Insulin and Insulin-like Growth Factor-I Cause Coronary Vasorelaxation In Vitro

David Hasdai, Robert A. Rizza, David R. Holmes, Jr, Darcy M. Richardson, Pinchas Cohen, Amir Lerman

Abstract—Insulin and insulin-like growth factor-I (IGF-I) may play a role in the modulation of coronary artery tone, yet there are few data regarding their vasoactive effects on the coronary vascular bed. We evaluated the vasorelaxation effects of insulin and IGF-I on porcine coronary epicardial vessels in vitro and elucidated possible mechanisms. Porcine epicardial arteries were contracted with 10^{-7} mol/L endothelin-1 and relaxed with cumulative concentrations of either insulin or IGF-I (10^{-12} to 10^{-7} mol/L). The above experiments were repeated in vessels without endothelium. Vessels were also incubated with the nitric oxide synthase inhibitor N^{G}-monomethyl-L-arginine (L-NMMA; 10^{-4} mol/L) with and without 10^{-3} mol/L L-arginine, the potassium channel blocker tetraethylammonium (TEA; 10^{-2} mol/L), and the guanylyl cyclase inhibitor 1H-[1,2,4]oxadiazolo[4,3-a]quinoxalin-1-one (ODQ; 10^{-5.5} mol/L); vessels were then contracted with endothelin-1 and relaxed with insulin or IGF-I. Insulin and IGF-I were also added after contraction with 60 mmol/L KCl. Insulin and IGF-I caused a similar decrease in coronary epicardial tension after contraction with endothelin-1 (relaxation of 28±4\% [n=7] and 25±3\% [n=8] with insulin and IGF-I, respectively; P<0.0001 for both peptides). Removal of the endothelium did not affect these responses. Incubation with L-NMMA, but not ODQ, attenuated the vasorelaxation response to insulin and IGF-I in vessels without endothelium. L-Arginine did not reverse this effect of L-NMMA. KCl and TEA attenuated the vasorelaxation effect of both insulin and IGF-I. Thus, both insulin and IGF-I caused non-endothelium-dependent coronary vasorelaxation in vitro, probably through a mechanism involving the activation of potassium channels. These findings suggest that insulin and IGF-I participate in the regulation of coronary vasomotor tone. (Hypertension. 1998;32:228-234.)

Key Words: insulin ■ growth factors ■ pigs ■ arteries ■ endothelium ■ potassium channels ■ nitric oxide

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he three peptide hormones in the IGF family—insulin, IGF-I, and IGF-II—have approximately 50% of their amino acids in common.1–3 Whereas insulin is produced and secreted by the pancreas as proinsulin, the liver is the main source of circulating IGF-I levels.1–3 Unlike insulin, however, IGF-I is also produced by various cell types, including endothelial4,5 and vascular smooth muscle cells,6–8 and is considered a significant paracrine/autocrine factor.1–3 Independent of their metabolic and growth-promoting properties, insulin and related peptides also have vasoactive actions9–24 ranging from vasoconstriction9,13,16,24 to vasodilation.9,12,14,15,17–24 Studies in animal models and humans have reported conflicting results regarding the vasoactive effects of insulin9–19,24 and IGF-I,9,19,21–23 with disparate effects reported for different vascular beds of the same species9 and even for different vessel types in the same organ (ie, afferent and efferent arterioles of the kidney25). The past several years have seen a major surge of interest in the cardiovascular actions of insulin and IGF-I.25 Specifically, the actions of the two peptides, or the lack thereof, may have pathophysiological consequences, such as abnormal vascular tone. The vascular effects of insulin and IGF-I have been extensively studied in peripheral vessels in physiological and pathophysiological states,25 but there are few data as yet regarding the direct actions of these 2 peptides on the coronary vasculature. In similarity to the peripheral vasculature, however, insulin and IGF-I potentially modulate coronary vascular tone, and an impairment in their actions may result in abnormal vascular tone. This possibility is underscored by the epidemiological evidence linking impaired insulin action with abnormal coronary artery tone26–29 and with increased morbidity attributed to coronary artery disease.30 The present study was therefore designed to examine the hypothesis that insulin and IGF-I are vasodilators of porcine epicardial arteries in vitro and to elucidate possible mechanisms for their actions.

Methods

Animals

The study procedures and handling of animals were reviewed and approved by the Mayo Foundation Institutional Animal Care and Use

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Committee. Juvenile domestic crossbred pigs were killed with an intravenous overdose of pentobarbital sodium (30 mg/kg; Sleepaway, Fort Dodge Laboratories). After death, the hearts were harvested for in vitro analysis.

In vitro determination of vascular reactivity was performed as we previously described. In brief, the hearts were placed into cold modified Krebs-Ringer bicarbonate solution of the following molar composition (control solution): 118.3 NaCl, 4.7 KCl, 2.5 CaCl₂, 1.2 MgSO₄, 1.2 KH₂PO₄, 25 NaHCO₃, 0.026 calcium EDTA, and 11.1 glucose. Segments 2 to 3 mm long of the left circumflex artery were dissected. When indicated, the endothelium was mechanically removed from the vessels. Each vessel was connected to an isometric force transducer (Grass Instruments) and was mechanically removed from the vessels. Each vessel was stabilized at a resting tension for 1 hour. Viability of the vessels was confirmed by a contractile response to 20 mmol/L KCl at baseline, at 2 g, at 4 g, and at 6 g, each time after the potassium had been washed out. At 6 g, all vessels were then exposed to 10⁻⁶ mol/L substance P (Sigma Chemical Co), an endothelium-dependent vasodilator, to verify the functional integrity of the vascular endothelium. All chambers were then washed out using the control solution.

After an equilibration period of 30 minutes, the agents detailed in the specific protocols below were added. In the vast majority of cases, the vasorelaxing response reached a plateau after 3 to 4 minutes, at which time the next concentration was added. In all cases, we waited until a plateau had been reached before adding the next dose. Stock solutions of each agent were prepared every day. Drugs were dissolved in distilled water such that volumes of <0.2 mL were added to the organ chambers. All concentrations are expressed as the concentration within the bath solution.

**Determination of Vasorelaxation Effects of Insulin and IGF-I**

To determine the coronary epicardial vasodilator effects of insulin and IGF-I, epicardial arteries were contracted with 10⁻⁷ mol/L ET-1 (Phoenix Pharmaceuticals); after equilibration for 20 minutes, arteries were relaxed with cumulative concentrations of either 10⁻¹² to 10⁻⁷ mol/L insulin (Eli Lilly) or 10⁻¹⁰ to 10⁻⁷ mol/L IGF-I (Sigma). ET-1 was chosen as the vasoconstrictor agent at this dose in these experiments for 2 reasons. First, 10⁻⁷ mol/L ET-1 produces sustained contraction of porcine coronary vessels. To support this observation, a control group was established to verify that the loss of tension was due to insulin and IGF-I, arteries with intact endothelium were then exposed to cumulative concentrations of either insulin or IGF-I. In addition, to examine whether the effects of L-NMMA on the vasorelaxation response to insulin and IGF-I in vessels without endothelium are related to the NO pathway, arteries without endothelium were exposed to 10⁻⁵ mol/L L-NMMA and the precursor for NO synthesis, 10⁻⁵ mol/L L-arginine hydrochloride (Sigma); after equilibration for 20 minutes, arteries were contracted with ET-1 and relaxed with cumulative concentrations of either insulin or IGF-I. The concentrations of L-NMMA and L-arginine were derived from prior studies, which also demonstrated that to reverse the effects of L-NMMA, L-arginine should be given at concentrations 3 to 10 times higher than the concentration of L-NMMA.

**Potassium Channels**

To determine whether potassium channels mediate the vasorelaxative effects of insulin and IGF-I, additional vessels with intact endothelium were exposed to 60 mmol/L KCl for 20 minutes before exposure to cumulative concentrations of insulin and IGF-I. Furthermore, to identify the potassium channel mediating the vasorelaxation effect of insulin and IGF-I, arteries with intact endothelium were exposed to the following potassium channel inhibitors for 20 minutes before contraction with ET-1 and the addition of insulin or IGF-I: the ATP-sensitive potassium channel inhibitor glyburide (10⁻⁷ mol/L; Research Biochemical International), the calcium-dependent potassium channel inhibitor charybdotoxin (10⁻⁷ mol/L; Sigma), and the potassium channel inhibitor TEA (10⁻² mol/L; Sigma). The reported concentration for half-block Kᵢ for glyburide is 20 to 200 mmol/L, for TEA 200 mmol/L, and 10 mmol/L (for calcium-dependent and voltage-dependent potassium channels, respectively), and for charybdotoxin 10 mmol/L.

**cGMP**

In additional experiments, vessels without endothelium were exposed to 10⁻⁵ mol/L ODQ (Biomol Research Laboratories), a potent inhibitor of soluble guanylyl cyclase, 20 minutes before contraction with ET-1 and the addition of insulin or IGF-I. ODQ at this dose inhibits the rise in cGMP induced by NO donors in vascular smooth muscle. In addition, in preliminary experiments, the incubation of porcine coronary arteries without endothelium with 10⁻⁵ mol/L ODQ caused a shift to the right (EC₅₀=10⁻⁴ mol/L versus EC₅₀=10⁻⁵ mol/L) in the relaxation response to cumulative concentrations (10⁻¹⁰ to 10⁻⁷ mol/L) of the NO donor diethylenamine NONOate (Cayman Chemical).

**L-Type Calcium Channel Blocker**

To examine whether the effects of insulin and IGF-I are exerted by inhibition of calcium influx through the L-type calcium channel, vessels with intact endothelium were exposed to the calcium channel blocker diltiazem (10⁻⁶ mol/L; Sigma) 20 minutes before contraction with ET-1 and the addition of insulin or IGF-I. In porcine coronary arterial strips, diltiazem at this dose has been shown to inhibit increases in intracellular calcium and tension development induced by cumulative applications of extracellular calcium during potassium-induced contraction.

**Data Analysis**

Results are presented as mean±SEM. The contraction attained with ET-1 for each vessel at baseline was considered as baseline (0%
relaxation). Subsequent measurements of coronary artery relaxation are expressed as a percent reduction in contraction (the maximal relaxation attained with papaverine being 100% relaxation). In all experiments, n refers to the number of vessels. Experiments were performed in parallel in harvested vessels, to preclude a situation whereby all vessels in 1 experiment were harvested from only 1 animal (on average each experiment was conducted using vessels from 3 to 4 animals). For statistical analysis, ANOVA or repeated-measure ANOVA followed by Bonferroni’s t test was used. A two-tailed value of P < 0.05 was considered significant.

Results
Vessel Integrity After Endothelium Removal
Substance P caused complete vasodilation after 20 mmol/L KCl-induced contraction in endothelium-intact vessels but did not cause any vasorelaxation in endothelium-denuded vessels. The maximal response to 20 mmol/L KCl was similar for endothelium-intact and endothelium-denuded vessels (8.8 ± 0.6 versus 8.1 ± 0.7 g for endothelium-intact and endothelium-removed vessels, respectively; P = 0.23).

Vasorelaxation Effects of Insulin and IGF-I
The mean contractile responses to ET-1 in the insulin and IGF-I experiments in vessels with intact endothelium were 8.5 ± 1.5 and 10.8 ± 1.8 g, respectively. Both insulin (Figure 1, left) and IGF-I (Figure 1, right) caused a significant decrease in coronary epicardial tension after contraction with ET-1 (relaxation of 28 ± 4% and 25 ± 3% with insulin and IGF-I, respectively; P < 0.0001 for each peptide). The vasorelaxation responses to both insulin and IGF-I were significant at concentrations $\leq 10^{-10}$ mol/L. There was no significant difference in the vasorelaxation response attained with both agents.

Role of Endothelium in Vasorelaxation Response to Insulin and IGF-I
The mean contractile responses to ET-1 in the insulin and IGF-I experiments in vessels without endothelium were 8.1 ± 1.4 and 5.9 ± 1.1 g, respectively. Removal of the endothelium did not affect the vasorelaxation response to insulin (Figure 1, left; P = 0.98 for comparison with intact endothelium) and IGF-I (Figure 1, right; P = 0.95 for comparison with intact endothelium).

Role of NO in Vasorelaxation Response to Insulin and IGF-I
The mean contractile responses to ET-1 after incubation with L-NMMA in the insulin and IGF-I experiments in vessels with intact endothelium were 11.8 ± 1.3 and 9.2 ± 1.1 g, respectively. In vessels without endothelium, the mean contractile responses were 7.0 ± 1.1 and 10.9 ± 1.2 g, respectively. The incubation of vessels with L-NMMA attenuated the vasorelaxation response to insulin in vessels with intact endothelium (Figure 2, left; P = 0.009 for comparison with the response to insulin without L-NMMA in vessels with intact endothelium), as well as in vessels without endothelium (Figure 2, left; P = 0.01 for comparison with the response to insulin without L-NMMA in vessels without endothelium). Similarly, the incubation of vessels with L-NMMA attenuated the vasorelaxation response to IGF-I in vessels with intact endothelium (Figure 2, right; P = 0.05 for comparison with the response to IGF-I without L-NMMA in vessels with intact endothelium), as well as in vessels without endothelium (Figure 2, right; P = 0.04 for comparison with the response to IGF-I without L-NMMA in vessels without endothelium).

In vessels without endothelium, the incubation of vessels with both L-arginine and L-NMMA before exposure to cumulative concentrations of either insulin (n = 6) or IGF-I (n = 6) did not reverse the attenuated vasorelaxation response observed with L-NMMA alone (data not shown).

Role of cGMP in Vasorelaxation Response to Insulin and IGF-I
The mean contractile responses to ET-1 after incubation with ODQ in the insulin and IGF-I experiments in vessels without endothelium were 8.9 ± 0.9 and 10.2 ± 1.4 g, respectively. The incubation of vessels without endothelium with ODQ did not affect the vasorelaxation response to insulin (Figure 3, left; P = 0.93 for comparison with the response to insulin without ODQ in vessels without endothelium) or the response to IGF-I (Figure 3, right; P = 0.70 for comparison with the response to IGF-I without ODQ in vessels without endothelium).
Role of Potassium Channels in Vasorelaxation Response to Insulin and IGF-I

The incubation of vessels with intact endothelium with 60 mmol/L KCl completely abolished the vasorelaxation response to insulin (Figure 4, left; \( P < 0.0001 \) for comparison with the response to insulin without KCl) and IGF-I (Figure 4, right; \( P < 0.0001 \) for comparison with the response to IGF-I without KCl). There was no statistically significant difference in the contraction to KCl in the insulin and IGF-I experiments (2.0 and 3.1 g, respectively). Neither glyburide (n=6) nor charybdotoxin (n=6) attenuated the vasorelaxation response to insulin after contraction with ET-1 (data not shown). Likewise, the ATP-sensitive potassium channel inhibitor glyburide (n=6) and the calcium-dependent potassium channel inhibitor charybdotoxin (n=7) did not attenuate the vasorelaxation response to IGF-I after contraction with ET-1 (data not shown). In contrast, the potassium channel inhibitor TEA significantly attenuated the vasorelaxation response to insulin (Figure 4, left; \( P = 0.005 \) for comparison with the response to insulin without TEA in vessels with intact endothelium) and IGF-I (Figure 4, right; \( P = 0.03 \) for comparison with the response to IGF-I without TEA in vessels with intact endothelium). The mean contractile responses to ET-1 after incubation with TEA in the insulin and IGF-I experiments in vessels with intact endothelium were 9.7 ± 0.7 and 9.9 ± 1.1 g, respectively. There was no difference in the contraction to ET-1 between vessels that were and were not exposed to TEA (\( P = 0.88 \)).

Role of L-Type Calcium Channels in Vasorelaxation Response to Insulin and IGF-I

The exposure of vessels with intact endothelium to diltiazem before the contraction with ET-1 did not affect the vasorelaxation response to insulin (n=6) or IGF-I (n=6) (data not shown).

Discussion

Main Findings

The principal finding of the present study was that both insulin and IGF-I caused dose-dependent coronary vasorelaxation of porcine epicardial arteries in vitro that were precon-
tracted with ET-1. Removal of the endothelium did not alter the vasoactive actions of insulin and IGF-I, suggesting that their effects were primarily exerted on the vascular smooth muscle and not through the endothelium. The underlying mechanism for the coronary vasorelaxation effect involved the activation of potassium channels and was independent of cGMP production. These findings support a role for insulin and IGF-I in the regulation of coronary vascular tone.

Insulin and IGF-I are known to have vasoactive properties ranging from vasoconstriction to vasodilation. These prior studies have demonstrated that insulin and IGF-I have similar vasoactive actions and exert different vasoactive actions on various vascular beds in the same species, and even in the same organ. Few data are available regarding the vasoactive actions of insulin and IGF-I on coronary arteries. A prior study demonstrated that incubation of porcine coronary epicardial arteries with insulin in vivo did not affect coronary artery tone, although insulin potentiated the coronary vasoconstrictor response to thromboxane A2. In the present study, when coronary epicardial arteries were first contracted with ET-1, both peptides exerted a concentration-dependent coronary vasorelaxation effect.

**Endothelium and NO**

Different mechanisms have been proposed to explain the vasoactive actions of insulin and related peptides. In several studies, insulin- or IGF-I--induced vasoconstriction or vasodilation was attenuated or abolished by the removal of the endothelium or by inhibition of the production of endogenous NO. These findings have led to speculation that NO derived from the endothelium mediates the vasodilator effects of insulin and IGF-I. However, several findings refute this possibility. First, the effects of L-NMMA were not reversed by the addition of L-arginine. In addition, the activation of endogenous NO results in an increase in cGMP production. Using ODQ, an agent that potently blocks the production of cGMP by soluble guanylyl cyclase, we did not detect an effect on the response to insulin and IGF-I. Finally, in our experiments, the duration of exposure to insulin or IGF-I was brief. Muniyappa et al have shown that NO levels increase significantly only after 4 hours of exposure to IGF-I (eg, in our experiments the exposure to cumulative concentrations of insulin or IGF-I lasted approximately 45 minutes). Thus, in our experimental conditions the vasorelaxation responses of porcine epicardial arteries in vitro to insulin or IGF-I were not dependent on the endothelium or on the NO pathway. However, in different conditions entailing prolonged exposure of vessels to insulin or IGF-I, the vascular smooth muscle NO pathway may mediate, at least in part, the vasoactive effects of insulin and IGF-I.

One may speculate as to the mechanism underlying the attenuation of the effects of insulin and IGF-I by L-NMMA in our experiments. Arginine analogues such as L-NMMA have recently been shown to have a direct effect on ATP-sensitive potassium channels in feline and rat pial arterioles. Low concentrations of L-NMMA inhibited the vasodilation mediated by the removal of ET-1. Removal of the endothelium did not alter the vasoactive actions of insulin and IGF-I, suggesting that their effects were primarily exerted on the vascular smooth muscle and not through the endothelium. The underlying mechanism for the coronary vasorelaxation effect involved the activation of potassium channels and was independent of cGMP production. These findings support a role for insulin and IGF-I in the regulation of coronary vascular tone.

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ated by ATP-sensitive potassium channels independently of an effect on NO and cGMP. Thus, in the present study, L-NMMA may have had a direct effect on potassium channels that was independent of NO activation.

**Potassium Channels**

In our study, potassium completely abolished the vasorelaxation effect of insulin and IGF-I, indicating that the mechanism involved potassium channels. Furthermore, the coronary vasorelaxation effect of insulin and IGF-I were attenuated by pretreatment with high doses of the potassium channel inhibitor TEA. Charybdotoxin, a specific inhibitor of the calcium-activated potassium channel, and glyburide, an inhibitor of the ATP-sensitive potassium channel, did not attenuate the response to insulin and IGF-I.

TEA blocks both calcium-dependent and voltage-dependent potassium channels. Higher concentrations of TEA are required to inhibit voltage-dependent potassium channels than calcium-dependent potassium channels. In our study, we used high concentrations of TEA to inhibit the effect of insulin and IGF-I. The lack of effect by charybdotoxin, an agent with no effect on voltage-dependent potassium channels but a selective effect on calcium-dependent potassium channels, supports the hypothesis that the effects of TEA were exerted on the former.

Voltage-dependent potassium channels are found in porcine coronary artery smooth muscle cells at a concentration of approximately 5000 channels per cell. There are several types of voltage-dependent potassium channels, differing in their voltage dependence and their sensitivity to inhibitors. Smooth muscle depolarization can both activate and inactivate these channels, and thus the current through the channels depends on the balance between these opposing processes. Our study did not determine the mechanism through which insulin and IGF-I activate these channels. However, the IGF axis may activate these channels by modulating the cation balance intracellularly or across the cell membrane through receptor-mediated and voltage-mediated mechanisms, including the inhibition of calcium L channels. In our study, the inhibitor of calcium L channels diltiazem had no effect on the coronary vasorelaxation response of insulin and IGF-I. Thus, the activation of voltage-dependent potassium channels may be a result of a direct effect of both insulin and IGF-I on the channel, or alternatively it may reflect the voltage changes resulting predominantly from intracellular kinetics of cations rather than a shift in cation balance across the cell membrane.

**Similar Effect With Insulin and IGF-I**

In our study, the concentrations of insulin and IGF-I that were examined ranged from the physiological to the pharmacological. A concentration-dependent vasorelaxation response was evident at low concentrations (≤10^{-10} mol/L). The type I IGF receptor binds IGF-I with high affinity and insulin with low affinity, whereas the insulin receptor binds IGF-I with a much lower affinity than insulin. Because of the vasorelaxation response attained with low concentrations of insulin and IGF-I, the vasoactive effects of each peptide may be attributed to its respective receptor. A prior study suggested that the vasoactive responses of insulin are mediated by the IGF-I receptor in the rat mesenteric artery. It is possible that in different vascular beds or species, or in vessels of different caliber, the role of the IGF-I receptor is more prominent. Alternatively, IGF-I may also exert its actions, at least in part, through receptor-independent mechanisms. It is also possible that hybrid IGF-I–insulin receptors mediate the effect of these peptides. These types of receptors are indeed common in the heart.

**Implications Regarding Pathophysiological States**

In pathophysiological states such as atherosclerosis, the NO pathway may be impaired, resulting in impaired coronary vasomotor tone. Given that the effects of insulin and IGF-I were not dependent on the NO pathway or on the generation of cGMP, the vasorelaxation effects of insulin and IGF-I may remain intact in pathophysiological states involving an impaired rise in cGMP in response to NO activation. Indeed, Najibi et al. have demonstrated that atherosclerotic rabbit carotid arteries may vasodilate through the activation of potassium channels even when the NO pathway is impaired. Manipulation of the IGF pathway in pathophysiological states may thus maintain coronary epicardial vasomotor tone.

In conclusion, both insulin and IGF-I have coronary vasorelaxation properties in vitro. The underlying mechanisms for the coronary vasorelaxation effects of both peptides may involve their interaction with vascular smooth muscle cell potassium channels. These findings suggest that insulin and IGF-I play a role in the regulation of coronary vasomotor tone and may have therapeutic implications in pathophysiological states.

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**References**

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