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

B.R. MADAN, R.S. GUPTA AND B.K. JAIN

Department of Pharmacology,
S.P. Medical College, Bikaner

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 $\mu g/kg$; propranolol hydrochloride, 0.5 mg/kg; and isoprenaline sulphate, 2 $\mu g/kg$. 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

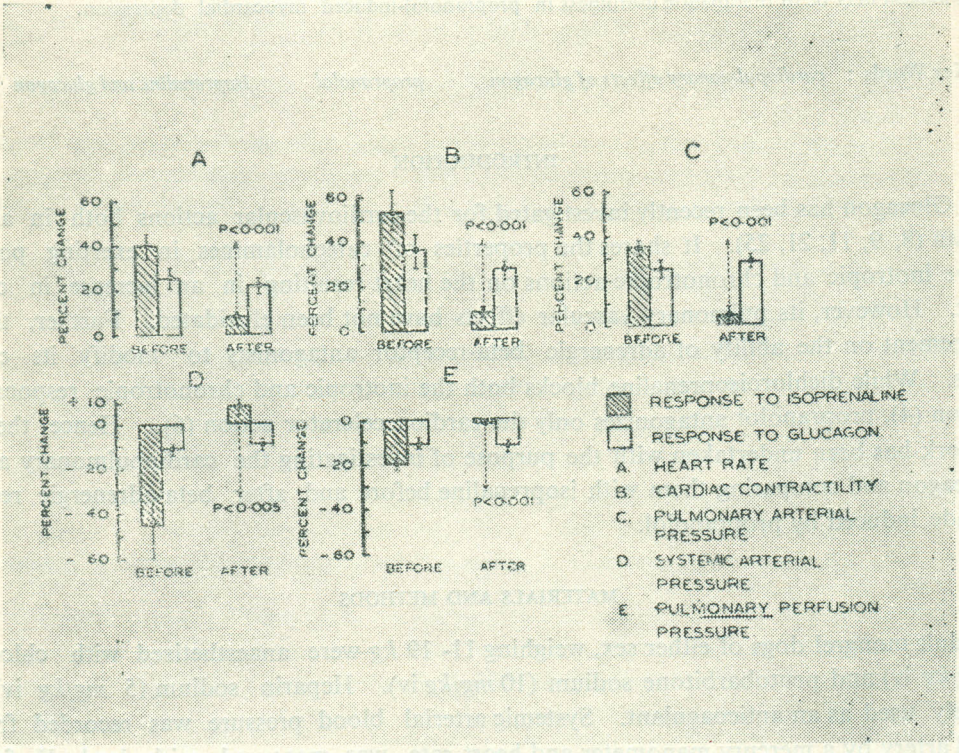

Fig. 1: *Effects of glucagon and isoprenaline before and after propranolol. Note that while isoprenaline effects are blocked by propranolol, the effects of glucagon which are similar to isoprenaline, are not blocked by propranolol.*

intact lung by 25%, a decrease in the pressure of the perfused lobe of the lung by 11%, enhancement of cardiac contractility and rate by 35% and 24% respectively and a fall of systemic arterial blood pressure by 11%. The effects occurred within 1 to 2 min after the injection, were maximal at 5 to 10 min and were dissipated at 20 to 30 min. Except for the systemic hypotensive and pulmonary perfusion pressure effects, changes in all the cardiopulmonary parameters were statistically significant (Table I). Similar but more marked effects were produced by isoprenaline. Treatment of the animal with the beta-adrenergic receptor blocking dose of propranolol (0.5 *mg/kg*), resulted in a reduction or abolition of the cardiopulmonary responses to isoprenaline but those to glucagon were not significantly modified (Fig 1).

TABLE I: *Cardiopulmonary actions of glucagon and isoprenaline.*

Parameters	*Number of observations*	*Before glucagon*	*After glucagon*	*P— value**	*Before isoprenaline*	*After isoprenaline*	*P— value**
Pulmonary arterial blood pressure (cm H_2O)	7	22.3±1.2	28.0±1.3	<0.01	21.1± 1.0	28.3± 1.1	<0.001
Pulmonary perfusion pressure (mm Hg.)	7	27.6±1.04	24.6±1.3	>0.05	27.5± 1.2	23.8± 1.7	<0.05
Systemic arterial blood pressure (mm Hg.)	18	121.7±8.7	108.0±9.5	>0.05	122.7± 3.7	67.5± 7.07	<0.001
Cardiac contractility (mm)	7	105.5±5.4	142.0±5.5	<0.001	91.8±10.9	138.3±16.5	<0.05
Heart rate/min	18	212.5±9.3	262.8±6.1	<0.001	210.5± 9.3	291.2± 8.3	<0.001

*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 cardiostimulatory actions 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 cardiostimulatory 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.

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