Opposing Effects of Angiotensin II on Muscle and Renal Blood Flow under Euglycemic Conditions

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Abstract. Angiotensin II (Ang II) enhances insulin sensitivity in humans, and this is associated with a paradoxical increase in skeletal muscle blood flow. It is unclear whether these effects are mediated via subtype 1 receptors of Ang II, because these receptors are thought to mediate vasoconstriction. Insulin-stimulated glucose uptake (euglycemic clamp technique) and leg muscle blood flow (plethysmography) were measured in nine healthy male volunteers (mean age, 24 ± 2 yr) on three occasions using a double-blind, placebo-controlled study design. The subjects were allocated in random order to (1) placebo premedication per os plus placebo infusion, (2) placebo premedication per os plus infusion of 5 ng Ang II/kg per min, and (3) premedication with 300 mg of the angiotensin II-1-receptor antagonist irbesartan per os plus infusion of 5 ng Ang II/kg per min. In addition, GFR and effective renal plasma flow were assessed using the steady-state inulin- and paraaminohippurate clearance. Insulin sensitivity (i.e., M value) and muscle blood flow after infusion of Ang II (9.3 ± 1.8 mg/kg per min; 17.7 ± 2.1 ml/100 g per min) were significantly higher than after placebo infusion (7.2 ± 1.6 mg/kg per min, P < 0.02; 13.5 ± 1.8 ml/100 g per min, P < 0.01). In contrast, after premedication with irbesartan, they were not significantly different (7.5 ± 1.7 mg/kg per min; 14.3 ± 1.9 ml/100 g per min) as compared with placebo infusion. Mean GFR and effective renal plasma flow were significantly lower (P < 0.01), and renal vascular resistance was significantly higher (P < 0.01) with Ang II infusion as compared with the placebo infusion study. Premedication with irbesartan almost completely blocked the vasoconstrictive effect of Ang II on renal vasculature. Under hyperinsulinemic euglycemic conditions, infusion of Ang II has opposing effects on regional arterial blood flow, i.e., an increase in skeletal muscle blood flow, but vasoconstriction of renal vasculature. Both effects are antagonized by blockade of subtype 1 Ang II receptors.

It has been documented recently that subpressor doses of angiotensin II (Ang II) enhance insulin-stimulated glucose uptake, i.e., increase insulin sensitivity, in healthy volunteers (1–5). The mechanism of this action has not been completely elucidated, but it seems to be mediated via increased blood flow to insulin-sensitive tissues, e.g., skeletal muscles (1–3,6). It has been speculated that Ang II increases muscle blood flow via “capillary recruitment” and that the increase in muscle blood flow and insulin-stimulated glucose uptake may reflect a homeostatically useful action of Ang II to shunt blood and nutrients, e.g., glucose, away from less insulin-sensitive (splanchnic) to more insulin-sensitive (skeletal muscles) tissues in the presence of hyperinsulinemia (2).

It is unclear whether the effect of Ang II on muscle blood flow and on insulin sensitivity is mediated via subtype 1 receptors of Ang II, because the usual response to stimulation of these receptors is vasoconstriction (7). To clarify this issue, we infused Ang II under euglycemic hyperinsulinemic conditions (euglycemic clamp) in a group of healthy volunteers with and without preadministration of irbesartan, an Ang II subtype 1 receptor antagonist, using a double-blind, randomized, placebo-controlled study design. In parallel to muscle blood flow, we assessed the effects of Ang II in a second vascular bed by measuring renal hemodynamics, i.e., GFR and effective renal plasma flow (ERPF).

Materials and Methods

Subjects and Protocol

The protocol was approved by the Ethics Committee of the University of Heidelberg; a double-blind, randomized, crossover protocol was chosen. Written informed consent was given by nine healthy male volunteers (mean age, 24 ± 2 yr; mean body mass index, 22.5 ± 1.0 kg/m²). They were normotensive nonsmokers who took no medication. Their family histories were negative for hypertension or metabolic diseases. At entry into the study, physical examination, routine chemistry, and urinalysis were performed. Normal glucose tolerance was documented using a 100-g oral glucose tolerance test with simultaneous determinations of insulin levels.

All subjects were allocated in random order to the three interventions: euglycemic clamp with (1) placebo premedication per os plus placebo infusion, (2) placebo per os plus infusion of 5 ng Ang II/kg per min (Hypertensin Ciba®, Ciba-Geigy Co., Basel, Switzerland), and (3) premedication with 300 mg of the Ang II-1-receptor antagonist irbesartan per os plus infusion of 5 ng Ang II/kg per min. The interval between these interventions was 7 d. For 3 d before each clamp study, all participants adhered to an isocaloric diet standardized with respect to sodium content. The subjects had constant weight (± 0.5%) for at least 4 wk before and during the study. Smoking and...
alcohol consumption were not allowed, and physical activity was maintained at its usual level throughout. All participants were admitted to the clinic at 9 a.m. on the day before the clamp experiments. On the morning of the next day, a euglycemic clamp experiment was performed in a quiet room from 9 a.m. to 11 a.m. after an overnight fast. At 8 a.m., either placebo or 300 mg of the Ang II-1-receptor blocker irbesartan was administered in random order. After the clamp was started, all participants were randomly assigned to receive either placebo (saline infusion) or 5 ng Ang II/kg per min dissolved in saline at identical infusion rates. On all study days, GFR and effective renal plasma flow were examined using steady-state inulin (C_inu) and paraaminohippurate (C_PAH) infusion techniques as described in detail elsewhere (8). In brief, a priming dose of 1500 mg of inulin/m² (Inutest®, Laevosan, Linz, Austria) and 500 mg of paraaminohippurate acid/m² (Nephrotest®, BAG GmbH, Lich, Germany) were given at 8 a.m. The bolus injection was followed by continuous infusions of inulin (10 mg/m² per min) and PAH (8 mg/m² per min) maintained with ultraprecise pumps (Perfusor FT®, Braun Melsungen, Melsungen, Germany). After an equilibration period, blood samples for measurements of GFR and ERPF were taken at regular intervals. In parallel, mean arterial BP and heart rate were monitored oscillometrically throughout the clamp experiments (Dynamap®, Critikon Co., Tampa, FL). Blood samples for measurements of serum insulin and potassium levels were taken at the start and thereafter at regular intervals until the end of each clamp. Muscle perfusion was measured using a standard strain-gauge occlusion plethysmograph (Periquant 803®, Gutmann Medizin Elektronik GmbH, Eurasburg, Germany) on the leg (calf) at the end of each clamp investigation (9). To assess the reproducibility of plethysmographic measurements, we measured leg muscle blood flow in our volunteers at admission to the metabolic ward, i.e., on the evening before the clamp experiments. The mean coefficient of variation for three repeated measurements in nine volunteers was 12.7 ± 4.2%.

**Measurements and Calculations**

A standard protocol of the euglycemic hyperinsulinemic clamp technique was used as described in detail elsewhere (10). In brief, a priming bolus infusion of 100 mU of insulin/m² per min (H-Insulin®, Hoechst AG, Frankfurt-Hoenchst, Germany) was given for 2 min. Thereafter, insulin administration was gradually decreased to a constant infusion rate of 40 mU/m² per min. Plasma insulin levels were raised by this mode of administration to approximately 750 to 800 pmol/L in healthy volunteers. To prevent adsorption of insulin to the infusion line, 2 ml of the subjects’ own blood was added to the insulin infusion. Four min after the start of the insulin infusion, glucose infusion (Glucosteril 20%®, Fresenius AG, Bad Homburg, Germany) was started. Blood samples for measurements of plasma glucose levels were taken from a retrograde dorsal hand vein cannula throughout the clamp at 5-min intervals. The hand was rested in a heated box (approximately 55°C) to arterialize the venous blood. Plasma glucose was measured with the Glucoanalyzer II® (Beckmann Instruments, Munich, Germany). The infusion rate was adapted so as to maintain a euglycemic blood glucose concentration. The coefficient of variation of the infusion rate for repeat clamp experiments in the same subject was 4.1%. The amount of glucose infused to maintain euglycemia was evaluated in the last 40 min of the clamp, i.e., after steady states of glucose infusion and plasma glucose levels were achieved. The mean M values were calculated from the glucose infusion rate and the plasma glucose concentrations for this period to assess insulin sensitivity as described elsewhere (10). The investigator performing the clamp studies was blinded with respect to the type of infusion, i.e., placebo or Ang II, and with respect to the BP measurements.

Serum insulin concentrations were measured using a double-sandwich radioimmunoassay (normal range, 40 to 150 pmol/L), and serum potassium levels were measured with flame photometry (AFM 5051®, Eppendorf AG, Eppendorf, Germany). Insulin was measured enzymatically using inulinsize as described by Kühnle et al. (11) and paraaminohippurate photometrically after Bratton and Marshall (12). Insulin and paraaminohippurate clearances were calculated from the delivered dose: C = (I_tr × I_con)/Sc, where C is the clearance, I_tr is the infusion rate (ml/min), I_con is the concentration of the analyte in the infusion fluid (mg/ml), and Sc is the plasma concentration of the analyte (mg/ml). Filtration fraction was calculated as the ratio C_inu/C_PAH, and renal vascular resistance was calculated using the following equation:

\[
\text{renal vascular resistance (mmHg/ml per min) = } \left(\frac{\text{mean arterial BP - 12}}{723/\text{effective renal plasma flow}}\right) \times (1 - \text{hematocrit})
\]

Vascular resistance in the calf was calculated as mean arterial BP (mmHg) divided by muscle blood flow (ml/100 ml per min) and expressed in resistance units.

**Statistical Analyses**

The primary study endpoints were (1) the M value from minute 80 to minute 120 of the clamp and (2) muscle blood flow. Normality of data distribution was assessed with the Shapiro-Wilk test. The intra-individual data on all three study days were evaluated with a two-way ANOVA using the SPSS statistical package (SPSS, Inc., Chicago, IL.). A paired t test was applied to compare means between groups when the ANOVA gave significant differences. Bonferroni correction was applied to correct for multiple comparison of data. The zero hypothesis was rejected when the P level was > 0.05. All data are presented as mean ± SD.

**Results**

With placebo infusion, the mean M value, i.e., insulin sensitivity, in healthy volunteers was 7.2 ± 1.6 mg/kg per min. It was significantly (P < 0.02) higher with infusion of 5 ng/kg per min of Ang II (9.3 ± 1.8 mg/kg per min). In contrast, after administration of the Ang II subtype 1 receptor blocker irbesartan, it was not significantly different (7.5 ± 1.7 mg/kg per min) from placebo infusion, but it was significantly (P < 0.05) lower than with infusion of Ang II. The individual responses to insulin of Ang II with and without coadministration of irbesartan are shown in Figure 1. The infusion of Ang II consistently increased insulin sensitivity in all nine volunteers, and the Ang II-induced increase in insulin sensitivity (M value) was blocked in part or completely in all volunteers examined. In contrast, mean serum glucose, insulin, and potassium levels did not differ significantly between treatments (Table 1).

The average mean arterial BP during the euglycemic clamp was unchanged during sham infusion; it increased significantly with infusion of Ang II (Table 1). Again, the increase was blocked with irbesartan pretreatment. Mean leg muscle blood flow was significantly higher with infusion of Ang II as compared with placebo infusion, but the Ang II-induced increase in muscle blood flow was almost completely obliterated with irbesartan pretreatment (Table 2 and Figure 1). Mean calculated vascular resistance in the calf decreased slightly but significantly with infusion of Ang II during euglycemic hyperinsulinemia as compared with placebo infusion, and this effect
ERPF (C PAH ) were significantly lower with Ang II infusion as individual M values with different treatments, respectively; placebo infusion, (25 ng Ang II/kg per min. angiotensin II-1 receptor antagonist irbesartan per os plus infusion of 3 ng Ang II/kg per min, and (1) in nine healthy volunteers with (1) placebo premedication per os plus infusion of 5 ng Ang II/kg per min. E, individual values of muscle blood flow and individual M values with different treatments, respectively; ○, mean muscle blood flow and mean M values, respectively.

Figure 1. Muscle blood flow (MBF) and insulin sensitivity (M value) in nine healthy volunteers with (1) placebo premedication per os plus placebo infusion, (2) placebo premedication per os plus infusion of 5 ng Ang II/kg per min, and (3) premedication with 300 mg of the angiotensin II-1 receptor antagonist irbesartan per os plus infusion of 5 ng Ang II/kg per min. ○, individual values of muscle blood flow and individual M values with different treatments, respectively; ○, mean muscle blood flow and mean M values, respectively.

was blocked by pretreatment with irbesartan as well. The difference between infusion of Ang II plus placebo per os and Ang II infusion after irbesartan administration did not reach statistical significance, however. Both mean GFR (C in) and ERPF (C PAH ) were significantly lower with Ang II infusion as compared with placebo infusion; filtration fraction and renal vascular resistance were significantly higher (Table 2). The Ang II-induced changes in renal hemodynamics were consistent in all nine volunteers examined; they were abolished with administration of irbesartan (Figure 2).

Discussion

The results of the present study document that in healthy subjects, Ang II caused an increase of muscle blood flow under euglycemic hyperinsulinemic conditions and in parallel, an increase of insulin sensitivity. Both effects are mediated via the Ang II subtype 1 receptor. The Ang II subtype 1 receptor blocker irbesartan almost completely inhibited the effect of Ang II on both insulin sensitivity and muscle blood flow. In contrast to its vasodilatory effect on skeletal muscle, Ang II induced vasoconstriction in the renal circulation and caused an increase of renal vascular resistance. The Ang II-1-receptor antagonist irbesartan abrogated both actions of Ang II, i.e., vasodilation as well as vasoconstriction. These observations point to opposing actions of Ang II on the (micro)vasculature of different vascular territories that are mediated via the same receptor subtype, i.e., the Ang II receptor subtype 1.

The results of a recent experimental study in rats suggested that the pressor action of Ang II, i.e., vasoconstriction, is mediated through Ang II receptor subtype 1 but that Ang II receptor subtype 2 mediates an opposing vasodepressor effect, i.e., vasodilation (13). This suggests a dual hemodynamic action of Ang II mediated via two different receptors. Indeed, some past experimental studies on isolated blood vessels showed a biphasic arteriolar response to Ang II, i.e., a brief increase in arteriolar resistance (reduction in blood flow) followed by a sustained decrease below baseline (increase in blood flow) (14,15). Both effects were blocked by saralasin, a nonspecific Ang II receptor antagonist. Specific Ang II receptor antagonists were not available at that time. Our observation in humans does not confirm the above hypothesis of a dual action of Ang II mediated by two different receptor subtypes. On the contrary, our results clearly demonstrate that a pressor dose of Ang II has opposing effects in different vascular territories, i.e., vasoconstriction in the kidney and vasodilation in the skeletal muscle vessels. Both effects were blocked by irbesartan, a highly specific Ang II subtype 1 receptor antagonist. Our finding of opposing effects of Ang II in different vascular beds is in line with results of recent experimental studies and studies in humans. For example, Motwani and Struthers (16) showed that in healthy subjects, infusion of Ang II caused a dose-dependent redistribution of cardiac output and intravascular volume from splanchnic to leg vessels. Similar observations were made by Buchanan et al. (2), who found a dose-dependent increase in femoral artery flow in healthy subjects during Ang II infusion. The authors did not calculate femoral vascular resistance, but from their data one can calculate that it decreased despite an increase in arterial BP. These findings suggest that Ang II induces pronounced vasoconstriction in the renal and splanchnic vascular beds, leading to an overall increase in total peripheral resistance and arterial BP. This view is corroborated by our finding and by observations of others that infusion of Ang II nearly obliterates insulin secretion via a marked reduction of blood flow to the pancreas, whereas it fails to affect myocardial blood flow (17–20). The role of specific Ang II receptors was not investigated in these studies, however.

The results of the present study confirm that a pressor dose of Ang II consistently increases insulin-stimulated glucose disposal and muscle blood flow in healthy subjects (1–3,5). We and Buchanan et al. (1,2) showed that the Ang II-induced increase of insulin sensitivity is dose-dependent and is demonstrable even after a maximal (plateau) blood insulin concentration has been achieved (2). Further increasing the rate of insulin infusion did not increase insulin-stimulated glucose disposal. Superimposition of Ang II infusion under conditions of maximal hyperinsulinemia further increased glucose dis-
Table 1. Metabolic and hemodynamic variables at the start and at the end of the clamp studies in nine healthy volunteers

<table>
<thead>
<tr>
<th></th>
<th>Placebo + Placebo</th>
<th>Placebo + Ang II</th>
<th>Irbesartan + Ang II</th>
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</thead>
<tbody>
<tr>
<td>Serum insulin (pmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>start</td>
<td>64 ± 13</td>
<td>63 ± 10</td>
<td>65 ± 11</td>
</tr>
<tr>
<td>end</td>
<td>765 ± 83</td>
<td>847 ± 91</td>
<td>790 ± 60</td>
</tr>
<tr>
<td>Serum glucose (mmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>start</td>
<td>4.10 ± 0.26</td>
<td>4.18 ± 0.17</td>
<td>4.21 ± 0.24</td>
</tr>
<tr>
<td>end</td>
<td>4.13 ± 0.30</td>
<td>4.21 ± 0.21</td>
<td>4.17 ± 0.18</td>
</tr>
<tr>
<td>Serum potassium (mmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>start</td>
<td>3.82 ± 0.19</td>
<td>3.83 ± 0.12</td>
<td>3.84 ± 0.11</td>
</tr>
<tr>
<td>end</td>
<td>3.50 ± 0.14</td>
<td>3.47 ± 0.13</td>
<td>3.53 ± 0.13</td>
</tr>
<tr>
<td>Mean arterial blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>start</td>
<td>80 ± 6</td>
<td>80 ± 5</td>
<td>79 ± 5</td>
</tr>
<tr>
<td>end</td>
<td>79 ± 5</td>
<td>89 ± 4</td>
<td>81 ± 4</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>start</td>
<td>63 ± 6</td>
<td>60 ± 8</td>
<td>61 ± 6</td>
</tr>
<tr>
<td>end</td>
<td>62 ± 6</td>
<td>62 ± 8</td>
<td>62 ± 5</td>
</tr>
</tbody>
</table>

Table 2. Muscle blood flow and renal hemodynamics during the clamp studies in nine healthy volunteers

<table>
<thead>
<tr>
<th></th>
<th>Placebo + Placebo</th>
<th>Placebo + Ang II</th>
<th>Irbesartan + Ang II</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBF (ml/100 g per min)</td>
<td>13.5 ± 1.8</td>
<td>17.7 ± 2.1</td>
<td>14.3 ± 1.9</td>
</tr>
<tr>
<td>CVR (resistance units)</td>
<td>5.9 ± 0.6</td>
<td>5.2 ± 0.7</td>
<td>5.7 ± 0.6</td>
</tr>
<tr>
<td>GFR (ml/min per 1.73m²)</td>
<td>120 ± 6</td>
<td>107 ± 6</td>
<td>118 ± 6</td>
</tr>
<tr>
<td>ERPF (ml/min per 1.73m²)</td>
<td>672 ± 51</td>
<td>461 ± 44</td>
<td>650 ± 36</td>
</tr>
<tr>
<td>FF (GFR/ERPF)</td>
<td>0.18 ± 0.02</td>
<td>0.24 ± 0.03</td>
<td>0.18 ± 0.02</td>
</tr>
<tr>
<td>RVR (mmHg/ml per min)</td>
<td>74 ± 6</td>
<td>126 ± 15</td>
<td>76 ± 6</td>
</tr>
</tbody>
</table>

*MBF, muscle blood flow; CVR, calf vascular resistance; GFR, glomerular filtration rate; ERPF, effective renal plasma flow; FF, filtration fraction; RVR, renal vascular resistance.

b P < 0.04; comparison between placebo infusion plus placebo per os and Ang II infusion plus placebo per os.

c P < 0.01; comparison between placebo infusion plus placebo per os and Ang II infusion plus placebo per os.

d P < 0.01; comparison between Ang II infusion plus placebo per os and Ang II infusion plus irbesartan per os.

The effect of Ang II is therefore not simply explained by a potentiation of the action of insulin but is probably mediated via recruitment of additional capillaries with an increase in (measurable) muscle blood flow (2). This suggests that there is interaction between the effects of insulin and of Ang II on skeletal muscles on different levels: (1) Ang II augments the metabolic effect of insulin, but (2) insulin in turn alters the hemodynamic action of Ang II. The latter proposal is based on the observation that the effect of Ang II on muscle blood flow was detectable under basal (fasting) insulinemia but was markedly potentiated under hyperinsulinemic (euglycemic) conditions. In contrast, the pressor response to Ang II was blunted during hyperinsulinemia as compared with basal (fasting) insulinemia (2). Taken together, Ang II redistributes cardiac output, i.e., blood flow, from less insulin-sensitive (splanchnic) to more insulin-sensitive (skeletal muscle) tissues, and this effect is augmented by insulin. This homeostatically useful action may be particularly important in the postprandial phase when glucose must be cleared from blood. It is therefore of interest that in patients with type 2 diabetes mellitus, the effect of Ang II on muscle perfusion and on insulin-stimulated glucose uptake is blunted, i.e., the clearance of glucose from the blood during hyperinsulinemia is markedly impaired (3). In some of these patients, infusion of Ang II under euglycemic conditions even decreased muscle perfusion and insulin sensitivity. In parallel, renal vasconstriction was more pronounced (3). These observations suggest that in patients with type 2 diabetes, the action of Ang II on muscle and renal microvasculature is altered, and this is reminiscent of the finding that endothelial relaxation is impaired in these patients (21,22). They further suggest that the interplay between the insulin and renin-angiotensin systems is...
abnormal in patients with type 2 diabetes mellitus and potentially in subjects with the metabolic syndrome (3). Indirect evidence supporting this idea comes from the recently published CAPPP trial (23). Patients with essential hypertension and who were treated with the angiotensin-converting enzyme inhibitor captopril developed significantly less type 2 diabetes mellitus during the follow-up as compared with patients who were treated with conventional antihypertensive therapy.

In a recent experimental study, the effect of Ang II on the intracellular action of insulin was explored in a rat aorta smooth muscle cell culture (24). It is interesting that Ang II inhibited the insulin-stimulated insulin receptor substrate-1-associated phosphatidylinositol 3-kinase activity in a dose-dependent manner, and this action resulted in the inhibition of normal interactions between the insulin signaling pathway components. Furthermore, the findings suggested that the effect of Ang II was not mediated via Ang II subtype 1 or Ang II subtype 2 receptors but via another pathway (24). The authors obtained similar results in a rat heart model and concluded that overactivity of the renin-angiotensin system is likely to impair insulin signaling and contribute to insulin resistance in essential hypertension (25). These findings contrast with our results and observations of other authors (1–5), which clearly document a stimulatory effect of Ang II on insulin sensitivity in humans, at least under hyperinsulinemic conditions. The divergent results are not necessarily contradictory, because the action of Ang II on cell cultures may be different from the effect in vivo. In line with this argument are observations in patients with renovascular hypertension and a stimulated renin-angiotensin system, where insulin sensitivity is not impaired (26,27). Additional studies are therefore warranted to explore in more detail the relationship between the renin-angiotensin and insulin system in humans.

To interpret our results correctly, it is useful to consider some methodologic points. The serum insulin levels achieved with our euglycemic clamp protocol were similar to those observed in most other studies where this standard protocol was applied, i.e., approximately 800 pmol/L (4,5,10,28). This standardized protocol has been adopted to allow comparison of different studies. The serum insulin concentrations achieved with this insulin dose are approximately 6 to 8 times higher than fasting serum insulin concentrations in healthy, nondiabetic subjects. Such levels are regularly observed, however, in insulin-resistant subjects after a glucose load, e.g., in patients with type 2 diabetes, in obese patients, and in patients with renal diseases (28,29). In such patients, postprandial serum insulin concentrations stay in this (patho)physiologic range for prolonged periods of time. Furthermore, we chose an infusion of 5 ng Ang II/kg per min to achieve a clear and definite effect on renal and muscle perfusion, but we are well aware that this dose yields pharmacologic Ang II plasma concentrations (1).

We conclude that in humans, (1) the Ang II-induced increase of muscle blood flow and of insulin sensitivity is mediated via Ang II-1 receptors and that (2) in the presence of euglycemic hyperinsulinemia, Ang II definitively has opposing effects on blood flow in different vascular territories, i.e., decrease of renal perfusion but increase of skeletal muscle blood flow. Both effects are mediated via the Ang II receptor subtype 1.

![Figure 2. GFR and effective renal plasma flow (ERPF) in nine healthy volunteers with (1) placebo premedication per os plus placebo infusion, (2) placebo premedication per os plus infusion of 5 ng Ang II/kg per min, and (3) premedication with 300 mg of the angiotensin II-1 receptor antagonist irbesartan per os plus infusion of 5 ng Ang II/kg per min. ○, individual values of GFR and effective renal plasma flow with different treatments, respectively; ●, mean GFR and mean effective renal plasma flow, respectively.](image-url)
Acknowledgment
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References

Access to UpToDate on-line is available for additional clinical information at http://www.jasn.org/