Effects of Chronic Beta Receptor Stimulation on Glucose Metabolism

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SUMMARY

The acute administration of a beta receptor-stimulating agent profoundly affects insulin-mediated glucose metabolism; however, little is known about the impact of chronic beta receptor stimulation on glucose metabolism and insulin sensitivity. We therefore investigated the effect of the chronic administration of a beta-2-agonist, terbutaline sulfate (TS), on glucose metabolism in 7 healthy, normal-weight, male volunteers between the ages of 21 and 30 yr. Studies were performed using the euglycemic, hyperinsulinemic (1.0 mU/min · kg) clamp technique before and after the oral administration of 5 mg of TS three times a day for 1 and 2 wk. Basal endogenous glucose production (EGP) (2.54 ± 0.11 versus 2.64 ± 0.14 mg/min · kg) and basal glucose oxidation (1.87 ± 0.16 versus 2.0 ± 0.2 mg/min · kg) were unchanged by the chronic administration of TS. However, insulin-stimulated total glucose metabolism increased by 29% (7.0 ± 0.47 versus 9.05 ± 0.67 mg/min · kg; $P < 0.02$). Insulin-stimulated, nonoxidative glucose disposal increased by 45% (3.62 ± 0.42 versus 5.26 ± 0.48 mg/min · kg; $P < 0.01$), while insulin-stimulated glucose oxidation did not change significantly (3.38 ± 0.15 versus 3.79 ± 0.22 mg/min · kg). EGP was completely suppressed under both conditions. Mean basal plasma insulin concentration (41 ± 9 versus 49 ± 15 pmol/L) and insulin clearance during the clamp procedure was unchanged (477 ± 45 versus 474 ± 37 ml/min · m²). We conclude that chronic beta receptor stimulation with TS improves insulin-stimulated glucose disposal in man, mostly by improving nonoxidative glucose disposal, i.e., "glucose storage." Mechanisms explaining these findings have not yet been elucidated. We suggest that an adaptive response of the sympathetic nervous system plays a role in this phenomenon. DIABETES 1984; 33:1144–49.

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The acute administration of a beta receptor-stimulating agent has a profound effect on glucose metabolism. Plasma glucose concentrations are increased by the administration of isoproterenol and the more selective beta-2-agonists terbutaline and salbutamol.[1-6] Despite concomitant increases in plasma insulin concentrations,[2-6] however, endogenous glucose production is increased.[5] This probably results from the stimulation of gluconeogenesis[7] as well as glycogenolysis by these drugs. Total glucose disposal is also increased,[5] although to a smaller degree than expected when considering the levels of hyperglycemia and hyperinsulinemia induced. These observations and the fact that the inhibitory effect of epinephrine on glucose uptake in man can be reversed by a beta blocking agent[8,9] suggest that the acute administration of a beta agonist has an inhibitory effect on peripheral glucose uptake and metabolism.

Despite widespread use of beta-adrenergic agents in the therapy of asthma, the effects of more prolonged or chronic administration of beta receptor-stimulating agents on glucose and insulin metabolism have not been carefully studied. Fasting concentrations of plasma glucose in patients with asthma treated with beta agonists are reported to be unchanged after 6 wk[10] or 30 mo[11,12] of therapy. It is established that tolerance or development of reduced sensitivity to beta receptor stimulation follows the chronic administration of beta agonists.[13,14] Biochemical and metabolic responses to an acute challenge with beta receptor-stimulating agents, such as generation of cyclic AMP,[15-19] secretion of insulin, and production of glucose and free fatty acids[17,20] are blunted after chronic administration of these drugs. Beta receptor numbers on polymorphonuclear leukocytes[20] and lymphocytes[19] are decreased after adrenergic therapy. These adaptive mechanisms might be expected to preclude

any long-term effects of repeated beta receptor stimulation on glucose metabolism. In the present study, we have investigated the effects of chronically administered terbutaline sulfate (TS), a beta-2-agonist, on glucose metabolism and insulin sensitivity using the euglycemic, hyperinsulinemic clamp technique. Unexpectedly, we found improved, rather than worsened, insulin-mediated glucose disposal.

MATERIALS AND METHODS

Subjects (Table 1). Seven healthy male volunteers between the ages of 21 and 30 yr (mean ± SEM, 25 ± 1) were studied (Table 1). Their mean weight and height were 69.8 ± 3.0 kg and 179 ± 2.5 cm, respectively. Their ideal body weight (based on medium-frame individuals from the Metropolitan Life Insurance Tables, 1959) ranged from 90 to 114% (101 ± 3%), and body fat (as estimated by underwater weighing[21]) ranged from 5 to 20% (11 ± 2%). All subjects were at a stable weight over several months before study with an average caloric intake of 10,200 kJ/day, as estimated by food records. Except for one individual, the carbohydrate content of the diet averaged at least 250 g/day. No subject had a family history of diabetes mellitus and none took other medications during the study. The subjects were encouraged to continue their usual eating habits and routine physical exercise throughout the study with the exception that exercise was precluded for at least 36 h before testing. The protocol was approved by the Committee on Human Experimentation for the Medical Sciences of the University of Vermont, the nature and potential risks of the study were carefully explained to all volunteers, and informed consent was obtained. The subjects were accustomed to the ventilated hood, indirect calorimetry system before the studies were performed.

Experimental protocol. All studies were begun between 6:00 and 6:30 a.m. The subjects fasted from 8 p.m. and slept the night before in the same room in the Clinical Research Center where the studies were performed. An indwelling catheter was placed in an antecubital vein for infusion of ^{3}H-3-glucose (New England Nuclear, Boston, Massachusetts), 20% glucose (Abbott, North Chicago, Illinois), and crystalline porcine insulin (Iletin II, Eli Lilly and Company, Indianapolis, Indiana). A second catheter was inserted in a dorsal hand or wrist vein of the other arm. The hand was kept in a heated box (70°C) to achieve arterialization of the blood samples.[22] A euglycemic, hyperinsulinemic clamp with measurements of endogenous glucose production in combination with measurements of energy expenditure by indirect calorimetry (as described below) was then conducted. Two days after these baseline studies, the subjects began taking terbutaline sulfate, 2.5 mg orally three times daily the first day, and then 5.0 mg three times daily thereafter with the last tablet taken with supper at 5:00 p.m. the night before the test. The glucose clamps and indirect calorimetry were then repeated after 1 wk of taking the drug in 3 subjects and after 2 wk in the other 4 volunteers. The results did not differ between these groups and are, therefore, presented together. In subject no. 1, the sequence of testing was reversed such that the clamp after chronic beta receptor stimulation was done first with the baseline clamp performed after a "washout" period of terbutaline for 3 wk.

Euglycemic clamp. The euglycemic clamp was performed as described by DeFronzo et al.[23] A primed, continuous infusion of insulin (40 mU/min/m^2) was administered to acutely raise and maintain the serum insulin concentration at approximately 680 pmol/L. The plasma glucose concentration was maintained constant at approximately 5.0 mmol/L by determining plasma glucose every 5 min and periodically adjusting the rate of infusion of a 20% glucose solution based on a negative-feedback principle.[24] Each glucose clamp lasted for 120 min. Although it is well documented[25–28] that endogenous glucose production in healthy, normal-weight men is almost completely suppressed during this procedure, we studied endogenous glucose production (EGP) in 3 of the volunteers to determine whether this was also the case after the chronic administration of terbutaline. After the catheters were placed, ^{3}H-3-glucose was administered as a priming (25 μCi) plus continuous (0.25 μCi/min) infusion. The glucose clamps were started 2.5 h later and infusion of labeled glucose was continued at the same rate. Arterialized plasma samples for determining glucose specific activity were obtained every 5–15 min over the last 45 min of the baseline period and every 10–15 min throughout the glucose clamp.

Indirect calorimetry. Energy expenditure during the last hour of the baseline period and throughout the clamp procedure was measured using a computerized, open-circuit, indirect calorimeter. A transparent, ventilated hood was placed over the subject's head and secured around the neck. The airflow through the hood was measured using a pneumotachograph (Vertek, Burlington, Vermont) attached to a Fleisch flow transducer. A sample of the expired air was physically dried by condensation at 2–4°C and continuously analyzed for oxygen using a zirconium fuel cell O_2 analyzer (Applied Electrochemistry, Sunnyvale, California) and for

TABLE 1
Subject characteristics

Subject	Age (yr)	Height (cm)	Weight (kg)	Body fat (%)	Fat-free mass (kg)
1	28	166	57.4	5.0	54.5
2	21	177	60.8	10.3	54.6
3	21	184	77.2	12.1	67.9
4	30	178	75.7	19.9	60.6
5	28	185	69.5	8.1	63.9
6	24	184	71.4	5.5	67.5
7	25	176	76.4	13.8	65.9
Mean ± SEM	25 ± 1	179 ± 2.5	69.8 ± 3.0	10.7 ± 2.0	62.1 ± 2.2

carbon dioxide by an infrared CO_2 analyzer (Applied Electrochemistry). The analyzers were calibrated before and after the procedure using room air and 1% CO_2 and 20% O_2 standard calibrated gases. The air flow and the fractions of O_2 and CO_2 in the outflowing air were recorded each second as an electrical output on a Hewlett Packard 85 computer using an analogue-digital converter interface. Every 5 min, the average fraction of O_2, CO_2, airflow measured and corrected for STP conditions, the oxygen uptake, and the respiratory quotient were automatically printed. Corrections for the reading drifts of the analyzers were made at the end of the tests. The nonprotein-respiratory quotient was then calculated from the calorimetric values and the urinary urea nitrogen production rates. The oxidation rates of carbohydrate and lipid were calculated according to the tables of Lusk.[29] The quantity of the urinary urea nitrogen excreted during the test was used as an index of protein oxidation assuming that the latter is constant (1 g nitrogen = 6.25 g protein).

Analytic procedure. Plasma glucose concentrations were determined in duplicate by the glucose-oxidase method using a YSI (Model 23A) glucose analyzer (Yellow Springs Instrument Co., Yellow Springs, Ohio). Plasma immunoreactive insulin was determined by a modification of the radioimmunoassay technique of Starr et al.[30] Epinephrine and norepinephrine were determined by a radioenzymatic assay kit (Upjohn Diagnostics, Kalamazoo, Michigan) in 4 subjects and by an HPLC-EC technique (Bio-Science, Van Nuys, California) in 3 subjects. Plasma samples for ^{3}H-3-glucose determinations were deproteinized by barium-zinc sulfate precipitation. The supernatant was decanted and evaporated to dryness with the vials placed in heated sand. The residue was resuspended in 0.5 ml distilled water and its radioactivity counted after addition of 10 ml Scinti-Verse II (Fischer Scientific Co., Silver Springs, Maryland). T_3, free T_3, and T_4 were measured as previously described.[31] Urinary urea nitrogen was measured using a Technicon (Tarrytown, New York) autoanalyzer.

Data analysis. The glucose infusion rates during the glucose clamp were calculated at 20-min intervals. The data are presented as the mean of the two 20-min intervals from 80 to 120 min, which did not differ significantly from each other. The total glucose uptake of the body equals the sum of the glucose infusion rate and the endogenous glucose production. Since, in our subjects, endogenous glucose production was completely suppressed during the hyperinsulinemic clamp, the total rate of glucose disposal (M-value) equals the rate of exogenous glucose administration. The glucose oxidation rates were calculated from the calorimetric measurements over 5-min intervals. Oxidation rates during the last 45 min of baseline measurements were compared with the values obtained during the last 40 min of the clamp. Nonoxidative glucose disposal was calculated by subtracting the carbohydrate oxidation rate from the M-value.

Steady-state plasma insulin concentrations are expressed as the mean of the values obtained during the last 40 min of the clamp. For the steady-state plasma glucose concentrations, we used the values of the last hour of the clamp. The metabolic clearance rate for insulin (MCR) was calculated as a ratio of the insulin infusion rate over the insulin concentration above baseline during the clamp. Since we did not apply corrections for changes in endogenous insulin production during the hyperinsulinemic state, the values for the MCR may be somewhat overestimated.[23] We further assumed that the insulin infusion had approximately the same effect on endogenous insulin production before and after administration of terbutaline, and that the distribution space for insulin remained unchanged by the drug. Basal endogenous glucose production was calculated by dividing the tritiated glucose infusion rate by the steady-state plateau of tritiated glucose specific activity achieved during the last 45 min before the clamp. Since a non-steady-state condition exists during the glucose clamp, endogenous glucose production during the clamp was determined by Steele's equations in their derivative form,[32] assuming a distribution volume of glucose of 40 ml/kg body wt.[33] The endogenous glucose production was then estimated as the difference between the isotopically derived glucose appearance rate and the exogenously infused glucose. All data are reported as the mean ± SEM. Statistical comparisons were performed by paired *t*-test. Coefficients of variation were determined by standard formulae.

RESULTS

Plasma glucose and insulin (Table 2). The fasting plasma glucose concentrations (5.3 ± 0.1 mmol/L) remained unchanged after administration of terbutaline (5.3 ± 0.2 mmol/L). During the last 60 min of the clamp, the steady-state

TABLE 2
Fasting plasma glucose and insulin and steady-state (SS) plasma glucose and insulin concentrations during the euglycemic-hyperinsulinemic clamp, and metabolic clearance rate (MCR) of insulin before and during treatment with terbutaline

	Fasting glucose (mmol/L)		Fasting insulin (pmol/L)		SS glucose (mmol/L)		SS insulin (pmol/L)		MCR insulin (ml/min · m²)	
Subject	Before	During	Before	During	Before	During	Before	During	Before	During
1	5.3	5.2	33.0	17.5	4.9	4.9	512	516	600	577
2	6.0	6.0	76.0	103.0	4.9	4.9	762	681	418	496
3	5.1	5.3	58.0	111.0	4.9	4.8	684	868	458	379
4	5.2	5.0	22.5	17.5	4.9	4.9	580	496	515	601
5	5.4	5.7	20.5	32.5	5.0	5.0	459	597	655	509
6	5.1	5.3	17.5	17.5	4.9	5.0	819	710	358	415
7	4.9	4.7	58.0	41.0	4.9	4.8	907	884	338	340
Mean ± SEM	5.3 ± 0.1	5.3 ± 0.2	41 ± 9	49 ± 15	4.9 ± 0	4.9 ± 0	675 ± 63	679 ± 59	477 ± 45	474 ± 37
P (before vs. during)	NS		NS		NS		NS		NS	

plasma glucose concentrations were 4.9 mmol/L on both occasions, with coefficients of variation both times of 3.0%. The fasting plasma insulin concentrations (41 ± 9 pmol/L) were not significantly changed after terbutaline (49 ± 15 pmol/L). The plasma insulin concentrations achieved during the baseline clamp (675 ± 63 pmol/L) were also the same as after chronic beta receptor stimulation (679 ± 59 pmol/L).

Glucose metabolism (Table 3). Basal endogenous glucose production (2.54 ± 0.11 versus 2.64 ± 0.14 mg/min · kg) and basal glucose oxidation (1.87 ± 0.16 versus 2.0 ± 0.2 mg/min · kg) were unchanged by the administration of terbutaline. During the clamp, the rate of glucose infusion to maintain euglycemia and, hence, total glucose disposal during the insulin infusions increased by 29% from 7.0 ± 0.47 to 9.05 ± 0.67 mg/min · kg ($P < 0.02$) after terbutaline (Figure 1). Endogenous glucose production was completely suppressed during both clamps. Insulin-stimulated nonoxidative glucose disposal increased by 45% from 3.62 ± 0.42 to 5.26 ± 0.48 mg/min · kg ($P < 0.01$), while insulin-stimulated glucose oxidation did not change significantly and averaged 3.38 ± 0.15 mg/min · kg before terbutaline and 3.79 ± 0.22 mg/min · kg after chronic beta receptor stimulation (Table 3). The increase over baseline in glucose oxidation during the last 40 min of the clamp, therefore, was not changed by terbutaline (1.52 ± 0.09 versus 1.8 ± 0.1 mg/min · kg). Before administration of terbutaline, 49% of the administered glucose was oxidized and 51% disposed of in a nonoxidative manner. The corresponding values after chronic beta receptor stimulation were 42% and 58%, respectively. The respiratory quotients (RQ) during the resting period before the glucose clamp were 0.85 ± 0.08 before, and 0.848 ± 0.12 after administration of terbutaline. The RQs during the last 40 min of the clamp (0.939 ± 0.06 versus 0.947 ± 0.08) and, hence, the insulin/glucose-induced increase of the RQs (0.089 ± 0.007 versus 0.099 ± 0.006) remained unchanged as well.

Energy expenditure. Basal resting metabolic rate was 4.989 ± 0.11 kJ/min before terbutaline and increased by 7.7% to 5.372 ± 0.148 kJ/min ($P < 0.01$) after chronic beta receptor stimulation. The corresponding values during the last 40 min of the clamp were 5.413 ± 0.12 and 5.858 ± 0.182 kJ/min ($P < 0.01$). Energy expenditure during the clamp, therefore, increased by 0.424 ± 0.027 kJ/min before and by 0.485 ± 0.072 kJ/min after terbutaline administration, respectively (P = NS).

Insulin clearance (Table 2). The metabolic clearance rate of insulin (477 ± 45 ml/min · m^2) was not changed by the administration of terbutaline (474 ± 37 ml/min · m^2). Expressed as a function of body weight, these same values were 13.0 ± 1.3 versus 12.7 ± 1.0 ml/min · kg. There was a significant inverse correlation between the M-value and the MCR of insulin ($r = 0.812$; $P < 0.025$), in agreement with the hypothesis that the processes of insulin action and degradation may be linked.[34] This correlation was still observed after beta receptor stimulation ($r = 0.755$; $P < 0.025$).

Epinephrine, norepinephrine, and thyroid hormones. Mean basal plasma concentrations of norepinephrine were 187 ± 27 pg/ml before and 136 ± 19 pg/ml after chronic beta receptor stimulation (P = NS). The values after 90 and 120 min of insulin/glucose infusions were 198 ± 38 and 195 ± 40 pg/ml, respectively, before and 186 ± 28 and 174 ± 30 pg/ml after administration of terbutaline sulfate. The mean increase in norepinephrine concentrations during the clamp, therefore, was at 90 min, 11 ± 20 pg/ml and 50 ± 28 pg/ml, and at 120 min, 8 ± 20 and 39 ± 28 pg/ml before and after chronic beta receptor stimulation, respectively. These changes were not significant. The plasma concentrations of epinephrine before and after chronic terbutaline treatment were 51 ± 14 and 30 ± 5 pg/ml before the clamp, 60 ± 31 and 59 ± 28 pg/ml after 90 min, and 63 ± 21 and 61 ± 18 pg/ml after 120 min of the glucose/insulin infusions, respectively. The values were not different for the two study periods.

The serum concentrations of thyroid hormones before and after prolonged administration of terbutaline were: 148 ± 10 versus 169 ± 13 ng/dl ($P < 0.05$) for T_3, 7.9 ± 0.6 versus 7.4 ± 0.6 μg/dl (P = NS) for T_4, and 354 ± 12 versus 400 ± 22 pg/dl ($P < 0.05$) for free T_3.

DISCUSSION

After chronic administration of terbutaline sulfate, a beta-2-agonist, normal subjects were studied using the euglycemic hyperinsulinemic clamp technique. There was a 45% increase in nonoxidative glucose disposal and a 29% increase in total glucose disposal. This finding is not related to percent body fat of the subjects, their lean body mass, or their physical activity. Results from this study suggest, but do not establish, possible mechanisms for the improved glucose metabolism.

To explain this observation, four major sites of action of chronic beta receptor stimulation on glucose metabolism must be considered: hormonal, pancreatic, hepatic, and pe-

TABLE 3
Glucose disposal (mg/min · kg) during the euglycemic-hyperinsulinemic clamp before and during treatment with terbutaline

	Total oxidative disposal		Total nonoxidative disposal		Total disposal	
Subject	Before	During	Before	During	Before	During
1	4.08	4.29	5.16	6.41	9.23	10.7
2	3.77	3.84	2.3	4.22	6.08	8.06
3	2.98	3.17	3.95	3.66	6.93	6.83
4	3.28	3.69	4.18	6.24	7.46	9.93
5	3.22	4.58	4.35	6.86	7.56	11.43
6	3.21	4.02	2.21	5.24	5.42	9.26
7	3.15	2.97	3.19	4.2	6.35	7.17
Mean ± SEM	3.38 ± 0.15	3.79 ± 0.22	3.62 ± 0.42	5.26 ± 0.48	7.0 ± 0.47	9.05 ± 0.67
P (before vs. during)	NS		<0.01		<0.02	

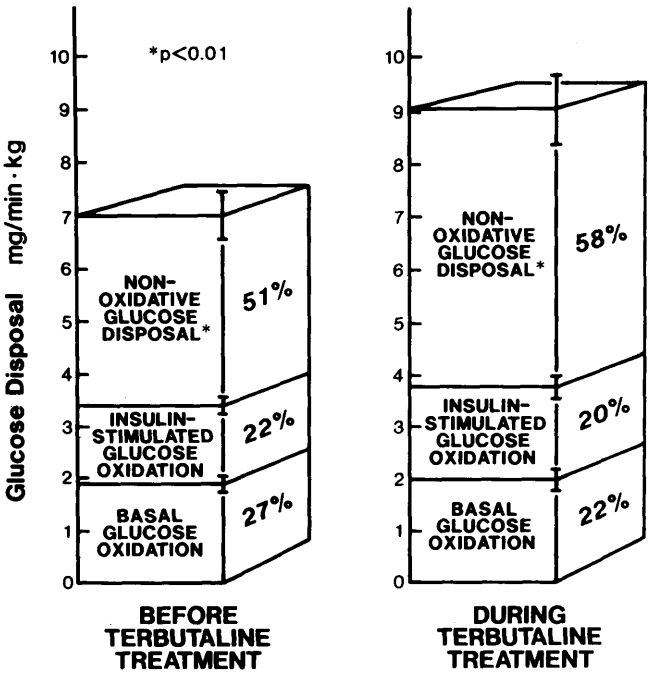

FIGURE 1. Oxidative and nonoxidative disposal (storage) of glucose during a euglycemic-hyperinsulinemic (1 mU/min · kg) clamp before and after the oral administration of terbutaline sulfate, 5 mg three times daily for 1 or 2 wk depicted in mg/min · kg and as percent (%) of total glucose disposal.

ripheral. Plasma concentrations of norepinephrine and epinephrine were unaltered by the prolonged administration of terbutaline in the basal state or after the insulin/glucose infusions. The range of plasma concentrations observed in this study was such that only sympathetic neurotransmitter function and not hormonal action should have occurred.[35] The increases in epinephrine and norepinephrine during the clamp were small. Therefore, no significant change in the anti-insulin effect of these catecholamines was suggested. It may be misleading to compare plasma catecholamine concentrations under the conditions of this study, because desensitization and/or downregulation of beta receptors follows the chronic administration of beta agonists. Indeed, in a separate series of experiments, we have reported that the cardiovascular, metabolic, and thermogenic responses to infusions of isoproterenol are clearly blunted after prolonged administration of terbutaline, thus demonstrating decreased in vivo sensitivity to beta receptor stimulation.[31] It is tempting to speculate that this decreased beta receptor sensitivity might be involved in the increased insulin sensitivity, particularly since it has been shown that intensive physical training, which also reverses insulin resistance,[36,37] leads to decreased numbers of beta receptors.[38] However, we were unable to establish a direct correlation between the changes in M-values and the altered beta receptor responsiveness.

Prolonged administration of terbutaline was associated with an increase in the serum concentrations of triiodothyronine (T_3) and free T_3, while thyroxine (T_4) concentrations tended to fall. Perhaps the most important observation was an increase in the T_3/T_4 ratio. There is evidence in the literature that T_3 improves glucose transport into cells.[39,40] However, the measured changes were small and we were unable to find a correlation with the improved glucose metabolism among the subjects. The exact mechanisms involved in the alterations of glucose metabolism by thyroid hormones are still poorly understood.[41-43]

There was no increase in the concentrations of plasma insulin or change in insulin clearance after chronic beta receptor stimulation. Therefore, increased secretion of insulin could not account for the increased glucose disposal.

The major part of the glucose infused during a euglycemic hyperinsulinemic clamp appears to be taken up in the periphery, primarily muscle.[27,44] Adipose tissue is responsible for the disposal of less than 2% of an oral or i.v. glucose load[45] and the direct uptake of glucose by the liver is small.[26,27,46] The glucose taken up by the muscle is either oxidized, stored as glycogen, or converted to three-carbon compounds. Whether the inhibitory effect of hyperinsulinemia on recycling[47] was reversed and, therefore, recycling was enhanced by chronic administration of beta agonists is an important issue. Equally important is the question of whether a change in the amount of glucose that was taken up directly by the liver could have occurred.

By combining the clamp technique with the measurement of metabolic rate by indirect calorimetry, it is possible to differentiate between oxidative and nonoxidative glucose disposal.[48] These measurements have their limitations[49] in non-steady-state conditions and, therefore, results of gaseous exchange should be interpreted cautiously. However, all the available evidence suggests that the changes in glucose metabolism that followed chronic beta receptor stimulation were primarily the result of increased nonoxidative glucose disposal. Since respiratory quotients over 1.0 were not observed during the clamps, no net lipogenesis occurred that could have led to the calculation of falsely high rates of carbohydrate oxidation. In addition, net glucose production (and probably gluconeogenesis) did not occur during any of the clamps, as estimated by the difference between the rate of glucose infusion and the isotopically measured rate of its appearance. Finally, even with the very unlikely assumption that after chronic beta receptor stimulation all of the glucose oxidized during the baseline period came from gluconeogenesis instead of glycolysis, the corrected glucose oxidation rates then could still not explain the entire increase in glucose disposal observed after terbutaline.

In summary, we have assessed glucose metabolism by using the euglycemic hyperinsulinemic clamp technique and found that chronic beta receptor stimulation with terbutaline sulfate improves glucose metabolism, primarily as a result of increased nonoxidative glucose disposal. Although we can eliminate several possible mechanisms, we cannot yet offer a precise explanation for these findings. If decreased beta receptor sensitivity is indeed a responsible factor in altering insulin sensitivity, as we suggest, this study could have an important impact on our understanding of the mechanisms of insulin resistance and non-insulin-dependent diabetes mellitus. The relevance of these observations on the future treatment of type II diabetes is also worth further investigation.

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