Prostaglandins and nitric oxide mediate insulin-induced vasodilation in the human forearm

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Abstract

Objective: To determine the involvement of prostaglandins, nitric oxide, and beta-adrenoceptor activation in insulin-induced vasodilation in the human forearm. Methods: Fifteen normal subjects were studied. Insulin was administered into the brachial artery in the presence of saline, the cyclo-oxygenase inhibitor indomethacin (0.65 \( \mu \)g/kg/min), the inhibitor of nitric oxide synthase N\(^G\)-monomethyl-L-arginine (L-NMMA, 30 \( \mu \)g/kg/min), or the non-selective beta-adrenoceptor blocker propranolol (0.2 \( \mu \)g/kg/min). Forearm vascular resistance (FVR) was derived from forearm blood flow and concomitantly measured intra-arterial blood pressure. Results: Insulin decreased FVR by 32 \( \pm \) 5\% (\( P < 0.01 \)). Both indomethacin and L-NMMA inhibited insulin-induced vasodilation, while propranolol had no effect. Single infusion of indomethacin was without effect on vascular tone, while single infusion of L-NMMA increased FVR by 81 \( \pm \) 19\% (\( P < 0.01 \)). Conclusions: Insulin has vasodilating properties in skeletal muscle vasculature that is mediated by increases in nitric oxide, that subsequently stimulates prostaglandin release. The latter appears to be a novel vascular action of insulin.

Keywords: Insulin; Vasodilation; Adrenergic receptors; Indomethacin; EDRF; Human; Diabetes

1. Introduction

Hyperinsulinemia, in combination with hypertension, central obesity, and hyperlipidemia, known as ‘syndrome X’ [1] or the ‘metabolic cardiovascular syndrome’ [2], is well recognized as a cluster of risk factors for the development of cardiovascular disease [2]. Patients with essential hypertension often have hyperinsulinemia and this is considered to be the result of a selective resistance for insulin-stimulated glucose uptake in skeletal muscle [1,3]. The mechanisms by which hyperinsulinemia may contribute to essential hypertension are: central stimulation of the sympathetic nervous system [4–7], stimulation of renal tubular sodium reabsorption [8–10], disturbances in transmembranous cation transport [7], and resistance to insulin-induced vasodilation [3,7,11–13].

Interestingly, although insulin stimulates muscle sympathetic nerve activity, the net result is vasodilation [14]. Several mechanism(s) may account for insulin’s vasodilator effect in man. Some investigators found evidence of nitric oxide release by insulin [15,16]. Creager et al. found that the vasodilator effect of insulin could be blocked by propranolol, suggesting that beta-adrenoceptors mediate vasodilation by insulin [17], while others have refuted this [18]. Recently, it was demonstrated that indomethacin treatment can induce a marked insulin-resistant state in rats [19]. Therefore, the aim of this study was to examine whether local release/production of prostaglandins and nitric oxide or stimulation of vascular beta-adrenoceptors is involved in insulin-induced vasodilation. In the human forearm we administered insulin intra-arterially, in pharmacological doses, with and without indomethacin, which inhibits synthesis of prostaglandins, N\(^G\)-monomethyl-L-arginine (L-NMMA), a specific inhibitor of nitric oxide synthase, or the non-specific beta-adrenoceptor blocker,
propranolol. The reproducibility of insulin-induced vasodilation, the intrinsic vascular effects of indomethacin and of L-NMMA, and the beta-blocking potency of propranolol were determined in separate sets of experiments.

2. Methods

2.1. Subjects

Fifteen healthy subjects participated in this study after providing informed consent. Only male subjects were studied because of possible sex differences in adrenoceptor function [20]. Medical history, physical examination, and routine laboratory tests showed no evidence of cardiovascular or other diseases. None of the subjects took any medication for at least 2 weeks before the study. The subjects were instructed to refrain from smoking cigarettes or drinking alcohol or caffeine-containing beverages for at least 12 h before the experiment. All tests were conducted in the morning after an overnight fast. The protocol of the study was approved by the Medical Ethics Committee of the Leiden University Hospital.

2.2. Forearm hemodynamic measurements

Each experiment was performed with the subject supine, in a quiet room at a temperature of 22–23°C. The brachial artery of the non-dominant arm was cannulated, with a 5 cm long, 1.3 mm outer diameter cannula (Autocath 1453.13 Plastimed, Saint-Leu-la-Forêt, France), for intra-arterial blood pressure monitoring, local infusions, and blood sampling. In the same arm, a deep antecubital vein was cannulated for blood sampling. Arterial blood pressure (Statham P-23Id pressure transducer and heart rate (cardiotachometer) were continuously recorded. Forearm blood flow of both arms was measured using a computerized, strain-gauge, R-wave-triggered, venous occlusion plethysmography system (D.E. Hokanson, Issaquah, WA) [21,22], and expressed as milliliters of blood flow per deciliter forearm tissue per minute (ml/dl/min). Forearm vascular resistance was derived from the ratio of each forearm blood flow measurement and the simultaneously measured intra-arterial blood pressure. Averages of 6 consecutive measurements, with a duration of 4 heart beats and performed at 15 s intervals, were used for further analysis. To ensure stable arterial concentrations and because the hand circulation contains mainly perfusion of skin and A–V anastomoses in the fingers, hand blood flow was excluded continuously from the circulation during each infusion experiment, using a small wrist cuff inflated to at least 40 mmHg above systolic blood pressure. Precision volumetric pumps (model 22, Harvard Apparatus, Manchester, UK) were used for infusions. Forearm volume was determined by water displacement before the study. The experiments started at least 30 min after the cannulation. Measurements were made during the last 2 min of each dose. Between infusions, intervals of 30–60 min were allotted to allow forearm blood flow to return to baseline before initiating a new infusion experiment.

2.3. Study protocol

2.3.1. Study A

Eight subjects received an intra-arterial infusion of insulin, 0.72 and 3.6 pmol/kg/min (resp. 0.1 and 0.5 mU/kg/min) for 10 min each, 5 min preceded by saline, 0.2 ml/min. After a pause of 30–60 min and attainment of stable baseline flow an intra-arterial infusion of propranolol, 0.2 μg/kg/min, was started. 5 min later followed by addition of insulin in the two doses as in the previous experiment. Similarly, the insulin infusions were repeated with intra-arterial infusion of indomethacin, 0.65 μg/kg/min [23], which was started 5 min before the insulin dose infusions. Maximal infusion volumes were 1.0 ml/min. Arterial blood was sampled at the beginning and end of each infusion for determination of glucose and potassium concentrations, and venous blood was drawn at the end of each dose for determination of plasma insulin, potassium and glucose.

2.3.2. Study B

In 7 other subjects the reproducibility of insulin’s vascular effect on forearm vascular resistance was studied by repeating the infusion experiment with the two doses of insulin twice. The beta-blocking potency of propranolol was tested by giving an intra-arterial infusion of the non-selective beta-adrenoceptor agonist isoproterenol, 0.2, 0.8, and 2.4 ng/kg/min, for 5 min per dose, which was repeated during concomitant infusion of propranolol, 0.2 μg/kg/min. Further, a single intra-arterial infusion of indomethacin, 0.65 μg/kg/min, was given for 20 min to study its intrinsic vascular effect. Maximal infusion volumes were 1.0 ml/min.

2.3.3. Study C

The effect of L-NMMA on insulin’s vascular effect in the forearm was studied in 9 subjects. A single infusion of L-NMMA, 30 μg/kg/min [24], was given for 20 min to study the time course of the vasoconstricting effect of L-NMMA. After a pause of at least 60 min and attainment of stable baseline flow an intra-arterial infusion of L-NMMA, 30 μg/kg/min, was started 5 min later followed by the insulin dose infusions. Maximal infusion volumes were 1.0 ml/min. Arterial blood was sampled at the beginning and end of each infusion for determination of glucose and potassium concentrations, and venous blood was drawn at the end of each dose for determination of plasma insulin, potassium and glucose.

2.4. Drug solutions, sample collection, and assay

The following drugs were aseptically prepared from sterile stock solutions and dissolved in 0.9% saline imme-
the arterial insulin concentration was calculated from the insulin infusion rate (IR, in pmol/kg/min), body-weight (W, in kg), hematocrit (Ht), forearm volume (V, in dl), forearm blood flow (FBF, in ml/dl/min), as:

\[ C_{\text{plasma}} = \frac{\text{IR} \times W}{(1 - \text{Ht}) \times \text{FBF} \times V} \times 1000. \]

To examine the effects of the various drugs on hemodynamics in the forearm, differences between the baseline value and serial repeated measurements were evaluated employing two-way analysis of variance on the measured values with post-hoc Scheffé testing (SuperANOVA, Abacus Concepts, Inc., Berkeley, CA). Effects on vascular resistance are expressed as percent change from baseline. Results are presented as means ± s.e. A P-value less than 0.05 defined statistical significance.

### 3. Results

Clinical characteristics are given in Table 1. In all experiments no significant changes were observed in arterial plasma glucose and potassium concentrations (Table 2). In Table 3 the forearm blood flow and forearm vascular resistance values of the insulin infusion experiments are presented.

#### 3.1. Study A

Insulin decreased the forearm vascular resistance in a dose-related manner to −32 ± 5% (Fig. 1 and Table 3, P < 0.01). The two doses of insulin increased the outflowing venous plasma insulin concentration from 57 ± 14 at baseline to 187 ± 65 and 4248 ± 596 pmol/l, respectively.

P < 0.01) at the highest dose. The two doses of insulin increased the outflowing venous plasma insulin concentration from 57 ± 14 at baseline to 187 ± 65 and 4248 ± 596 pmol/l, respectively.

In a subsequent infusion experiment the concomitant infusion of propranolol did not influence the vasodilator effect of insulin. The decrease in forearm vascular resistance (−24 ± 8%, Fig. 1 and Table 3, P < 0.01) was similar to that caused by the single infusion of insulin. Outflowing venous plasma insulin increased from 79 ± 103 to 969 ± 280 and 4111 ± 739 pmol/l, respectively.

During the infusion of insulin with indomethacin no significant changes in forearm vascular resistance occurred (Fig. 1, Table 3). The two doses of insulin increased outflowing venous plasma insulin from 108 ± 29 to 854 ± 136 and 5510 ± 940 pmol/l, respectively.

Venous plasma glucose and potassium concentrations in the infused forearm decreased during infusion of insulin with saline (Table 2, both P < 0.01) and did not change significantly during insulin combined with propranolol or indomethacin (Table 2).

#### 3.2. Study B

In the 7 other subjects, we tested the reproducibility of the hemodynamic effects of insulin by repeating the infusion of the two intra-arterial insulin doses of 0.72 and 3.6 pmol/kg/min. Forearm vascular resistance was lowered in the first infusion by −12 ± 5% (P < 0.05) and in the repeated infusion experiment by −16 ± 5% (P < 0.05).

 Adequate blockade of beta-adrenoceptors was assured by measuring the forearm vascular response to the non-selective beta-adrenoceptor agonist isoproterenol, with and without propranolol 0.2 μg/kg/min i.a. Isoproterenol decreased forearm vascular resistance by −80 ± 5%, which was abolished by the concomitant infusion of propranolol, to +15 ± 8% (difference P < 0.01).
Table 2
Mean arterial blood pressure, heart rate, and arterial and venous plasma glucose and potassium concentrations during the intra-arterial insulin infusion experiments

<table>
<thead>
<tr>
<th></th>
<th>Mean arterial blood pressure (mmHg)</th>
<th>Heart rate (beats/min)</th>
<th>Arterial glucose (mmol/l)</th>
<th>Venous glucose (mmol/l)</th>
<th>Arterial potassium (mmol/l)</th>
<th>Venous potassium (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>85.9 ± 1.9</td>
<td>59.4 ± 3.1</td>
<td>4.5 ± 0.2</td>
<td>3.8 ± 0.1</td>
<td>4.2 ± 0.2</td>
<td>4.3 ± 0.2</td>
</tr>
<tr>
<td>Insulin-1</td>
<td>84.0 ± 2.0</td>
<td>59.9 ± 3.3</td>
<td>4.4 ± 0.2</td>
<td>4.0 ± 0.1</td>
<td>4.2 ± 0.2</td>
<td>4.2 ± 0.2</td>
</tr>
<tr>
<td>Insulin-2</td>
<td>85.6 ± 2.8</td>
<td>59.8 ± 3.5</td>
<td>4.4 ± 0.2</td>
<td>3.1 ± 0.2 * **</td>
<td>4.2 ± 0.2</td>
<td>4.1 ± 0.2</td>
</tr>
<tr>
<td>Propranolol</td>
<td>84.4 ± 1.5</td>
<td>57.8 ± 2.4</td>
<td>4.5 ± 0.2</td>
<td>2.8 ± 0.2</td>
<td>4.2 ± 0.2</td>
<td>3.9 ± 0.2</td>
</tr>
<tr>
<td>Insulin-1 + propranolol</td>
<td>83.5 ± 1.7</td>
<td>58.6 ± 2.5</td>
<td>4.4 ± 0.2</td>
<td>3.2 ± 0.2</td>
<td>4.1 ± 0.2</td>
<td>3.9 ± 0.2</td>
</tr>
<tr>
<td>Insulin-2 + propranolol</td>
<td>85.1 ± 2.0</td>
<td>59.1 ± 2.1</td>
<td>4.3 ± 0.2</td>
<td>2.9 ± 0.3</td>
<td>4.1 ± 0.1</td>
<td>3.9 ± 0.2</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>86.6 ± 1.9</td>
<td>58.2 ± 2.8</td>
<td>4.8 ± 0.2</td>
<td>3.0 ± 0.2</td>
<td>4.2 ± 0.2</td>
<td>4.0 ± 0.2</td>
</tr>
<tr>
<td>Insulin-1 + indomethacin</td>
<td>86.3 ± 1.8</td>
<td>58.7 ± 2.3</td>
<td>4.6 ± 0.2</td>
<td>3.2 ± 0.2</td>
<td>4.2 ± 0.2</td>
<td>4.0 ± 0.2</td>
</tr>
<tr>
<td>Insulin-2 + indomethacin</td>
<td>90.2 ± 1.9</td>
<td>57.6 ± 2.7</td>
<td>4.4 ± 0.2</td>
<td>3.3 ± 0.2</td>
<td>4.2 ± 0.2</td>
<td>3.9 ± 0.1</td>
</tr>
<tr>
<td>L-NMMA</td>
<td>88.9 ± 2.6</td>
<td>58.4 ± 3.1</td>
<td>4.6 ± 0.3</td>
<td>3.3 ± 0.3</td>
<td>4.2 ± 0.2</td>
<td>3.8 ± 0.1</td>
</tr>
<tr>
<td>Insulin-1 + L-NMMA</td>
<td>90.3 ± 2.4</td>
<td>59.4 ± 2.9</td>
<td>4.7 ± 0.3</td>
<td>3.3 ± 0.3</td>
<td>4.1 ± 0.2</td>
<td>3.7 ± 0.1</td>
</tr>
<tr>
<td>Insulin-2 + L-NMMA</td>
<td>96.0 ± 2.7</td>
<td>62.2 ± 3.0</td>
<td>4.8 ± 0.3</td>
<td>2.8 ± 0.3 * **</td>
<td>4.2 ± 0.2</td>
<td>4.0 ± 0.3</td>
</tr>
</tbody>
</table>

Insulin-1 = insulin 0.72 pmol/kg/min (0.1 mU/kg/min); Insulin-2 = insulin 3.6 pmol/kg/min (0.5 mU/kg/min); Propranolol dose = 0.2 µg/kg/min; Indomethacin dose = 0.65 µg/kg/min. L-NMMA = N<sup>-</sup>monomethyl-L-arginine, 30 µg/kg/min. â ¶ < 0.05 vs baseline (i.e., during single infusion of saline, propranolol, indomethacin, or L-NMMA, resp.). * * P < 0.01 vs baseline.

During single infusion of indomethacin no significant changes in forearm vascular resistance of the infused and the control arm, systemic hemodynamic, or metabolic parameters were observed.

3.3. Study C

During infusion of insulin with L-NMMA (in 9 of the previous subjects) forearm vascular resistance was increased during the first dose of insulin by 25 ± 10% (Fig. 1, P < 0.05) and during the second dose by 20 ± 10% (Fig. 1). During this experiment mean arterial blood pressure increased by 9 ± 3% (Table 2, P < 0.05). The two doses of insulin increased venous plasma insulin from 6 ± 2 to 109 ± 40 and 953 ± 195 mU/l. Venous plasma glucose decreased by −20 ± 6% (Table 2, P < 0.05).

During a single infusion of L-NMMA (in 7 of the previous subjects) forearm vascular resistance was increased by 44 ± 3, 71 ± 5, and 81 ± 19% at 5, 10, and 20 min of L-NMMA infusion, respectively (see Fig. 2, P < 0.01). Between 5 and 10 min of this infusion there was a clear (P < 0.05) increase in forearm vascular resistance.

Table 3
Forearm blood flow and forearm vascular resistance values in infused and control arm during the intra-arterial insulin infusion experiments

<table>
<thead>
<tr>
<th></th>
<th>Forearm blood flow infused arm (ml/dl/min)</th>
<th>Forearm blood flow control arm (ml/dl/min)</th>
<th>Forearm vascular resistance infused arm (U)</th>
<th>Forearm vascular resistance control arm (U)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>3.7 ± 0.7</td>
<td>4.0 ± 1.5</td>
<td>27.5 ± 3.4</td>
<td>33.7 ± 5.9</td>
</tr>
<tr>
<td>Insulin-1</td>
<td>4.3 ± 0.8</td>
<td>3.9 ± 1.5</td>
<td>23.3 ± 3.3 * **</td>
<td>36.5 ± 8.8</td>
</tr>
<tr>
<td>Insulin-2</td>
<td>5.4 ± 0.9 * **</td>
<td>4.1 ± 1.4</td>
<td>18.4 ± 2.8 * **</td>
<td>30.4 ± 5.4</td>
</tr>
<tr>
<td>Propranolol</td>
<td>4.2 ± 0.5</td>
<td>3.7 ± 1.2</td>
<td>22.1 ± 2.5</td>
<td>33.5 ± 5.6</td>
</tr>
<tr>
<td>Insulin-1 + propranolol</td>
<td>4.7 ± 0.5</td>
<td>3.9 ± 1.4</td>
<td>18.9 ± 1.8</td>
<td>32.8 ± 6.3</td>
</tr>
<tr>
<td>Insulin-2 + Propranolol</td>
<td>5.7 ± 0.5 * **</td>
<td>4.0 ± 1.3</td>
<td>16.0 ± 1.8 * **</td>
<td>31.8 ± 6.3</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>3.9 ± 0.4</td>
<td>3.5 ± 1.0</td>
<td>25.4 ± 3.9</td>
<td>35.0 ± 5.7</td>
</tr>
<tr>
<td>Insulin-1 + indomethacin</td>
<td>3.9 ± 0.4</td>
<td>3.7 ± 1.1</td>
<td>24.5 ± 3.6</td>
<td>34.7 ± 6.8</td>
</tr>
<tr>
<td>Insulin-2 + Indomethacin</td>
<td>4.4 ± 0.5</td>
<td>3.7 ± 1.1</td>
<td>23.6 ± 4.3</td>
<td>35.0 ± 6.7</td>
</tr>
<tr>
<td>L-NMMA</td>
<td>2.6 ± 0.4</td>
<td>2.7 ± 0.7</td>
<td>47.5 ± 13.9</td>
<td>43.9 ± 6.1</td>
</tr>
<tr>
<td>Insulin-1 + L-NMMA</td>
<td>2.1 ± 0.4</td>
<td>2.8 ± 0.7</td>
<td>54.0 ± 11.9</td>
<td>44.3 ± 6.3</td>
</tr>
<tr>
<td>Insulin-2 + L-NMMA</td>
<td>2.2 ± 0.4</td>
<td>3.1 ± 1.0</td>
<td>57.4 ± 11.8</td>
<td>47.0 ± 7.6</td>
</tr>
</tbody>
</table>

Insulin-1 = insulin 0.72 pmol/kg/min (0.1 mU/kg/min); Insulin-2 = insulin 3.6 pmol/kg/min (0.5 mU/kg/min); Propranolol dose = 0.2 µg/kg/min; Indomethacin dose = 0.65 µg/kg/min. L-NMMA = N<sup>-</sup>monomethyl-L-arginine, 30 µg/kg/min. U = mmHg/ml/dl/min. "P < 0.05; " "P < 0.01, vs baseline (i.e., during single infusion of saline, propranolol, indomethacin, or L-NMMA, resp.) Baseline values during saline, propranolol, indomethacin, and L-NMMA were not significantly different.
whereafter forearm vascular resistance did not change significantly further. Mean arterial blood pressure increased by $5 \pm 2\% \ (P < 0.05)$.

4. Discussion

In this study we examined whether local release of prostaglandins and nitric oxide, and vascular beta-adrenoceptors are involved in insulin’s vascular effects in the human forearm.

The major new finding of the present study is that the cyclo-oxygenase inhibitor, indomethacin, markedly decreases the insulin-induced vasodilation in the forearm resistance vessels of healthy humans. Insulin’s vasodilating effect was also abolished by $l$-NMMA, while propranolol had no influence. This suggests that insulin stimulates production/release of vasodilating prostaglandins and of nitric oxide.

Although there is ample evidence in animals and humans that insulin stimulates the blood flow in skeletal muscles, the underlying mechanisms have not been fully elucidated [14,17,25,26]. Interestingly, during intravenous insulin infusion muscle sympathetic nerve activity increases, while the net result is vasodilation [14,27]. Even small increments of plasma insulin, to 25 mU/l, produce sympathetic activation, similar to that caused by a high level, without a change in forearm vascular resistance [28]. This has been ascribed to a balance between sympathetic vasoconstrictor tone and some depressor effector(s) [11]. Indeed, it has already been shown that insulin-induced vasodilation is dependent on local nitric oxide release from the endothelium [15,16]. We have also found evidence that nitric oxide production is involved in insulin’s vasodilator effect in the forearm. In addition, our present observation shows that the vasodilator action of insulin can also be markedly decreased by pretreatment with the cyclooxygenase inhibitor, indomethacin. This suggests that insulin stimulates the release of nitric oxide, which subsequently promotes the production of vasodilating prostaglandins in the forearm vasculature. Support for this notion comes from animal data showing that prostaglandins and nitric oxide can be co-released, for example, in the rat heart by stimulation with corticotropin-releasing factor [29], in the rat cremaster muscle by tumor necrosis factor-alpha [30], and in isolated arterioles of rat gracilis muscle by flow/shear stress-induced dilation [31]. Moreover, it has recently been demonstrated that nitric oxide can directly activate cyclo-oxygenase I and lead to the enhanced production of prostaglandins, especially PGE$_2$ [32]. In view of these findings and those of Robinson et al. [33], it seems that PGE$_2$ may be the prostaglandin involved in insulin’s vasodilatory action in the forearm. For definitive identification, measurement of the local production of prostaglandins will be necessary.

It has also been demonstrated that norepinephrine, released into hypothalamic fragments, activates nitric oxide synthase leading to the production of nitric oxide, which subsequently activates cyclo-oxygenase and results in the production of PGE$_2$ [34]. Also in rat glomeruli, stimulation of prostaglandin release by norepinephrine has been observed [35]. These observations suggest that insulin-induced enhancement of norepinephrine release from sympathetic nerves [6] may also increase nitric oxide and PGE$_2$ synthesis, which in turn may compensate for the vasoconstrictor effect of the released norepinephrine. This could explain the puzzling finding that although insulin stimulates muscle sympathetic nerve activity, the net result is vasodilation [14].

Apart from the stimulating effect of insulin on prostaglandins and nitric oxide synthesis, an intrinsic vasodilator effect of insulin may be present. Standley et al. recently demonstrated that insulin attenuates vascular smooth muscle Ca$^{2+}$ influx by both receptor- and voltage-operated channels [36]. The effects exerted by insulin on vascular smooth muscle cells may be attributable to an increase of both cAMP and cGMP through receptor-mediated activation of adenylate and of guanylate cyclases [37]. The effect of insulin on cGMP is mediated by nitric oxide [37]. These provide potential mechanisms for a decrease in vascular smooth muscle tone by insulin and for diminished responsiveness to vasoconstrictor agents.

Our finding that the insulin-induced vasodilation could not be inhibited by a beta-blocking dose of propranolol contrasts with the findings of Creager et al. [17]. They reported that intra-arterial infusion of similar doses of insulin decreased forearm vascular resistance by 30 and 42% respectively, which could be blocked by propranolol but not by the combination of propranolol with the alpha-adrenoceptor blocker, phentolamine [17]. In contrast, Randin et al. recently reported that in human calf muscle insulin-induced vasodilation could not be inhibited by propranolol [16]. As insulin stimulates sympathetic nerve...
activity, propranolol may allow unopposed alpha-adrenergic vasoconstriction [38]. Therefore, the reason for the variable effects of propranolol may be related to differences in resting sympathetic tone in subjects between different studies. The fact that plasma potassium concentrations in the venous effluent of the infused arm slightly but significantly decreased during single infusion of insulin and did not change during the infusions of insulin with propranolol or indomethacin, also indicates that the vasodilating effect of insulin is not directly related to beta-adrenoceptors, as cellular potassium uptake is mediated via beta-adrenoceptors [39].

In conclusion, insulin has vasodilating properties in forearm skeletal muscle resistance vessels that most likely are mediated through release of nitric oxide, which subsequently promotes the production of vasodilating prostaglandins.

References


