Angiotsin II induces insulin resistance independent of changes in interstitial insulin

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Richey, Joyce M., Marilyn Ader, Donna Moore, and Richard N. Bergman. Angiotsin II induces insulin resistance independent of changes in interstitial insulin. Am. J. Physiol. 277 (Endocrinol. Metab. 40): E920–E926, 1999.—We set out to examine whether angiotensin-driven hypertension can alter insulin action and whether these changes are reflected as changes in interstitial insulin (the signal to which insulin-sensitive cells respond to increase glucose uptake). To this end, we measured hemodynamic parameters, glucose turnover, and insulin dynamics in both plasma and interstitial fluid (lymph) during hyperinsulinemic euglycemic clamps in anesthetized dogs, with or without simultaneous infusions of angiotsin II (ANG II). Hyperinsulinemia per se failed to alter mean arterial pressure, heart rate, or femoral blood flow. ANG II infusion resulted in increased mean arterial pressure (68 ± 16 to 94 ± 14 mmHg, P < 0.001) with a compensatory decrease in heart rate (110 ± 7 vs. 86 ± 4 mmHg, P < 0.05). Peripheral resistance was significantly increased by ANG II from 0.434 to 0.507 mmHg·ml⁻¹·min⁻¹ (P < 0.05). ANG II infusion increased femoral artery blood flow (176 ± 4 to 187 ± 5 ml/min, P < 0.05) and resulted in additional increases in both plasma and lymph insulin (93 ± 20 to 122 ± 13 µU/ml and 30 ± 4 to 45 ± 8 µU/ml, P < 0.05). However, glucose uptake was not significantly altered and actually had a tendency to be lower (5.9 ± 1.2 vs. 5.4 ± 0.7 mg·kg⁻¹·min⁻¹, P > 0.10). Mimicking of the ANG II-induced hyperinsulinemia resulted in an additional increase in glucose uptake. These data imply that ANG II induces insulin resistance by an effect independent of a reduction in interstitial insulin.

lymph insulin; euglycemic hyperinsulinemia; endogenous glucose production; blood flow

RECENT STUDIES regarding the effects of angiotsin II (ANG II) on insulin action have been quite controversial. Buchanan et al. (6) and Townsend and DiPette (33) both reported increases in glucose uptake during systemic ANG II infusion in conscious humans and attributed their findings to hemodynamic effects, because ANG II increased calf muscle flow. Similarly, Jamerson et al. (14), with the isolated insulin-perfused forearm model, support their findings of hemodynamic factors being responsible for the increase in whole body glucose utilization. In contrast, Widgren et al. (34) also reported enhanced glucose uptake with ANG II during euglycemic hyperinsulinemia but concluded that hemodynamic factors were not responsible, because ANG II reduced calf muscle flow. Furthermore, Morris et al. (19) demonstrated that acute infusion of subpressor and pressor doses of ANG II for 3 h in healthy male subjects had no effect on glucose disposal. Studies by Rao (26) in anesthetized rats found evidence of ANG II-induced insulin resistance. Moreover, epidemiological studies demonstrate that some hypertensives manifesting insulin resistance exhibit improvement with angiotensin-converting enzyme (ACE) inhibitors (17, 18). The mechanism for the improvement is speculated to be hemodynamic, given that ACE inhibition results in a buildup of the vasodilator bradykinin, and this action may act to increase the access of insulin and glucose to skeletal muscle, the primary site of insulin-mediated glucose uptake.

In the present study, we set out to examine whether ANG II-driven hypertension can alter insulin action and whether these changes are reflected in interstitial insulin. To this end, we measured hemodynamic parameters, plasma and interstitial (lymph) insulin, and glucose turnover kinetics during euglycemic hyperinsulinemic clamps in anesthetized dogs, with or without simultaneous infusions of ANG II. Our data indicate that ANG II alters insulin action without a reduction in interstitial insulin. Hence, the site of resistance induced by ANG II appears to be downstream of interstitial insulin.

METHODS

Animals

Experiments were performed on anesthetized male mongrel dogs (23 ± 2 kg). Dogs were housed in the Keck School of Medicine of the University of Southern California (USC) Medical School Vivarium under controlled kennel conditions (12:12-h light-dark cycle) and were fed standard chow (49% carbohydrate, 25% protein, 9% fat; Alfred Mills, Chicago, IL) once each day. Dogs were used for experiments only if judged to be in good health as determined by body weight, hematocrit, and body temperature. All protocols were approved by the USC Institutional Animal Care and Use Committee.

Surgery

Surgery was performed on the morning of each experiment, after an overnight fast. Dogs were preanesthetized with acepromazine maleate (Prom-Ace, Aueco, Fort Dodge, IA; 0.6 ml) and atropine sulfate (0.10 ml/kg; H. Schein, Port Washington, NY). Anesthesia was induced with sodium thiamylal (Biotal, Bioceutic Labs, St. Joseph, MO) and maintained with halothane and nitrous oxide. Indwelling catheters were implanted for sampling of arterial blood from the carotid artery and interstitial fluid from hindlimb lymphatics. In addition, intravenous catheters were placed in the left saphenous vein and right and left cephalic veins for infusions of porcine insulin, insulin, somatostatin, and ANG II. The hindlimb lymphatic vessel was catheterized as previously described (1).
An ultrasonic perivascular flow probe (2 mm diameter; Transonic, Ithaca, NY) was implanted around the femoral artery on the hindlimb contralateral to the lymphatic catheterization for measurement of femoral artery blood flow. Incisions were kept moist with saline-soaked gauze, and body temperature, measured rectally, was maintained with a heating pad. A small (child-size) cuff was placed around the leg for measurements of blood pressure and heart rate using a Dinamap vital signs monitor (Tampa, FL).

Experimental Protocol

A total of 10 euglycemic clamp experiments were performed on individual animals as described in protocol I and protocol II. Each protocol consisted of a 120-min equilibration period, which included a 60-min basal period, followed by two sequential 3-h clamp periods. In protocol I (n = 5), insulin (1.0 mU·kg\(^{-1}·\text{min}^{-1}\)) was infused for the entire 360 min; in addition, a pressor infusion of ANG II (20 ng·kg\(^{-1}·\text{min}^{-1}\)) was superimposed on the insulin infusion from 180 to 360 min. In protocol II (n = 5), insulin was infused at 1.0 mU·kg\(^{-1}·\text{min}^{-1}\) from time 0 to 180 min and was then increased to a higher rate of 1.30 mU·kg\(^{-1}·\text{min}^{-1}\) from 180 to 360 min. The purpose of increasing the insulin infusion rate during 180–360 min in protocol II was to match the hyperinsulinemia that occurred with ANG II infusion in protocol I.

Protocol I. At time 180 min, a primed tracer infusion of [3-\(^3\)H\]glucose (a 35-µCi bolus followed by 0.25 µCi/min) was initiated. After the tracer equilibration period of 120 min, seven basal samples were collected at -60, -50, -40, -30, -20, -10, and -1 min. Beginning at time 0 and continuing for 360 min, porcine insulin was infused at 1 µU·kg\(^{-1}·\text{min}^{-1}\); somatostatin was infused at 0.8 µg·kg\(^{-1}·\text{min}^{-1}\); and \[^{14}\text{C}\]inulin was infused at 0.09 µCi/min. A variable-rate labeled (2.7 µCi/g) glucose infusion was used to clamp plasma glucose at the basal level (23). Blood and hindlimb lymph samples were obtained every 5 min between 0 and 30 min and every 10 min between 30 and 179 min. Starting at time 180 min, an ANG II infusion (Bachem California, Torrance, CA) of 20 ng·kg\(^{-1}·\text{min}^{-1}\) was superimposed on the insulin infusion, and the sampling schedule was repeated for an additional 180 min (+180 to 360 min). During ANG II infusions, blood and lymph samples were taken every 5 min between 180 and 210 min and every 10 min between 210 and 360 min.

Protocol II. This protocol was similar to that employed for protocol I, except that at time 180 min, ANG II was not infused. Instead, the insulin infusion rate was increased by 30% to mimic the relative hyperinsulinemia observed during ANG II infusions in protocol I (see RESULTS).

Blood and Intersitial Fluid Sampling

Arterial blood (3 ml) and hindlimb lymph samples (~500 µl) were collected in tubes containing heparin and sodium fluoride and stored on ice until centrifugation. After separation, all samples were stored at ~20°C until assayed for insulin.

Sampling of hindlimb lymph was accomplished by allowing fluid to drip into microcentrifuge tubes beginning 2.5 min before and finishing 2.5 min after each blood sample point. To obtain sufficient hindlimb lymph volume, lymph flow was stimulated by gentle massaging throughout the collection period. Lymph flow rate averaged ~100 µl/min.

Assays

Plasma samples were assayed for insulin, glucose, \[^{14}\text{C}\]inulin, and [3-\(^3\)H\]glucose. Because of the difficulty of obtaining sufficient sample volume from hindlimb lymphatics, priority was given to the insulin assay. Plasma glucose was assayed by the glucose oxidase technique on an automated analyzer (model 2700, Yellow Spring Instruments, Yellow Springs, OH). Insulin concentrations in plasma and lymph were measured in duplicate by the ELISA kindly donated by Dr. Bo Dinesen of Novo-Nordisk. The assay is based on two murine monoclonal antibodies that bind to different epitopes on the insulin molecule, which does not include proinsulin (3).

Plasma and lymph samples from each experiment were measured in the same assay. [3-\(^3\)H\]glucose and \[^{14}\text{C}\]inulin in plasma were determined as previously described (1, 25).

Materials

Porcine insulin was purchased from Sigma (St. Louis, MO). Dextrose (50%) was obtained from Kendall McGaw Laboratories (Irvine, CA). Tritiated glucose and \[^{14}\text{C}\]inulin were purchased from Du Pont-NEN (Boston, MA). Somatostatin and ANG II were obtained from Bachem California.

Data Analysis and Calculations

Tracer-determined glucose disposal (R\(_d\)) and endogenous glucose production (EGP) were calculated according to Finegood et al. (12). Plasma glucose and tracer data were smoothed by the optimal segments technique, or OOPSEG, before analysis (5a, 11a). Steady-state values were calculated by averaging data from the final hour of each phase of the clamp. Limb muscle vascular resistance was calculated from the ratio of mean arterial pressure (MAP) to the hindlimb femoral flow.

\[
\text{vascular resistance} = \frac{\text{MAP}}{\text{femoral flow}}
\]

The peripheral insulin sensitivity index for the clamp (S\(_{\text{IP,clamp}}\)) was calculated from the ratio of incremental increase in glucose uptake to the incremental increase in plasma insulin (Ins), divided by the ambient glucose concentration (G).

\[
S_{\text{IP,clamp}} = \frac{\Delta R_d}{\Delta \text{Ins}·G}
\]

Insulin clearance was calculated from the ratio of the insulin infusion rate (I\(_{\text{inf}}\); normalized to body weight) to the insulin concentration (C\(_i\)).

\[
\text{insulin clearance} = \frac{I_{\text{inf}}}{C_i}
\]

Statistical Analysis

Statistics were performed on a personal computer by use of the statistical software package MINITAB. Data are expressed as means ± SE. Comparisons were performed by Student’s paired and unpaired t-tests. Linear regression analysis was used to correlate glucose uptake and insulin dynamics. Significance was defined at the P < 0.05 level.

RESULTS

Basal Levels

Ambient plasma glucose was elevated presumably because of the employment of general anesthesia and surgical stress (Table 1). However, neither basal plasma glucose nor basal specific activity differed between the two protocols (Table 1). Likewise, plasma insulin concentrations were the same (Table 1). As previously noted, insulin levels were significantly higher in plasma than in lymph. However, there were no interprotocol differences in plasma or lymph insulin values. There was
Table 1. Basal values for protocols I and II

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<th>Protocol I</th>
<th>Protocol II</th>
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<tr>
<td>Glucose, mg/dl</td>
<td>128 ± 16</td>
<td>121 ± 4</td>
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<tr>
<td>Insulin, µU/ml</td>
<td>11 ± 4</td>
<td>11 ± 3</td>
</tr>
<tr>
<td>Plasma</td>
<td>4 ± 1</td>
<td>6 ± 1</td>
</tr>
<tr>
<td>Specific activity, dpm/mg</td>
<td>8,441 ± 148</td>
<td>7,749 ± 288</td>
</tr>
<tr>
<td>Rₜ and EGP, mg·kg⁻¹·min⁻¹</td>
<td>2.4 ± 0.3</td>
<td>2.7 ± 0.2</td>
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</table>

Values are means ± SE. Rₜ, glucose uptake; EGP, endogenous glucose production.

also no significant difference between basal glucose turnover values.

Insulin Dynamics

Despite constant insulin infusion, adding ANG II from 180 to 360 min resulted in a further increase in plasma insulin by 30%, and lymph insulin was also proportionally increased (P < 0.05 compared with insulin-only period for both; Fig. 1A). The glucose level was clamped at the same level during both experimental periods, and somatostatin was infused, indicating that glucose was not the stimulus to increase insulin secretion. Therefore, the resultant ANG II-induced hyperinsulinemia can be attributed to an ANG II-induced reduction in insulin clearance (Table 2).

In protocol II, insulin infusion was increased from 180 to 360 min to mimic the modest hyperinsulinemia caused by ANG II in protocol I. Thus increasing the insulin infusion rate by 30% (1.30 mU·kg⁻¹·min⁻¹) in protocol II achieved levels of plasma and lymph insulin of 111 ± 13 and 49 ± 5 µU/ml, respectively (Fig. 1B), not significantly different from those observed in protocol I during the same 180- to 360-min period. In contrast to the decrease in insulin clearance observed during ANG II-induced hyperinsulinemia in protocol I, insulin clearance was not significantly altered between the earlier and later periods in protocol II (Table 2). Thus achieving similar insulin levels, albeit by different mechanisms, made it possible to compare glucose uptake dynamics from the two protocol designs.

Inulin Dynamics

Plasma inulin dynamics serve as an index of renal clearance. During protocol I, plasma inulin significantly increased during ANG II infusion, reflecting a decrease in renal inulin clearance (Table 2). Plasma inulin kinetics were not significantly different during either period of insulin infusion in protocol II (Table 2). Hence, ANG II appeared to reduce both insulin and inulin clearance.

Glucose Turnover Dynamics

Plasma glucose was successfully maintained in both protocols (Table 2). During the insulin-only period in protocol I, Rₜ increased from 2.4 ± 0.2 to 5.9 ± 1.2 mg·kg⁻¹·min⁻¹ (P < 0.01; basal vs. steady state, Fig. 1C). Glucose disposal dynamics were highly correlated with lymph inulin dynamics (r = 0.97, P < 0.001; Fig. 2). However, during the ANG II infusion period (180-360 min), significantly higher insulin levels in plasma and lymph did not result in concomitant increases in Rₜ. Glucose utilization was virtually unchanged and demonstrated a tendency to be slightly reduced relative to the insulin-only steady-state period, 5.4 ± 0.7 vs. 5.9 ± 1.2 mg·kg⁻¹·min⁻¹ [P = not significant (NS)]. Thus, during ANG II infusion, there was a dissociation (r = 0.10, P > 0.10) between insulin dynamics and glucose utilization, such that an incremental increase in insulin did not induce an incremental increase in Rₜ (Fig. 2B). In fact, insulin sensitivity decreased by nearly 60% during ANG II infusion (Table 2).
In contrast, secondary elevation of insulin levels in the absence of ANG II (protocol II) resulted in the expected increase in glucose utilization (Fig. 1D). Hence, the relationship between lymph insulin and glucose uptake was maintained during the increased insulin (1.3 mU·kg\(^{-1}\)·min\(^{-1}\)) infusion period (r = 0.90, Fig. 2).

EGP was suppressed upon initiation of insulin infusion (Fig. 1, C and D). Neither ANG II nor additional insulin infusions further altered EGP rates.

**DISCUSSION**

The present study demonstrates that ANG II infusion during hyperinsulinemic euglycemic clamps is associated with a decrease in insulin sensitivity in anesthetized dogs. ANG II infusion increased femoral artery blood flow and insulin levels in both plasma and lymph. However, even in the face of higher interstitial insulin (the signal to which insulin-sensitive cells respond to increase glucose uptake), there was no net change in glucose utilization. Thus it can be concluded that the site of ANG II-induced insulin resistance is downstream from interstitial insulin levels, suggesting that a receptor or postreceptor defect is the most probable site of resistance.

Despite a constant insulin infusion rate (1.0 mU·kg\(^{-1}\)·min\(^{-1}\)), plasma and lymph insulin concentrations increased during ANG II administration. Given

![Fig. 2. Relationship between glucoseturnover and hindlimb lymph insulin. Each data point represents the mean value of insulin and glucoseturnover at each time point sampled during clamp (protocol I, A and B, and protocol II, C and D). Glucose uptake and hindlimb lymph insulin were strongly correlated (P < 0.001) during insulin infusion in the absence of ANG II. In protocol II, infusion of ANG II totally disrupted the association between glucose uptake and lymph insulin (P < 0.10).](http://ajpendo.physiology.org/)

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**Table 2. Steady-state values for protocols I and II**

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<tr>
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<th>Protocol I</th>
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<tr>
<td></td>
<td>INS, 1.0 mU·kg(^{-1})·min(^{-1})</td>
<td>ANG II, 20 ng·kg(^{-1})·min(^{-1})</td>
</tr>
<tr>
<td>Glucose, mg/dl</td>
<td>126 ± 14</td>
<td>131 ± 16</td>
</tr>
<tr>
<td>Insulin, µU/ml Plasma</td>
<td>93 ± 20</td>
<td>122 ± 13*</td>
</tr>
<tr>
<td>Lymph</td>
<td>30 ± 4</td>
<td>45 ± 8*</td>
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<tr>
<td>Clearance, ml/min</td>
<td>248 ± 39</td>
<td>183 ± 13*</td>
</tr>
<tr>
<td>Insulin, dpn/ml</td>
<td>1,591 ± 33</td>
<td>2,191 ± 32*</td>
</tr>
<tr>
<td>Clearance, ml/min</td>
<td>124 ± 11</td>
<td>90 ± 9</td>
</tr>
<tr>
<td>Glucose turnover, mg·kg(^{-1})·min(^{-1})</td>
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<tr>
<td>Ginf</td>
<td>5.7 ± 1.0</td>
<td>5.0 ± 0.7</td>
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<tr>
<td>Rd</td>
<td>5.9 ± 1.2</td>
<td>5.4 ± 0.7</td>
</tr>
<tr>
<td>EGP</td>
<td>0.22 ± 0.1</td>
<td>0.39 ± 0.2</td>
</tr>
<tr>
<td>Insulin sensitivity, 10(^{-4}) dl·min(^{-1})·kg(^{-1}) per µU/ml</td>
<td>6.64 ± 2.0</td>
<td>3.90 ± 1.2*</td>
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Values are means ± SE. INS, insulin infusion; ANG II, angiotensin II; Ginf, glucose infusion rate. *P < 0.05 vs. intraprotocol 1.0 mU·kg\(^{-1}\)·min\(^{-1}\); †P < 0.05, interprotocol differences.
that somatostatin was infused and plasma glucose was not altered, it is doubtful that the elevation in insulin was mediated by an increase in insulin secretion. In addition, there are no known effects of ANG II on insulin secretion. However, several studies have demonstrated that ANG II alters regional blood flow, reducing circulation to the liver and kidneys (9, 13, 20, 22, 32). Consequently, a reduction in blood flow to these organs would increase plasma concentrations of any substance cleared by these organs. This idea is consistent with the fact that plasma inulin, which is cleared only by the kidneys and is not taken up by cells, was also increased during ANG II infusion.

A particularly striking observation was that, during ANG II infusion, increased interstitial insulin failed to augment glucose utilization. Parallel increases in both plasma and interstitial insulin suggest that the delivery mechanism to the target cell was unaffected by ANG II infusion. Thus the present data are consistent with the resistance to insulin being at the level of the target cell. Previous reports from our lab have demonstrated the extremely powerful relationship between lymph insulin and glucose utilization (1, 25, 35) during euglycemic hyperinsulinemic clamps. The present study not only reconstructs that relationship ($r = 0.97$, $P < 0.001$), but via pharmacological manipulations with ANG II demonstrates a potential mechanism to abolish that relationship ($r = 0.10$, $P = NS$).

Although ANG II is an extremely potent vasoconstrictor and could potentially diminish blood flow to muscle tissue (15), we and others (6, 33) have found that femoral arterial blood flow is paradoxically increased during ANG II infusion. This finding is in accordance with both human and animal studies, which indicate that the arterial tree supplying muscle tissue is less responsive than other arteries to the vasoconstrictor effect of ANG II (7, 9, 20, 22, 32). We did find an increase in peripheral resistance to flow of skeletal muscle; however, the fact that blood flow increased during ANG II indicates that the change in blood flow in muscle per se is not the primary determinant in ANG II-induced hypertension. It is reasonable to assume that the pronounced increase in MAP during ANG II infusions is dependent primarily on constriction of other vascular beds more responsive to the constrictor effect of ANG II, including renal and splanchnic beds. These observations suggest that the most likely explanation for the increase in limb blood flow is redistribution of blood volume to muscle from the highly responsive constricted vascular beds. Therefore, the extensive network of arteries supplying muscle may not contribute significantly to the marked increase in total peripheral resistance observed during most ANG II infusion studies (9, 13, 20, 22, 32). In the present study, we did not monitor cardiac output and therefore were unable to assess total peripheral resistance. However, limb vascular resistance was found to be increased.

Previous reports by Baron and colleagues (4, 5, 16) and Lithell and colleagues (17, 18) have suggested that changes in glucose utilization follow the Fick principle, whereby an increase in capillary flow and/or recruitment leads to greater tissue exposure and, therefore, an increase in glucose utilization. However, the resultant increase in skeletal muscle perfusion in the present study was not accompanied by a significant increase in glucose uptake, suggesting a reduction in glucose extraction. Two possible mechanisms may explain this phenomenon: 1) hemodynamic factors involv-

<table>
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<th>Table 3. Steady-state hemodynamic values for protocols I and II</th>
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<td>Basal</td>
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<tr>
<td>MAP, mmHg</td>
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<tr>
<td>Femoral blood flow, ml/min</td>
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<tr>
<td>Resistance, mmHg·ml⁻¹·min⁻¹</td>
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<td>Heart rate, beats/min</td>
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Values are means ± SE. MAP, mean arterial pressure. *$P < 0.05$, vs. basal or 1.0 μU·kg⁻¹·min⁻¹.

Fig. 3. Dynamics for mean arterial pressure (MAP, cuff measurement) and femoral artery blood flow (flow probe) during euglycemic hyperinsulinemic clamps. Clamps were performed as described in Fig. 1. Infusion of ANG II resulted in significant increases in both MAP ($P < 0.001$) and femoral artery blood flow ($P < 0.05$).
ing redistribution of blood flow via arteriovenous (a-v) shunt pathways, or 2) direct inhibition of cellular glucose transport. If redistribution of blood flow via a-v shunt pathways served as the primary mechanism, blood flow would bypass the capillaries and might result in no change or a decrease in interstitial insulin. We found that interstitial insulin was increased during ANG II infusion, suggesting that capillary permeability was not altered, because permeability is rate limiting to the supply of insulin to the interstitial space. A limitation to the current study is that a-v glucose differences across the limb were not measured, therefore preventing assessment of limb glucose utilization. The possibility exists that glucose extraction across the hindlimb was increased, which would be consistent with our finding of an increase in hindlimb lymph insulin. However, an increase in limb glucose extraction would need to be counterbalanced by a reduction in glucose extraction in other vascular beds to account for the observed no net change in whole body glucose utilization.

The most probable mechanism for the ensuing resistance is direct inhibition of cellular glucose transport. Lymph insulin increased and glucose utilization failed to increase. Once insulin is transported into the interstitial space, it binds to cellular insulin receptors and initiates the insulin action cascade, leading to increased cellular facilitative glucose diffusion (28). At what level, receptor vs. postreceptor, ANG II alters the insulin action cascade cannot be determined from the present study. In addition, ANG II may have indirectly affected cellular glucose transport. ANG II has been shown to stimulate sympathetic activity, thereby increasing circulating catecholamines, which could contribute to the observed decrease in insulin sensitivity (16). Catecholamines are well known to acutely induce resistance to insulin-mediated glucose uptake in skeletal muscle (8). However, catecholamines were not measured in the current study; therefore, we are unable to determine the importance of this systemic mechanism.

Anesthetics have also been shown to interfere with carbohydrate metabolism by decreasing insulin sensitivity (2). Both halothane and nitrous oxide can increase plasma glucose, which could explain the elevated basal glucose levels. However, in protocol II, the insulin infusion rate was increased to match the ANG II-induced hyperinsulinemia in protocol I, and glucose utilization was appropriately increased. Hence, the observed suppression of glucose utilization in the presence of hyperinsulinemia during ANG II infusion is related to ANG II but does not exclude the possibility of an interaction between ANG II and anesthetics.

In the present study, we observed no hemodynamic effects associated with insulin per se. This observation is consistent with our previous results, which demonstrated that insulin infusion in conscious normal and baroreceptor-denervated dogs did not affect blood pressure (27). Several published reports have demonstrated that insulin infusion results in a dose-dependent increase in leg blood flow, independent of hypoglycemia (4, 5, 16). However, we did not observe any alterations in femoral blood flow during insulin infusion.

In summary, infusion of ANG II during euglycemic hyperinsulinemia results in a complete dissociation in lymph insulin and glucose utilization, such that an incremental increase in interstitial insulin does not reflect an incremental increase in Rg. The insulin resistance associated with ANG II-induced hypertension appears to reflect a defect in insulin action at the level of the target cell (muscle tissue) rather than changes in interstitial insulin. These observations may hold some important implications as to the mechanisms involved in the pathogenesis of insulin resistance in hypertension.

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