Insulin Increases Sympathetic Activity but Not Blood Pressure in Borderline Hypertensive Humans

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We have previously demonstrated that physiological hyperinsulinemia in normotensive humans increases sympathetic nerve activity but not arterial pressure since it also causes skeletal muscle vasodilation. However, in the presence of insulin resistance and/or hypertension, insulin may cause exaggerated sympathetic activation or impaired vasodilation and thus elevate arterial pressure. This study sought to determine if insulin causes a pressor response in borderline hypertensive humans by producing exaggerated increases in sympathetic neural outflow or impaired vasodilation. We recorded muscle sympathetic nerve activity (microneurography, peroneal nerve), forearm blood flow, heart rate, and blood pressure in 13 borderline hypertensive subjects during a 1-hour insulin infusion (38 microunits/m²/min) while holding blood glucose constant. Plasma insulin rose from 12 ±3 microunits/ml (mean±SEM) during control to 73±7 microunits/ml during insulin infusion and fell to 9±2 microunits/ml 2 hours after insulin infusion was stopped. Muscle sympathetic nerve activity, which averaged 25±2 bursts per minute in control, increased significantly during insulin infusion (+9 bursts per minute) and remained elevated 1.5 hours into recovery (+7 bursts per minute, p<0.001). Despite increased muscle sympathetic nerve activity, there were significant (p<0.001) increases in forearm blood flow and decreases in forearm vascular resistance during insulin infusion. Further, systolic and diastolic pressures fell approximately 3 and 6 mm Hg, respectively, during insulin infusion (p<0.01). This study suggests that acute physiological increases in plasma insulin elevate sympathetic neural outflow in borderline hypertensive humans but produce vasodilation and do not elevate arterial pressure. (Hypertension 1992;19:621-627)

KEY WORDS • insulin • sympathetic nervous system • borderline hypertension • norepinephrine • microneurography

It has been proposed that hyperinsulinemia may contribute to elevated arterial pressure. For example, there is a correlation between obesity, insulin resistance, hyperinsulinemia, and hypertension. In addition, humans with essential hypertension have insulin resistance and hyperinsulinemia even in the absence of obesity. Treatment of hypertension fails to reverse the insulin resistance, suggesting that it is not secondary to elevated arterial pressure.

In rats, insulin infusion increases arterial pressure. Hyperinsulinemia produced by feeding rats sucrose or fructose has been associated with elevated catecholamine secretion and arterial pressure.

In normotensive humans, Rowe et al reported that plasma norepinephrine levels increased during hyperinsulinemic/euglycemic clamp. Physiological increases in plasma insulin did not increase arterial pressure, but supraphysiological levels (i.e., 400–500 microunits/ml) produced moderate pressure increases.

We recently reported that acute physiological elevations in plasma insulin (i.e., 75 and 150 microunits/ml) caused marked and prolonged increases in muscle sympathetic nerve activity (MSNA) in normal humans while also causing substantial vasodilation. The net effect of the sympathoexcitatory (pressor) and vasodilator (depressor) actions was no increase in arterial pressure; indeed, diastolic pressure fell slightly. Gans et al have also recently reported that acute physiological hyperinsulinemia does not increase arterial pressure in normal humans.

Hypertension is reportedly associated with insulin resistance. If hypertension and insulin resistance are associated with exaggerated sympathetic or impaired vasodilator responses, or both, to insulin, this could result in pressor response to hyperinsulinemia in hypertensive humans despite the absence of a pressor response in normotensive humans. There is evidence from recent studies in our laboratory that insulin causes...
exaggerated sympathetic neural responses in spontaneously hypertensive rats. Baron and colleagues have suggested that insulin resistance is associated with impaired vasodilator responses to insulin in skeletal muscle. They reported that insulin stimulates skeletal muscle blood flow in a dose-dependent fashion in normal subjects. This response was markedly reduced in obese subjects.

This study was designed to determine the effect of acute physiological elevations in plasma insulin on sympathetic nerve activity, forearm vascular resistance, and blood pressure in borderline hypertensive humans. We measured MSNA, forearm blood flow, and forearm vascular resistance in borderline hypertensive humans during physiological increases in plasma insulin while blood glucose was maintained at control levels (hyperinsulinemic/euglycemic clamp).

Methods

Subjects

Subjects were 13 borderline hypertensive humans (nine male and four female) with a mean age of 27.3 ± 1.7 years (range, 20–40), mean weight of 86.8 ± 4.3 kg (range, 52–114), mean body mass index of 28.4 ± 1.2 kg/m² (range, 21–35), mean waist/hip ratio of 0.87 ± 0.02, and mean percent body fat of 28.8 ± 2.6%. None was receiving medications, and all had normal electrocardiograms, urinalysis, blood counts, electrolytes, and renal and liver function.

Borderline hypertension was defined as diastolic pressure intermittently >90 mm Hg on three occasions. Means of three supine, sitting, and standing systolic pressures were 132 ± 3.0, 128 ± 3.3, and 127 ± 3, respectively. Mean supine, sitting, and standing diastolic pressures were 85 ± 2.2, 91 ± 1.0, and 91 ± 1.3, respectively. Human Institutional Review Board approval and written informed consent were obtained.

Measurements

Heart rate was calculated from an electrocardiogram. Blood pressure was recorded by automatic sphygmomanometer (Life Stat 200, Physio Control Corp., Redmond, Wash.). Forearm blood flow was measured by venous occlusion plethysmography using an air cuff. Central venous pressure was measured from a catheter inserted in an antecubital vein and advanced into an intrathoracic vein.

Intraneural recording techniques (microneurography) were used to obtain multifiber recordings of postganglionic MSNA from a muscle fascicle of the peroneal nerve posterior to the fibular head as previously described.

Hyperinsulinemic/Euglycemic Clamp

Insulin (Humulin, Eli Lilly & Co., Indianapolis, Ind.) diluted in saline with 1 ml of subject’s blood was infused intravenously by digital infusion pump (Bard Medsystems, North Reading, Mass.). Insulin infusion rate (targeted to produce a 75 microunit/ml plasma insulin level for 1 hour as determined by the technique of DeFronzo et al.) included a 10-minute priming infusion and a 50-minute infusion at 38 microunits/min/m². Fasting blood glucose levels were maintained by variable 20% dextrose infusion using an infusion pump (Flo-Gard 6200, Travenol Laboratories, Deerfield, Ill.). Glucose infusion was tapered after insulin infusion until no longer required to maintain normal glucose levels.

Procedures and Assays

Subjects were placed in the supine position and instrumented for measurement of heart rate and blood pressure. Intravenous catheters were placed in the right and left antecubital fossa for insulin/glucose infusion, obtaining blood for glucose and insulin analysis, and measurement of central venous pressure. Forearm blood flow was measured in the right arm. After a sympathetic nerve recording site was found, control measurements were taken for 20 minutes followed by 1 hour of insulin infusion and 2 hours of recovery. MSNA and hemodynamic measurements were recorded for 5 of every 10 minutes throughout the study. Blood glucose was analyzed by a YSI glucose analyzer (model 27, Yellow Springs Instruments, Yellow Springs, Ohio). Plasma insulin levels were measured using radioimmunoassay with interassay and intra-assay coefficients of variation in our laboratory of 7% and 5.1%, respectively.

Statistical Analyses

MSNA, forearm blood flow, and heart rate were recorded and measured as previously described. Forearm vascular resistance was calculated by dividing mean arterial pressure by flow and expressed in arbitrary units.

Five minutes of MSNA, blood pressure, heart rate, and forearm blood flow data were collected every 10 minutes and averaged to a single value for each variable. Plasma insulin and blood glucose levels were determined once every 5 minutes.

Data were analyzed by repeated-measures analysis of variance (ANOVA) by using planned contrasts (control versus the 1-hour insulin infusion period and control versus 1- and 2-hour recovery periods). Post hoc comparisons were made by the least squares means procedure. A 0.05 significance level was used for statistical tests. Data are presented as mean ± SEM.

Results

Blood Glucose and Plasma Insulin

Figure 1 shows that the maximal variation in blood glucose was 3.3 mg/dl (4%) during insulin infusion. Blood glucose levels remained stable during insulin infusion but fell to a nadir of 72 mg/dl at 80 minutes into recovery as glucose infusion rate tapered. Three subjects had blood glucose values below 65 mg/dl (mild hypoglycemia) during recovery while 10 remained above that level throughout recovery. Plasma insulin averaged 12.5 ± 2.8 microunits/ml during control and reached a peak of 73 ± 7.6 microunits/ml during insulin infusion (p < 0.001). Insulin levels fell to 8.6 ± 1.8 microunits/ml at the end of the recovery period (NS versus control). M values (milligrams per kilogram per minute of metabolized glucose), calculated from glucose infusion rates during 20–60 minutes of insulin infusion, averaged 4.5 ± 0.5 (range, 2.1–7.8).

Muscle Sympathetic Nerve Activity

Figures 2 and 3 show that, during insulin infusion, MSNA (expressed as either bursts per minute or integrated activity) rose significantly (p < 0.001). Follow-up
analyses revealed that MSNA did not increase significantly until 20 minutes after insulin treatment was begun. There was a significant ($p<0.001$) linear increase in MSNA during insulin infusion. MSNA remained significantly ($p<0.001$) elevated throughout recovery while plasma insulin levels returned to control levels. This continued MSNA elevation was not due to hypoglycemia since data analysis of 10 subjects whose blood glucose remained above 65 mg/dl showed comparable increases.

**Blood Pressure, Heart Rate, Forearm Blood Flow, and Vascular Resistance**

Figure 4 shows that both systolic and diastolic pressures fell significantly (approximately 3 and 5 mm Hg,
FIGURE 3. Tracings of muscle sympathetic nerve activity (MSNA) and forearm blood flow in one subject during control and insulin infusion. Insulin rose from 7 microunits/ml during control to 69 microunits/ml during insulin infusion. MSNA rose from 27 to 42 bursts per minute. Despite this increase, forearm blood flow rose and forearm vascular resistance declined from 46 to 26, respectively; $p<0.01$) during the insulin infusion. The decreases were significant within 10 minutes of the start of insulin infusion. During the first hour of recovery, systolic and diastolic pressures remained below control levels ($p<0.01$). Only diastolic pressure remained below control levels during the second hour of recovery ($p<0.01$).

Heart rate increased slightly but significantly during insulin infusion ($p<0.02$ versus control) and remained elevated throughout recovery (control versus hours 1 and 2 of recovery, $p<0.001$ and 0.04, respectively; see Figure 4).

Central venous pressure decreased from 6.1±3.3 mm Hg during control to an average of 5.5±0.1 mm Hg during insulin infusion ($p<0.01$) and 5.8±0.1 and 5.5±0.1 mm Hg during hours 1 and 2 of recovery ($p<0.01$) (Figure 4).

Forearm blood flow increased significantly during insulin infusion ($p<0.001$) with significant linear increase during insulin infusion ($p<0.01$). Forearm blood

FIGURE 4. Line graphs show systolic, diastolic, and mean blood pressures (SBP, DBP, and MAP, respectively; top left panel), heart rate (bottom left panel), forearm blood flow (top right panel), and forearm vascular resistance (bottom right panel) during control, insulin infusion, and recovery. Both SBP and DBP declined significantly after 10 minutes of insulin infusion. DBP remained below control levels throughout recovery, whereas SBP returned to control levels during the second hour of recovery. Heart rate increased slightly but significantly during insulin infusion and remained elevated during recovery. Forearm blood flow rose and forearm vascular resistance declined during insulin infusion. Forearm vascular resistance remained below control level throughout recovery. Heart rate increased after 20 minutes of insulin infusion and remained elevated during recovery. b/min, Beats per minute.
flow remained elevated during the first hour of recovery 
\((p<0.01)\) with significant \((p<0.01)\) linear decline during 
that hour; however, during the second hour of recovery, forearm blood flow was not significantly dif-
ferent from control (Figure 4).

Forearm vascular resistance declined significantly 
\((p<0.001)\) over the first hour of insulin infusion with a 
significant linear decrease \((p<0.01)\) and returned to-
ward control during the first hour of recovery but remained significantly below control values.

**Insulin Resistance and Responses to Insulin**

To determine whether degree of insulin resistance was related to responses during insulin infusion, 
MSNA, systolic and diastolic pressures, forearm blood flow, and forearm vascular resistance responses to insu-
lin (calculated as control values minus values after 1 hour of insulin infusion) were correlated with subjects' 
M values. In no case did the correlations approach signi-
ficance. However, these results should be inter-
preted cautiously because of the relatively narrow range 
of M values and small sample size.

**Vehicle and Time Control Experiments**

To determine whether volume infusion or time could alter nerve activity, forearm vascular resistance, or blood pressure, four subjects returned for control ex-
periments that followed the same protocol as insulin 
infusion but without insulin or glucose infusion (i.e., 
same duration and volume infusion). Time and volume 
infusion were not accompanied by substantial changes in 
MSNA, blood pressure, or forearm blood flow and vascular resistance. The maximum change from control at any time over 3 hours was +4.2 bursts per minute and +73 units for MSNA, −3.9 mm Hg for systolic pressure, −3.1 mm Hg for diastolic pressure, +2.5 beats per minute for heart rate, +0.01 ml/min/100 ml for forearm blood flow, −3.4 units for forearm vascular resistance, and −0.8 mm Hg for central venous pressure.

**Comparison With Responses in 
Normotensive Subjects**

We have previously reported the effects of insulin in 
normotensive subjects. To determine whether the 
responses seen in borderline hypertensive subjects were comparable to responses previously reported from our 
laboratory for normotensive subjects, changes in MSNA and hemodynamic variables from control to the end of 1 hour of insulin infusion were compared by \(t\) test. The expectation of increased MSNA responses and reduced forearm blood flow and vascular resistance responses in borderline hypertensive subjects was marginally sup-
ported \((p<0.10\) and \(>0.05\) by one-tailed test). 
Differences in heart rate and blood pressure responses were similar in borderline hypertensive subjects and the normotensive subjects previously studied.

**Discussion**

It has been proposed that the sympathoexcitatory effects of insulin contribute to hypertension. However, we have previously shown that acute hyperinsulinemia increases MSNA in normotensive humans but also causes vasodilation with a net result of a slight decrease in blood pressure. The major contribution of the present study is the finding that acute, physiological increases in plasma insulin levels in borderline hypertensive humans pro-
duced substantial increases in MSNA, but as in nor-
motensive humans, insulin also caused forearm vasodi-
lation and slight but significant decreases in blood pressure. Thus, the effects of insulin in borderline hypertensive patients parallel our previous findings in 
normotensive humans.

**Potential Limitations of Study**

We studied borderline hypertensive humans, and it 
could be argued that the effects of insulin may differ in 
humans with severe hypertension or with greater insulin 
resistance. However, subjects in the current studies 
metabolized less glucose during insulin infusion than did the normotensive subjects in our previous study 
\((4.5 \pm 0.5\) versus \(7.5 \pm 0.9\) mg/kg/min). Thus, the current 
subjects displayed insulin resistance compared with 
normotensive subjects. In addition, O’Hare et al have 
previously reported that acute hyperinsulinemic/eugly-
cemic clamp does not elevate arterial pressure in obese, 
insulin-resistant subjects.

Although separate time and vehicle control experi-
ments were not performed on all subjects, control studies 
in four subjects suggested that time and vehicle infusion cannot explain the responses to insulin infusion.

We measured forearm blood flow and vascular resis-
tance while recording MSNA in the leg. MSNA re-
corded simultaneously from radial and peroneal nerves 
(i.e., arm versus leg) are usually remarkably similar, 
but differences have been reported under conditions 
such as mental stress. Thus, we cannot exclude that 
insulin may differentially affect MSNA or vascular re-
sistance in arm and leg. However, Frandsen et al (per-
sonal communication, 1991) have found that acute 
hyperinsulinemia/euglycemic clamp produces vasodila-
tion in the calf in normal humans.

Finally, we recorded sympathetic nerve activity to 
muscle and cannot extrapolate the results to sympa-
thetic neural outflow to other vascular beds.

**Mechanisms of Increases in Muscle Sympathetic 
Nerve Activity**

As discussed in greater detail, possible mechanisms 
for the effects of insulin on MSNA include 1) altered 
blood glucose, 2) baroreceptor reflex-mediated in-
creases, and 3) central nervous system actions.

Changes in blood glucose concentrations cannot ex-
plain the increased MSNA since glucose levels did not 
fall below control values except during recovery.

During insulin infusion, there were small decreases in 
systolic, diastolic, and central venous pressures that 
could increase MSNA by reducing arterial and cardio-
pulmonary baroreceptor inhibition of MSNA. Although 
the increased MSNA may represent baroreceptor reflex 
increases secondary to the slight fall in blood pressure and central venous pressure, two observations suggest 
that this is not the sole mechanism. First, there was a 
lack of parallelism between the changes in blood pres-
sure and MSNA. Specifically, arterial and central ve-
nous pressures decreased within 10 minutes of insulin 
infusion while MSNA and heart rate remained at con-
trol levels. Second, the magnitude of the MSNA in-
Mechanisms of Vasodilation

As discussed previously, the observed forearm vasodilation may reflect a direct local dilator action of insulin or indirect humoral or neural action. Creager et al. reported that local intra-arterial infusion of insulin caused dose-dependent increases in forearm vascular resistance in humans. However, others have found no evidence for a local vasodilator action of insulin.

Possible indirect humoral and neural mechanisms underlying the vasodilation during systemic infusion of insulin include β-adrenergically mediated vasodilation. Insulin might activate sympathetic neural vasodilator pathways to skeletal muscle. We have previously determined that the insulin-induced increases in MSNA are paralleled by increased plasma norepinephrine, indicating that insulin increases sympathetic noradrenergic vasoconstrictor activity. However, insulin might also produce simultaneous activation of sympathetic neural vasodilator pathways (e.g., cholinergic vasodilation) that override the increased sympathetic noradrenergic activity.

Our studies do not indicate the mechanism or mechanisms of vasodilator actions.

Physiological Significance

It has been hypothesized that insulin elevates arterial pressure through its sympathoexcitatory and antinatriuretic effects. Previous studies suggest that acute physiological increases in plasma insulin do not elevate arterial pressure in normotensive humans. The current study demonstrates that acute physiological increases in plasma insulin produce marked sympathoexcitatory effects in borderline hypertensive humans but do not elevate arterial pressure, presumably because of the offsetting vasodilator actions of insulin.

These observations do not exclude a possible role for hyperinsulinemia in promoting increases in arterial pressure. First, with higher insulin concentrations, the pressor actions of insulin might predominate, as suggested by the study of Rowe et al. Second, with more severe insulin resistance that attends android obesity or more severe hypertension, the balance between the pressor and depressor actions of insulin could be altered in favor of a pressor action. Finally, chronic trophic actions of insulin could promote structural vascular changes that contribute to hypertension. However, the current and previous studies suggest that acute physiological increases in plasma insulin do not increase arterial pressure in normotensive or borderline hypertensive humans.

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References

17. Landsberg L: Diet, obesity and hypertension: An hypothesis involving insulin, the sympathetic nervous system, and adaptive thermogenesis. J Med 1986;236:1081-1090
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