Metabolic Consequences of Prolonged Hyperinsulinemia in Humans

Evidence for Induction of Insulin Insensitivity

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SUMMARY

Hyperinsulinemia is frequently associated with a variety of insulin-resistant states and has been implicated causally in the development of insulin resistance. This study examines the metabolic consequences of prolonged hyperinsulinemia in humans. Basally and 1 h after cessation of a 20-h infusion of insulin (0.5 mU · kg^{-1} · min^{-1}, aimed at elevating plasma insulin levels to ~30 mU/L) or normal saline, subjects were assessed for *1*) glucose turnover with 3-[^{3}H]glucose; *2*) insulin sensitivity, as measured by either the euglycemic glucose-clamp technique or the intravenous glucose tolerance test (IVGTT) minimal model method of Bergman; and *3*) monocyte insulin-receptor binding. Hepatic glucose production (Ra) was suppressed by >95% during each euglycemic clamp and during the 20-h insulin infusion. After the insulin infusion, Ra and glucose utilization rate returned to the initial basal level within 1 h, as did insulin levels. At that time, insulin sensitivity was significantly decreased, as measured by the "insulin action" parameter during the 40- to 80-min phase of the clamp (0.049 ± 0.003 vs. 0.035 ± 0.007 min^{-1}, $P < .05$) and during the 80- to 120-min phase (0.047 ± 0.005 vs. 0.039 ± 0.007 min^{-1}, $.05 < P < .1$). The IVGTT minimal model analysis revealed a fall in the rate of glucose disposal (KGTT) (2.8 ± 0.6 vs. 1.9 ± 0.2 min^{-1}, $P < .05$), which was entirely explained by a decrease in insulin sensitivity (SI, 9.4 ± 0.3 vs. 3.8 ± 0.2 min^{-1} · μU^{-1} · ml^{-1}, $P < .02$); there was no change in glucose-mediated glucose disposal (SG, 0.029 ± 0.004 vs. 0.029 ± 0.004 min^{-1}) or pancreatic β-cell responsiveness (φ1, 2.7 ± 0.4 vs. 2.6 ± 0.5 μU · ml^{-1} · min · mg^{-1} · dl^{-1}; φ2, 7.8 ± 2.4 vs. 7.8 ± 2.4 μU · ml^{-1} · min^{-2} · mg^{-1} · dl^{-1}). Monocyte insulin-receptor binding was unaffected by the prolonged hyperinsulinemia.

Our studies indicate that modest sustained hyperinsulinemia may lead to decreased insulin action in the presence of normal monocyte insulin-receptor binding and normal pancreatic insulin secretion. If the monocyte reflects insulin binding in the key insulin-sensitive tissues, this defect in insulin action probably lies at a postreceptor level. DIABETES 1986; 35:1383–89.

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The association of hyperinsulinemia with insulin resistance in several pathological conditions, e.g. obesity,[1,2] type II diabetes,[3,4] cirrhosis,[5] chronic renal disease,[6] and insulinoma,[7,8] is well recognized. It is generally believed that hyperinsulinemia occurs in response to insulin resistance.[4] However, the possibility exists that the reverse may be true; i.e., hyperinsulinemia may be important in the development of insulin resistance. For example, in studies in mice, endogenous hyperinsulinemia precedes the emergence of insulin resistance.[9] Furthermore, a decrease in insulin-receptor binding with diminished glucose transport has been observed in the isolated rat adipocyte after prolonged exogenous hyperinsulinemia.[10,11] In contrast, however, it has recently been demonstrated in rats that prolonged exogenous hyperinsulinemia resulted in increased in vivo and in vitro insulin action.[12] There has been only one study of the effect of prolonged hyperinsulinemia in humans; a relatively small decrease in insulin action was observed.[13]

Because all current forms of insulin therapy in diabetic patients produce peripheral hyperinsulinemia, it is important to determine in humans whether hyperinsulinemia can directly cause impairment of insulin action. Therefore, we have examined in normal subjects the metabolic consequences of prolonged hyperinsulinemia (at levels similar to those observed in insulin-resistant states[2]) employing two different methods for the assessment of insulin action. In addition, glucose turnover and monocyte insulin-receptor binding were determined before and after prolonged hyperinsulinemia. An important aspect of the experimental design was that the acute effects of the experimental hyperinsulinemia

were allowed to decay before formal testing of insulin action was made.

MATERIALS AND METHODS

Subjects and protocol. Studies were carried out on 22 normal nonobese healthy ambulant volunteers [19 men and 3 women, aged 23–39 yr, at 90–110% of ideal body weight (based on Metropolitan Life Insurance Tables)] without a family history of diabetes. Studies were performed with the volunteers' written consent and the approval of the St. Vincent's Hospital Ethics Committee. For 3 days before the study, subjects consumed a diet containing at least 100 g carbohydrate daily. After an overnight fast and at least a 30-min period of recumbency, each subject was assessed for basal levels of insulin sensitivity by either the hyperinsulinemic-euglycemic clamp technique[14] or the intravenous glucose tolerance test (IVGTT) technique with analysis by the minimal model method of Bergman.[15,16] This was followed by a 20-h infusion either of insulin (neutral porcine insulin, Velosulin, Nordisk, Gentofte, Denmark) in 5% hemaccel (1/20 saline dilution of degraded gelatin polypeptide, Hoechst Australia) delivered at a rate of 0.52 mU · kg^{-1} · min^{-1} by an IMED Pump (San Diego, CA) or of 0.9% saline. Thus, four groups of subjects were studied: groups 1 and 2 had paired euglycemic clamps (N = 7) or IVGTT (N = 7), respectively, before and after the insulin infusion; groups 3 and 4 had paired euglycemic clamps (N = 4) or IVGTT (N = 4), respectively, before and after the normal saline infusion. During the insulin infusion, glucose (10 g/100 ml) was infused to maintain euglycemic blood glucose levels over the 20-h period. The glucose infusion rate was adjusted empirically at regular intervals to maintain blood glucose within 10% of the basal levels: groups 1 and 2 received 323 ± 25 and 313 ± 24 g glucose, respectively, during the 20-h insulin infusions. Subjects ingested three meals (total kcal, 2000; 45% carbohydrate) at 1300, 1800, and 2200 h in all studies. In addition, five subjects, who were assessed by the euglycemic clamp technique, had a primed 3-[^{3}H]glucose infusion for determination of glucose turnover basally, during the initial euglycemic clamp on day 1, during the final 2 h of sustained hyperinsulinemia, and during the second euglycemic clamp on day 2. Blood was also collected for monocyte insulin-receptor studies. Blood samples for insulin, glucagon, C-peptide, catecholamines, nonesterified fatty acids, and glucose measurements were taken at regular intervals throughout each study; plasma was separated and stored frozen at −20°C until the time of assay.

Assessment of insulin action and glucose turnover. Solutions were infused via a 20-cm catheter placed in an antecubital vein. For the euglycemic clamp, the method of De Fronzo et al.[17] as modified by Pacini et al.[14] was used. This gives an objective non–operator-biased estimate of glucose infusion requirements, which is equivalent to net glucose disposal (mg · kg^{-1} · min^{-1}) and an estimate of insulin action that is independent of the ambient glucose level.[14] Insulin was infused for the clamp studies at a rate of 1 mU · kg^{-1} · min^{-1}, and blood samples were obtained at 10-min intervals for estimation of glucose infusion requirements.

For the IVGTT, a 300-mg/kg body wt glucose load was given over 1 min; blood samples for glucose and insulin were collected at the following times: −20, −10, −1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 25, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 140, 160, and 180 min. Glucose turnover was measured with 3-[^{3}H]glucose. After a loading dose of 15 μCi, 3-[^{3}H]glucose was infused at a rate of 9 μCi/h to achieve steady state as previously described.[5]

Analytic methods and statistical analyses. Plasma glucose was measured with an automatic analyzer (Yellow Springs, Yellow Springs, OH) by a glucose oxidase method. Plasma insulin and glucagon were estimated by radioimmunoassay with dextran-charcoal separation of bound and free fractions.[18,19] C-peptide was assayed by the Novo C-peptide radioimmunoassay kit (Novo, Copenhagen, Denmark) with synthetic human C-peptide and guinea pig anti–human C-peptide antiserum, as previously described.[20] Nonesterified fatty acids (NEFA) were measured with a modification of the method of Carruthers and Young.[21] Catecholamines were measured by radioenzymatic techniques with the Upjohn kit (Kalamazoo, MI).[22] The relevant plasma samples from the 3-[^{3}H]glucose studies were processed as previously described.[5] Endogenous glucose production was calculated at steady state by subtracting the exogenous glucose infusion rate from the isotopically determined total glucose appearance rate.[23] Binding of ^{125}I-labeled insulin to human monocytes was measured with the Ficoll-Hypaque method of Boyum.[24,25] Statistical analyses were made with the paired and unpaired Student's t test. All data are expressed as means ± SE. Modeling of IVGTT data was by a modification of the method of Bergman et al.,[15] with the simulation program SAAM[26] in which paired data are compared to reduce the error estimate.

TABLE 1
Glucose disposal and insulin action[14] as measured by hyperinsulinemic-euglycemic clamp

	Hyperinsulinemia study (N = 7)		Normal saline study (N = 4)	
	Day 1	Day 2	Day 1	Day 2
Glucose disposal (mg · kg^{-1} · min^{-1})				
40–80 min	6.9 ± 0.4	5.0 ± 1.2	6.4 ± 1.1	5.9 ± 0.9
80–120 min	5.9 ± 0.7	4.8 ± 0.9	7.4 ± 1.5	7.0 ± 1.2
Insulin action (min^{-1})				
40–80 min	0.049 ± 0.003	0.035 ± 0.007*	0.048 ± 0.006	0.044 ± 0.004
80–120 min	0.047 ± 0.005	0.039 ± 0.007	0.054 ± 0.010	0.051 ± 0.006

Measurements were made before (day 1) and after (day 2) 20-h infusion of insulin (0.5 mU · kg^{-1} · min^{-1}) or normal saline. Values are means ± SE.
*P < .05 comparing day 1 and day 2 values.

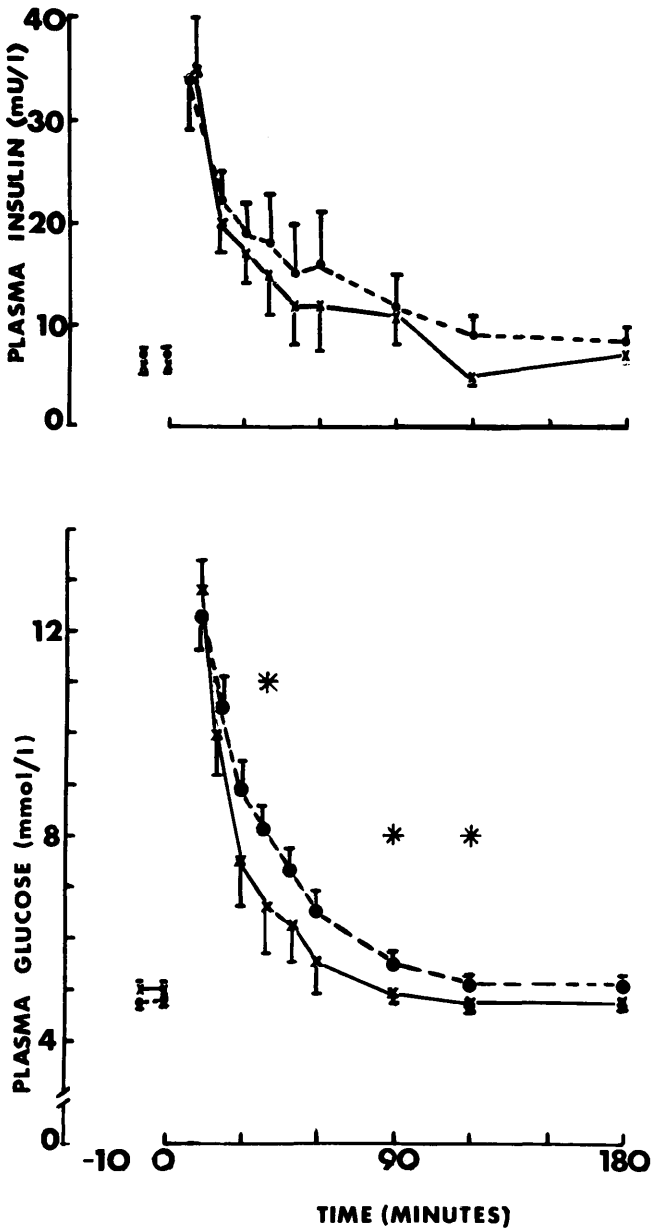

FIG. 1. Plasma insulin (*top*) and glucose (*bottom*) responses to glucose load (300 mg/kg i.v.) basally (*solid line*) and after (*dashed line*) 20-h hyperinsulinemia. *$P < .05$.

RESULTS

During the 20-h period of sustained hyperinsulinemia, plasma glucose was maintained at 5.0 ± 0.3 mM, and plasma insulin was held at 30 ± 4 mU/L. During the 20-h saline control studies, plasma glucose was similar at 5.0 ± 0.2 mM, but plasma insulin was significantly lower at 4 ± 1 mU/L ($P < .003$).

Glucose turnover studies. Basal hepatic glucose production (Ra) was 14.3 ± 1.1 μmol · kg^{-1} · min^{-1} on day 1 and 14.8 ± 1.0 μmol · kg^{-1} · min^{-1} on day 2, 1 h after cessation of sustained hyperinsulinemia, just before commencement of the second euglycemic clamp. Endogenous Ra was markedly suppressed by the end of the 20-h insulin infusion (Ra, 0.9 ± 1.5 μmol · kg^{-1} · min^{-1}). During the matched euglycemic clamps, Ra was suppressed to undetectable levels. Basal glucose utilization rates were 14.3 ± 1.1 μmol · kg^{-1} · min^{-1} on day 1 and had returned to normal (14.8 ± 1.0 μmol · kg^{-1} · min^{-1}) 1 h after cessation of the insulin infusion, before commencement of the second clamp.

Euglycemic clamp studies (groups 1 and 3). Steady-state blood glucose levels were similar during the 40- to 80-min phase for both the first and second euglycemic clamps. Levels were 4.4 ± 0.1 mM [coefficient of variation (C.V.) 7.4 ± 0.9%] vs. 4.5 ± 0.1 mM (C.V., 6.1 ± 1.1%) for hyperinsulinemic studies and 4.3 ± 0.2 mM (C.V., 4.0 ± 1.6%) vs. 4.4 ± 0.2 mM (C.V., 5.2 ± 2.1%) for the saline control studies. During the 80- to 120-min phase, blood glucose levels were also well matched from day 1 to day 2. Levels were 4.6 ± 0.1 mM (C.V., 8.5 ± 1.8%) vs. 4.5 ± 0.1 mM (C.V., 7.1 ± 1.3%) for hyperinsulinemic studies and 4.3 ± 0.2 mM (C.V., 9.7 ± 1.7%) vs. 4.4 ± 0.2 mM (C.V., 6.5 ± 0.5%) for saline control studies. Steady-state plasma insulin levels were 55 ± 9 mU/L during the first clamp vs. 60 ± 8 mU/L during the second clamp for hyperinsulinemic studies, and 56 ± 2 mU/L vs. 54 ± 4 mU/L for saline studies. Sustained hyperinsulinemia resulted in a reduction of glucose disposal by 27% during the 40- to 80-min period of the clamp (6.9 ± 0.4 vs. 5.0 ± 1.2 mg · kg^{-1} · min^{-1}, $P < .1$) and by 19% during the 80- to 120-min period (5.9 ± 0.7 vs. 4.8 ± 0.9 mg · kg^{-1} · min^{-1}, $P < .1$). When these data are expressed by a glucose-level–independent measure of insulin action,[14] a significant fall in glucose disposal of 29% was observed in the 40- to 80-min period of the clamp after sustained hyperinsulinemia (0.049 ± 0.003 vs. 0.035 ± 0.007 min^{-1}, $P < .05$). A smaller change of 19% occurred in the 80- to 120-min period (0.047 ± 0.005 vs. 0.039 ± 0.007 min^{-1}, $P < .1$) (Table 1).

IVGTT studies (groups 2 and 4). The glucose and insulin profiles for the IVGTT studies demonstrate that the glucose levels were significantly higher at 40, 90, and 120 min after prolonged hyperinsulinemia. Despite the higher glucose values on day 2, the corresponding insulin responses were similar for day 1 and day 2 (Fig. 1). Saline control subjects showed no significant difference in either glucose or insulin profiles from day 1 to day 2 (data not shown). Analyses of these data by the minimal model method of Bergman[15] showed that after hyperinsulinemia there were significant decreases of 32% in the rate of glucose disposal (KGTT) (2.7 ± 0.5 vs. 1.9 ± 0.2 min^{-1}, $P < .05$) and of 53% in the insulin sensitivity index (SI, 9.4 ± 2.9 vs. 3.9 ± 0.6 min^{-1} · μU^{-1} · ml^{-1}, $P < .02$) (Fig. 2). There was no change in glucose-mediated glucose disposal (SG, 0.029 ± 0.004 vs. 0.029 ± 0.004 min^{-1}) or β-cell responsiveness (ϕ1, 2.7 ± 0.4 vs. 2.6 ± 0.5 μU · ml^{-1} · min · mg^{-1} · dl^{-1}; ϕ2, 7.8 ± 2.4 vs. 7.8 ± 2.4 μU · ml^{-1} · min^{-2} · mg^{-1} · dl^{-1}).

Saline control studies showed no significant change in any of these parameters between day 1 and day 2: KGTT, 2.1 ± 0.7 vs. 1.8 ± 0.5 min^{-1}; SI, 8.7 ± 2.3 vs. 8.2 ± 2.0 min^{-1} · μU^{-1} · ml^{-1}; SG, 0.020 ± 0.004 vs. 0.017 ± 0.004 min^{-1}; ϕ1, 2.6 ± 0.7 vs. 2.3 ± 0.7 μU · ml^{-1} · min · mg^{-1} · dl^{-1}; and ϕ2, 22.0 ± 17.0 vs. 14.9 ± 9.9 μU · ml^{-1} · min^{-2} · mg^{-1} · dl^{-1}.

Monocyte insulin-receptor studies. There was no significant difference in monocyte insulin-receptor binding characteristics between day 1 and day 2 in the hyperinsulinemia study (Fig. 3). Binding at tracer concentrations was 2.7 ±

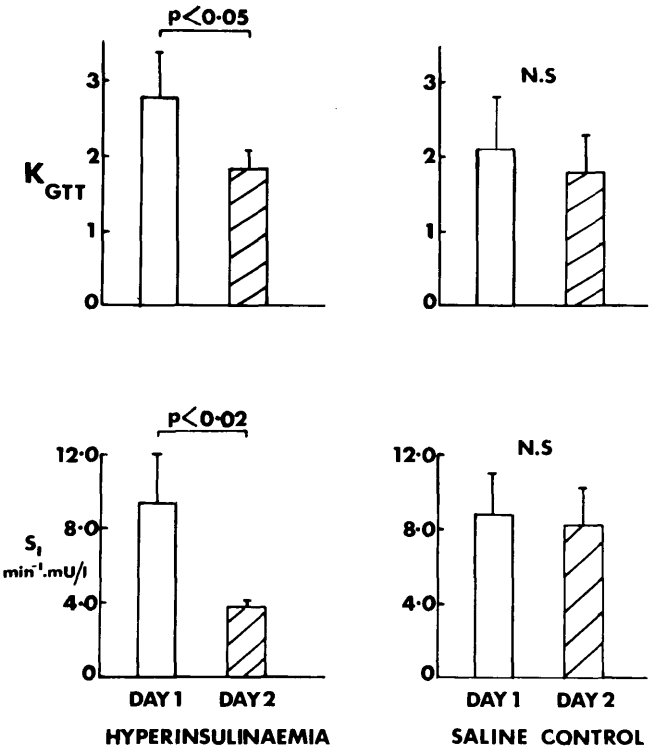

FIG. 2. K_{GTT} (*top*) and insulin sensitivity index (SI; *bottom*) values in subjects after 20 h hyperinsulinemia (*N* = 7) and saline (*N* = 4).

0.3% on day 1 and 2.2 ± 0.3% on day 2. Insulin concentration at half-maximum binding was 2.8 ± 0.4 ng/ml on day 1 and 2.8 ± 0.3 ng/ml on day 2.

Hormones and metabolites. The results for C-peptide, glucagon, NEFA, and catecholamines are shown in Table 2. C-peptide was reduced during the first clamp and tended to be lower during sustained hyperinsulinemia. C-peptide had not returned to the basal level of day 1 at the start of the second clamp but was suppressed during the second clamp. Glucagon tended to be suppressed during both clamps, and there was no difference between day 1 and day 2 basal levels. NEFA were significantly suppressed during the first clamp ($P < .02$) and remained low during sustained hyperinsulinemia. NEFA were also suppressed during the second clamp, without significant difference between day 1 and day 2 basal levels. Epinephrine levels did not change significantly throughout the study. Norepinephrine tended to rise during both clamps, with no significant difference between day 1 and day 2 basal levels.

DISCUSSION

This study demonstrates that 20 h of sustained exogenous hyperinsulinemia at levels matching those observed in insulin-resistant states[1,2,3] leads to a decrease in insulin action, as measured by two separate techniques. Thus, with the glucose clamp method,[14,17] a 20–30% fall in glucose disposal occurred, whether this was assessed by calculating the traditional M value[17] or by a glucose-level–independent measure.[14] When the dynamic IVGTT minimal model method was used,[15] the K value fell by ~32% and SI decreased by 53%.

Our data are similar to the only other reported study on the effects of hyperinsulinemia in humans. Rizza and colleagues[13] also found a significant decrease in insulin action, as assessed by the euglycemic clamp method, after a 40-h period of comparable hyperinsulinemia. However, the 10–15% decrease in insulin action observed in that study was smaller than the decrease that we observed. This smaller response may reflect differences in their experimental design: they continued the insulin infusion up to the performance of the clamp study.[13] That is, the priming effect induced by the antecedent insulin infusion may have been different for the two studies and therefore may have influenced the magnitude of the decrease in insulin action observed. During our study, the ongoing effects of the previously infused insulin were permitted to decay before commencing the day 2 study. That a significant deactivation of the insulin action on glucose turnover had occurred within this 1-h period was demonstrated by the fact that both hepatic glucose production and glucose utilization had returned to basal levels at the time of the second insulin sensitivity test.[27] In contrast, NEFA levels in the day 2 study had not returned to those seen on day 1, and this reduction may have theoretically enhanced overall insulin action, thereby masking any trend toward basal hyperglycemia at the time of the day 2 study.[28] However, despite the lower NEFA levels, measured insulin sensitivity was decreased with the euglycemic clamp and IVGTT insulin sensitivity tests.

In this study, two different techniques were used to assess insulin action; the euglycemic clamp[14] and the IVGTT minimal model method.[15,16] Comparable results were obtained with both techniques, although SI from the IVGTT analysis showed a more striking decrease in insulin action. This difference may reflect the fact that the IVGTT tests the dynamic response to endogenous insulin, whereas the euglycemic clamp tests the steady-state response to exogenous insulin and may examine a different aspect of insulin action.[29] In addition, the IVGTT permits assessment of the glucose-dependent fractional glucose disappearance rate (glucose

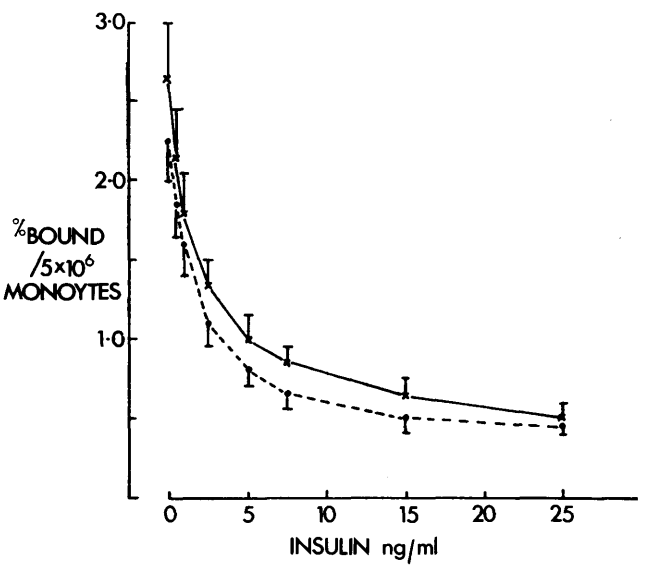

FIG. 3. Insulin binding to monocytes harvested basally (*solid line*) and after 20 h hyperinsulinemia (*dashed line*).

TABLE 2
Hormone and metabolic levels

	Day 1		During 20 h insulin infusion	Day 2	
	Basal	Clamp		Basal	Clamp
C-peptide (nM)	0.26 ± 0.08	0.12 ± 0.08	0.16 ± 0.06	0.18 ± 0.04	0.10 ± 0.02
Glucagon (ng/L)	27 ± 6	14 ± 2	32 ± 9	33 ± 9	22 ± 7
NEFA (mM)	0.78 ± 0.06	0.28 ± 0.02*	0.36 ± 0.02	0.56 ± 0.12	0.28 ± 0.06
Epinephrine (pg/ml)	32 ± 11	33 ± 5		41 ± 12	44 ± 7
Norepinephrine (pg/ml)	302 ± 40	448 ± 101		257 ± 25	317 ± 71

Values are means ± SE.
Clamp values were during hyperinsulinemic-euglycemic clamps.
*$P < .02$ comparing basal and clamp values.

effectiveness) and the magnitude of the pancreatic insulin response.[15,16] In our study, glucose effectiveness was unchanged by prolonged hyperinsulinemia. Similarly, during the day 2 study, basal insulin levels had returned to normal, and dynamic β-cell responsiveness was apparently not reduced after the 20-h hyperinsulinemia, as shown by the similar ϕ1 and ϕ2 values obtained on day 1 and day 2. However, even in the presence of the higher blood glucose levels obtained in the second IVGTT, insulin levels were not significantly elevated after the 20-h insulin infusion. Furthermore, basal C-peptide levels at the time of the second insulin sensitivity tests were somewhat lower compared with the day 1 basal C-peptide levels. Therefore, despite the apparently normal ϕ1 and ϕ2 values, β-cell responsiveness may have been blunted by the prolonged hyperinsulinemia.

Together, the euglycemic clamp and IVGTT data indicate there was a clear decrease of overall glucose tolerance after prolonged hyperinsulinemia. This decrease probably resulted from a decrease of insulin action at the periphery because hepatic glucose production during the paired clamp studies was completely suppressed in the five subjects in whom it was measured. We assume that hepatic glucose production was equally suppressed in all clamp studies after the prolonged hyperinsulinemia and that the site of the decreased insulin action is therefore at the level of muscle. However, if hepatic glucose production was not completely suppressed in all subjects, part of the observed insulin resistance may be at the level of the liver. In addition, because the IVGTT method does not distinguish between hepatic and peripheral insulin action, the IVGTT studies do not localize the site of the insulin resistance observed after the sustained hyperinsulinemia.

The effects of sustained hyperinsulinemia in experimental animals are unclear. Jeanrenaud and co-workers have demonstrated in hyperinsulinemic ventromedial-lesioned *fa/fa* rat models the development of marked in vivo hepatic and peripheral insulin resistance.[30,31] On the other hand, Trimble et al.[12] found increased in vivo insulin action and glucose disposal in rats made hyperinsulinemic by exogenous administration of insulin. Similarly, in vitro metabolic data on adipocytes isolated from hyperinsulinemic rats is conflicting, with reports of both increased[13,32,33] and decreased[10,11,34] responses to insulin. This apparent confusion in the animal studies of insulin action may reflect marked differences in animal models, experimental designs, insulin sensitivity, and metabolic tests employed.

Monocyte insulin-receptor binding was not altered by the 20-h low-dose insulin infusions (plasma insulin, 30 mU/L), which is similar to the findings of Rizza et al.[13] In addition, like these workers,[35] we (unpublished observations) have found normal adipocyte insulin-receptor binding with sustained hyperinsulinemia. In contrast, investigators have observed diminished insulin-receptor binding to monocytes after higher infusion rates of insulin.[36] Similarly, monocyte and adipocyte insulin-receptor binding data in subjects with endogenous hyperinsulinemia and insulin resistance are also conflicting.[25,37–39] The reasons for the variable responses of the insulin receptor to hyperinsulinemia are unclear but may be related to differences in the level of the postreceptor defect.[40]

The relevance of monocyte insulin-receptor binding data to insulin binding in insulin-sensitive target tissues is unresolved.[41,42] Nevertheless, if one assumes that binding of insulin to the monocyte and adipocyte insulin receptor is representative of all insulin-dependent tissues, particularly muscle, it appears that the decreased glucose disposal observed after prolonged low-dose hyperinsulinemia is due to a postbinding defect of insulin action.[2] This hypothesis is supported by the recent finding of Mandarino et al.,[35] who demonstrated a defect in insulin-stimulated glucose transport in adipocytes isolated from individuals infused for 6 h with comparable doses of insulin. However, the explanation for this postbinding decrease in insulin action is not known. [Glucagon and catecholamines were similar in day 1 and day 2 studies and therefore cannot be implicated in the genesis of insulin insensitivity.[43–45]]

During the insulin infusions, glucose was infused throughout each study to avoid hypoglycemia; thus, subjects received >300 g i.v. glucose during the 20-h insulin infusions. In addition, subjects consumed 2000 cal with their three meals and were therefore exposed to a considerable increase in total carbohydrate over this period. We are not able to determine whether the hyperinsulinemia alone or the combined effects of hyperinsulinemia and the increased carbohydrate load led to the overall decrease in insulin action. Without direct data about which intracellular postbinding metabolic pathways are altered by the combined insulin-glucose infusion, it is not possible to postulate the exact mechanisms for the decrease of insulin action obtained here.

In conclusion, our study demonstrates that prolonged modest hyperinsulinemia in humans leads to diminished insulin action in the presence of normal monocyte insulin-re-

ceptor binding and normal pancreatic β-cell function. Given the complexities of the interactions between hyperinsulinemia, insulin-receptor binding, and postbinding intracellular insulin action, it is not now possible to define the site or sites of hyperinsulinemia-induced defects of insulin action. However, current data are consistent with the defect of insulin action being at a postbinding level. Because endogenous hyperinsulinemia is seen in several diseases frequently associated with insulin resistance and is an invariable feature of insulin-treated diabetes,[46,47] our study suggests that in some of these conditions the hyperinsulinemia may contribute to the development of the insulin resistance.

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