SHORT COMMUNICATION

THE CARDIAC INOTROPIC RESPONSES TO INSULIN IN THE RAT HEART

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Summary: Insulin (5 to 40 I.U.) produced dose-dependent positive inotropic effect in the isolated rat heart. The responses to insulin were markedly inhibited in the presence of propranolol (1.1x10^{-6} M). Insulin responses were markedly reduced in reserpine pretreated (5 mg/kg, i.p.) rats. Theophylline (4.4 mM), the phosphodiesterase inhibitor, potentiated the responses to insulin, whereas imidazole (20 mM), the phosphodiesterase stimulator inhibited the responses to insulin. The data suggest that the positive inotropic effects of insulin in rat heart is mediated through the release of cardiac catecholamines which stimulates beta-adrenoceptors. The final mediator of cardiac action seems to be cyclic-AMP.

Key words: insulin propranolol theophylline imidazole rat heart

INTRODUCTION

Insulin exerts profound metabolic effects on a variety of tissues (5,6,9,12,16). The importance of the role of insulin in cardiac metabolism has been emphasized by various authors (3,7,17,18). However, the complex interrelationship between cardiac performance and insulin activity have not been fully elucidated. Recent studies have shown, that in the intact lamb intravenous injection of insulin results in a positive inotropic response (4). The increase in cardiac contractility was not prevented by propranolol, the beta-adrenoceptor blocker, suggesting that insulin may have a direct positive inotropic effect on the myocardium (4). Klinge and Waf (10) and Sassine et al. (15) reported the positive inotropic effects of insulin in rabbit and canine hearts (10,15). Lucchesi et al. (11) reported the inotropic action of insulin in the canine heart. Lee et al. (8) reported insulin-induced biphasic inotropic responses in piglet moderator band and positive responses in both cat and kitten papillary muscle. Insulin has been reported to alter cyclic-AMP levels in various tissues such as adipose tissue (14), diaphragm (21) and fat cells (2).

The present study was undertaken to investigate the effects of insulin on contractile performance of isolated rat heart. An attempt has also been made to study the interaction
of insulin with drugs affecting the enzyme phosphodiesterase, namely theophylline and imidazole (19,20).

MATERIALS AND METHODS

Albino rats of either sex weighing between 150-250 g were injected with heparin sodium (8 mg/kg sc) 60 min prior to sacrifice. The animals were stunned by a blow on the head. The heart was rapidly excised and perfused by Langendorff's technique as recently described by Verma and McNeill (19) with oxygenated buffer solution (1) at a flow rate of 2.8 ml/min. The temperature of the perfusion fluid was 37°C and pH was 7.4. The composition of perfusion buffer solution was: (mEq/lit) NaCl, 119; KCl, 5.6; CaCl₂, 2 H₂O, 3.2; MgCl₂·6H₂O, 2.0 and NaHCO₃, 25 mM. The contractility was monitored by means of a Palmer clip placed at the apex of the heart and connected to a heart lever. The force of contraction was recorded on a smoked drum. The heart was allowed to stabilize for 10 min prior to the addition of any drug. The responses to graded doses of insulin (5 to 40 I.U.) were recorded.

In the second series of experiments the interaction of insulin with propranolol, imidazole or theophylline were studied. Hearts were perfused for 10 min with the perfusion buffer solution containing propranolol (1.1x10⁻⁶ M), imidazole (20 mM) or theophylline (4.4 mM). Thereafter, insulin responses were recorded. The responses to insulin were also studied in reserpinized rats. The animals were pretreated with reserpine (5 mg/kg ip) 24 hr prior to sacrifice.

The following drugs were used in the present study. Heparin sodium (Biological Evans Ltd.), insulin I.P. (The Boots Company Ltd.), propranolol (Imperial Chemicals Ltd.), reserpine (Sigma Labs.), theophylline (Cadila Labs.), imidazole (Lab-Chem Industries).

RESULTS

The results are summarized in Fig. 1. Insulin produced a dose-dependent increase in positive inotropic action on isolated rat heart. Propranolol (1.1x10⁻⁶ M) pretreatment and the inotropic reserpinisation markedly reduced the inotropic responses to insulin.

Theophylline (4.4 mM) pretreatment significantly potentiated the responses to insulin. Imidazole (20 mM) pretreatment markedly inhibited the positive inotropic responses to insulin.
DISCUSSION

Insulin has been reported to produce positive inotropic responses in Lamb model (4), in canine heart (11), in the rabbit auricle (15), in moderator band of piglet and papillary muscle of cat and kittens (18). Our findings demonstrate that insulin also produces positive inotropic responses in rat heart.
The study of Lucchesi et al. (11) indicates that the inotropic effect of insulin on canine cardiac muscle is not related to the ability of insulin to facilitate glucose transport (13). Dowling et al. (8) suggested the possibility that the inotropic effect of insulin in cardiac tissue may be mediated via the process of translocation of Ca²⁺ from binding sites to contractile protein, thus increasing the amount of intracellular Ca²⁺ available at the myofilaments and augmenting the strength of contraction. Sassine et al. (15) have reported the involvement of catecholamines in insulin-induced positive inotropic action on rabbit auricle. The blockade of insulin effects by propranolol indicate the involvement of beta adrenoceptors and the marked reduction in the insulin effects following reserpinization suggest the involvements of endogenous catecholamines. Our findings support the results of Sassine et al. (15) that insulin produces inotropic effect through the release of cardiac catecholamines.

The potentiation of insulin responses after theophylline (a phosphodiesterase inhibitor) perfusion and its inhibition after imidazole (a phosphodiesterase stimulator) perfusion may suggest the involvement of cyclic-AMP in insulin-induced positive inotropic action. It seems that insulin releases catecholamines from rat heart which, by acting on beta-adrenoceptors, stimulate adenylate cyclase. The final mediator of inotropic activity of insulin may be cyclic-AMP.

REFERENCES


