.2±8.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Statistical analysis was performed by using Student’s ‘t’ test.

**DISCUSSION**

**Pulmonary vascular effects:** Drug-induced changes in the pressure of the perfused lobe of the lung are known to represent the local effects on pulmonary blood vessels (2, 18). Hence the reduction of pulmonary perfusion pressure by glucagon and isoprenaline is indicative of their local pulmonary vasodilator action. However, in the intact lobe of the lung, both the compounds produce a rise of pulmonary arterial blood pressure. This is interpreted to mean that glucagon and isoprenaline-induced increase in cardiac output (13, 17) resulting from their cardiostimulatory effects (see Table I) overshadows the local pulmonary vasodilator component of action and leads to elevation of pulmonary arterial blood pressure in the intact lung. This confirms the dominant role of cardiac output in influencing the pulmonary arterial pressure in the intact preparation (1, 5, 7). This is further corroborated by the present observation that propranolol, which blocks the cardiac effects of isoprenaline and not those of
glucagon, antagonizes the pulmonary hypertensive response (in the intact lung) to the former drug but not that to the latter compound.

**Cardiac effects**: Glucagon, like isoprenaline, augmented cardiac contractility and rate (8, 21). Evidence from many sources now suggest that the enzyme, adenyl cyclase, is the adrenergic beta-receptor and its stimulation results in accumulation of cyclic AMP which in turn induces the effector response (19). The observations that glucagon increases cyclic AMP in a variety of tissues and exhibits metabolic and cardiac actions similar to catecholamines have led Sutherland et al (24) to postulate that adenyl cyclase system (or beta adrenergic receptor) may be the common mediator for the effects of glucagon and catecholamines on the heart. The present results contradict this hypothesis since the cardiotonic effects of glucagon are not antagonized by propranolol in a dose which is effective in blocking the positive chronotropic and inotropic responses to isoprenaline. It is possible that either the adenyl cyclase is not affected by glucagon or a separate adenyl cyclase system, which is resistant to beta receptor blockade, exists for glucagon. The possibility of the latter has been suggested for liver from which only glucagon-sensitive enzyme has been isolated (16). In any case, the basic molecular mechanisms underlying the cardiac and pulmonary vascular effects of glucagon and isoprenaline do not appear to be identical.

**Clinical significance**: In view of the ability of glucagon to exert cardiotonic actions in the presence of adrenergic beta receptor blockade, support is lent to the viewpoint of Manchester et al (14) that this hormone may be of therapeutic value in overcoming the severe myocardial depression produced by propranolol, for which catecholamines are obviously ineffective and which, if left untreated, may aggravate congestive heart failure (3, 22) or precipitate cardiac asystole (20, 23, 26) with fatal outcome.

**REFERENCES**

26. Wolfson, S. J. Robbins and, clinical and experimen
contractility and rate of the heart. Adenyl cyclase, the enzyme that catalyzes the formation of cyclic AMP from ATP, increases cyclic AMP levels. Cyclic AMP, in turn, activates protein kinase, which is a key enzyme in regulating cellular processes. Cyclic AMP can be suppressed by beta adrenergic receptor blockers, which are used clinically to manage cardiovascular conditions.

In any case, the effects of glucagon are important to consider in the context of cardiototoxicity and anti-hypertrophic actions of glucagon. Glucagon is also known to have cardiostimulatory effects and has been found to improve blood flow in the pulmonary circulation. This is particularly relevant in the context of pulmonary hypertension, where the use of glucagon has been found to be beneficial.

The immediate effect of intravenous propranolol on various cardiac arrhythmias has been extensively studied. Pohl et al. (1969) observed that propranolol can have a positive inotropic effect, while others have reported that it can also have a negative inotropic effect. Similarly, the immediate effect of glucagon on the sinus node has also been studied, with Whitehouse and James (1966) demonstrating that glucagon can have chronotropic effects on the heart.

In the context of cardiac arrhythmias, the treatment of cardiac arrhythmias with beta adrenergic blocking agents has been extensively studied. Wolfson et al. (1966) compared the effects of propranolol and atenolol on cardiac arrhythmias and concluded that propranolol was more effective in reducing the incidence of cardiac arrhythmias.

Overall, the use of glucagon in the management of cardiovascular conditions continues to be an area of active research, with new studies exploring the potential of glucagon in treating various cardiovascular conditions.

References: