Mental Stress Increases Glucose Uptake During Hyperinsulinemia: Associations With Sympathetic and Cardiovascular Responsiveness

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Infusion of epinephrine and norepinephrine reduces insulin-mediated glucose disposal, ie, induces insulin resistance. Mental stress increases concentrations of both plasma catecholamines. However, the effect of acute mental stress on insulin-mediated glucose uptake has not been examined. We observed in pilot studies that a mental stress test (MST) during a euglycemic glucose clamp decreased blood glucose concentration. In a prospective study, euglycemic hyperinsulinemia was established during 120 minutes of glucose clamping; the subjects (N = 74) then underwent 5 minutes of intense mental arithmetics with infusion rates of glucose and insulin kept constant. During MST, plasma epinephrine and norepinephrine increased (by 0.23 ± 0.02 and 0.50 ± 0.05 nmol/L) together with blood pressure ([BP] by 18 ± 8/9 ± 1 mm Hg) and heart rate ([HR] by 21 ± 1 beats per minute), with *P* less than .0001 for all changes. During mental stress, blood glucose concentration decreased by 0.4 ± 0.1 mmol/L (*P* < 0.0001), followed by full recovery after another 10 minutes. Serum insulin was unchanged, indicating an acute but transient increase in glucose uptake. This finding was unrelated to age, sex, body mass, and BP status. Fifty-nine subjects with a decrease in glucose concentrations during MST were characterized by accentuated epinephrine response to MST (a change of 0.25 ± 0.03 *v* 0.12 ± 0.02 nmol/L, *P* = .001), increase in systolic BP (by 20 ± 2 *v* 10 ± 3 mm Hg, *P* = .008), and increase in HR (by 23 ± 2 *v* 15 ± 2 beats per minute, *P* = .008) as compared with 15 subjects with unchanged/increased glucose concentration. Thus, when mental stress is applied while insulin-mediated glucose uptake is already stimulated, sympathetic overactivity is initially accompanied by increased glucose uptake. This finding is unexpected and cannot be fully explained. The increase in skeletal muscle blood flow during mental stress, with increased substrate delivery to the metabolically active muscle cells, or other unknown interactions between insulin and the sympathetic nervous system (SNS) may explain the observation.

INSULIN RESISTANCE is a well-established feature of essential hypertension,[1-4] but the mechanism behind the association remains unknown. The relationship between hypertension and insulin resistance may not be causal, but may reflect involvement of other mechanisms, ie, increased sympathetic nervous system (SNS) activity.[5,6] Increased SNS activity has been identified repeatedly in essential hypertension,[7-9] in which high levels of plasma catecholamines are associated with high blood pressure (BP) and heart rate (HR). In infusion studies, epinephrine can acutely reduce insulin sensitivity.[10,11] Norepinephrine has similar but less powerful effects.[12] Furthermore, when SNS activity is physiologically increased, insulin sensitivity is acutely decreased.[13]

There have been some studies of the effect of acute mental stress on blood glucose concentration in type I and II diabetics, and unchanged,[14] decreased,[15] and increased[16,17] blood glucose levels have been reported. We are aware of only four studies on healthy subjects.[18-21] Two of the studies on diabetics have included healthy control groups,[14,17] and all[14,17,18-21] report unchanged glucose concentrations after mental stress. However, these studies were typically small (<10 subjects) and glucose concentrations were usually determined after ≥30 minutes of stress.

In pilot studies, we applied mental stress during euglycemic glucose clamp examinations, and observed an unexpected decrease in glucose concentration. The glucose clamp technique measures insulin-mediated glucose uptake and creates stable exogenous hyperinsulinemia with suppression of endogenous insulin production.[22] This allows the study of physiologic increases in epinephrine, eliminating a possible epinephrine-mediated suppression of pancreatic insulin release. We examined the effect of mental stress in a prospective study. Thus, 74 normotensive and hypertensive subjects undertook a strictly standardized mental arithmetic challenge test after 120 minutes of a glucose clamp.

SUBJECTS AND METHODS

We studied two groups: young men aged 21 years (n = 48) screened at the medical examination during the military draft procedure and women aged 44 to 46 years (n = 26) recruited from the ongoing screening of all 40-year-old women in Oslo. On reexamination, 40 men had baseline laboratory BP less than 140/90 mm Hg and eight had systolic BP between 140 and 160 and diastolic BP less than 90. The women had undergone medical examination in a previous study.[23] They were either hypertensive (BP, 149 ± 5/99 ± 2 mm Hg; n = 14) or normotensive (BP, 128 ± 4/81 ± 2; n = 12). All subjects underwent physical examination, blood biochemistry analysis including renal and liver function tests, and urinalysis to exclude illness. All were healthy, and none regularly used medication. The study was approved by the Regional Ethics Committee, and informed consent was obtained from each subject.

The euglycemic-hyperinsulinemic glucose clamp was performed using a modification of the method described by DeFronzo et al,[22] as previously detailed.[24] Insulin was infused at a fixed rate of 1 mU/kg/min. Mean serum insulin concentration during the clamp was 130 ± 4 mU/L. After 120 minutes of the euglycemic glucose clamp, we announced a strictly standardized mental arithmetic stress test ([MST] repeated subtraction of 13 from 1,079 for 5 minutes) while infusions of glucose and insulin were continued at constant rates. BP, HR, and plasma catecholamine levels were measured before and 1 minute after announcement of MST, and at the beginning, middle, and end of MST. Maximal values are

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presented for the different parameters. The total duration of MST was 7 minutes, including 2 minutes of anticipation, in which much of the increase in SNS activity occurs.[25] Serum glucose and insulin levels were measured immediately before and after MST. To control for circumstantial changes during the study procedure, nine subjects underwent the same procedure with saline instead of insulin and glucose infusions.

We used a Reflolux II (Boehringer, Mannheim, Germany) to measure glucose concentration every 5 minutes during the glucose clamp procedure and before and after MST (within-run coefficient of variation, <2%). After the first 30 minutes of glucose clamp, blood glucose concentration had stabilized, and the mean value did not deviate beyond 0.1 mmol/L from the fasting value throughout the clamp. Two different investigators measured these glucose concentrations; one of them was blinded to the purpose of the MST. Insulin level was measured by radioimmunoassay using a specific antibody from Linco Research (St Louis, MO), with an intraassay coefficient of variation less than 9% at all levels. Plasma levels of catecholamines from arterialized venous blood were measured by the radioenzymatic technique of Peuler and Johnson as previously detailed.[9] BP and HR were measured oscillometrically with an Omega 1000 Adult/Pediatric Blood Pressure Recorder (INVIVO Research Laboratories, Tulsa, OK).

Data are presented as the mean ± SEM. Differences were tested by two-tailed Student's *t* test after the data had been checked for normal distribution. *P* less than .05 was considered the limit for statistical significance.

RESULTS

During MST, blood glucose concentration decreased from 4.9 ± 0.1 to 4.5 ± 0.1 mmol/L ($P < .0001$; Fig 1), while serum insulin concentration remained unchanged (133 ± 5 *v* 129 ± 5, $P = .57$). The decrease in glucose was uniform: 59 subjects had a lower glucose concentration after MST, and 15 had higher or unchanged concentrations.

Plasma epinephrine increased from 0.23 ± 0.02 to a maximum of 0.46 ± 0.04 nmol/L ($P < .0001$; Fig 2), and norepinephrine increased from 1.20 ± 0.06 to 1.70 ± 0.08 nmol/L ($P < .0001$). Systolic and diastolic BP also increased from 137 ± 2/74 ± 1 mm Hg to a maximum of 155 ± 2/83 ± 1 ($P < .0001$) during MST, and HR increased from 63 ± 1 to 84 ± 2 beats per minute ($P < .0001$). There were no statistically significant direct relationships between the decrease in serum glucose and the changes in any of these variables.

The decrease in glucose concentration was virtually the same in women (0.3 ± 0.1 mmol/L) and men (0.4 ± 0.1) and in normotensive (0.4 ± 0.1) and mildly hypertensive (0.4 ± 0.2) subjects. The mean body mass index in this study was 23.6 kg/m^2, and the decrease in glucose was identical in groups with higher- and lower-than-average body mass index (0.4 ± 0.1 mmol/L). The two investigators recorded identical changes in glucose concentration (0.4 ± 0.1 mmol/L).

We compared subjects with reduced glucose concentrations after MST (n = 59) with subjects with unchanged or increased glucose concentrations (n = 15). The group with a decrease in glucose had higher plasma catecholamine responses (epinephrine increase, 0.25 ± 0.03 *v* 0.12 ± 0.02 nmol/L, $P = .001$, and norepinephrine 0.52 ± 0.06 *v* 0.39 ± 0.08 nmol/L, $P = .22$; Fig 3) and a higher increase in BP (systolic BP increase, 20 ± 2 *v* 10 ± 3 mm Hg, $P = .008$, and diastolic BP increase, 10 ± 1 *v* 7 ± 2 mm Hg, $P = .19$), as well as HR (23 ± 2 *v* 15 ± 2 beats per minute, $P = .008$).

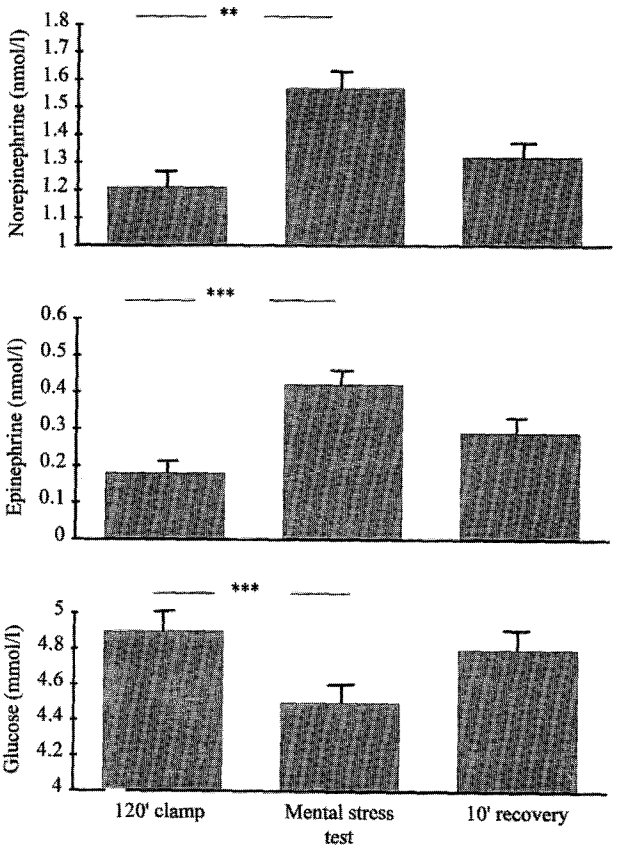

Fig 1. Glucose, epinephrine, and norepinephrine concentrations after 120 minutes of glucose clamp, during MST, and after 10 minutes' recovery. **$P < .01$, ***$P < .001$.

In the time-control group (n = 9), blood glucose tended to increase during MST (4.3 ± 0.1 to 4.5 ± 0.2 mmol/L, $P = .056$). Serum insulin did not change (7 *v* 7 mU/L). Plasma epinephrine increased from 0.18 ± 0.02 to a maximum of 0.42 ± 0.07 nmol/L ($P = .001$), and norepinephrine changed from 1.21 ± 0.12 to 1.57 ± 0.14 nmol/L ($P = .002$). Systolic and diastolic BP also increased from 130 ± 4/72 ± 2 mm Hg to a maximum of 147 ± 3/86 ± 3 ($P < .001$) during MST, and HR increased from 59 ± 2 to 93 ± 5 beats per minute ($P < .001$).

DISCUSSION

The main finding of this study is an increased glucose uptake during hyperinsulinemia plus acute mental stress, even though plasma epinephrine and norepinephrine concentrations increased at the same time. Changes in plasma catecholamines, HR, or BP could not directly account for changes in glucose uptake, and neither could age, sex, body weight, or BP. However, subjects with a decrease in glucose were characterized by sympathetic and cardiovascular hyperreactivity to MST. When the MST was performed without concomitant hyperinsulinemia, blood glucose concentrations tended to increase.

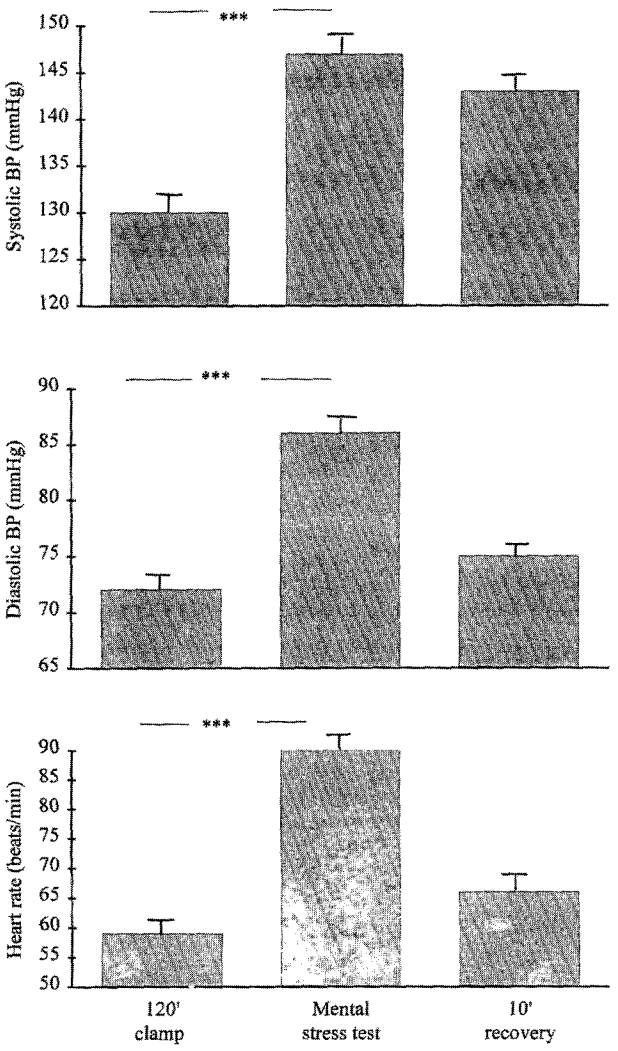

Fig 2. HR and diastolic and systolic BP after 120 minutes of glucose clamp, during MST, and after 10 minutes' recovery. ***$P < .001$.

The euglycemic-hyperinsulinemic glucose clamp technique measures insulin-mediated glucose uptake, ie, insulin sensitivity, as milligrams of glucose metabolized per kilogram body weight and minute. Insulin sensitivity (usually reported as M value or glucose disposal rate) is thus calculated from the mean infusion rate of glucose, typically during the last 20 or 60 minutes of the clamp. We do not report an M value during MST, since 10 minutes is not enough time to allow a new steady-state glucose uptake to occur. Instead, we used the change in glucose concentration as a measure of glucose uptake/insulin sensitivity, ie, our results indicate an increase in insulin sensitivity during acute mental stress.

The uniform decrease in glucose uptake observed in this study was unexpected, since both epinephrine and norepinephrine impair glucose tolerance and induce insulin resistance.[10-12] Glucose intolerance or insulin resistance have been observed during mild viral illness[26] and after surgical stress.[27] Epinephrine infusion stimulates hepatic gluconeogenesis and impairs peripheral insulin-stimulated glucose uptake,[10,11] the latter being the most important. Inhibition of glucose uptake in peripheral tissues is mediated through stimulation of the β-receptor.[28] However, in animals there are experimental data to support the existence of a central parasympathetic pathway that may increase glucose uptake during stress.[29]

The decrease in glucose concentration could be caused by either decreased hepatic glucose production or increased peripheral glucose uptake. Since we did not measure these parameters separately, we cannot exclude a reduction in hepatic glucose production during mental stress. However, we find this explanation unlikely, since the hyperinsulinemic glucose clamp suppresses hepatic glucose production, and the effect of epinephrine (and norepinephrine) is to increase rather than decrease hepatic glucose production.[10-12]

The mental arithmetic challenge test has been used in numerous studies, and effects on both the SNS and the cardiovascular system have been well characterized. A sharp increase in SNS activity is accompanied by an increase in cardiac output, a redistribution of blood flow from viscera to skeletal muscle, and reduced peripheral resistance.[30] As blood flow increases in metabolically active skeletal muscle, so does delivery of insulin and glucose, and this increases glucose uptake.[31-33] Whether this increase is only due to a mass effect of higher glucose delivery or if insulin-mediated glucose uptake is also accelerated remains unknown.

A reverse mechanism for the relationship between epinephrine and glucose changes during stress may also be considered, since a decrease in glucose will stimulate epinephrine release. In a study of glycemic thresholds for counterregulatory systems, epinephrine release increased

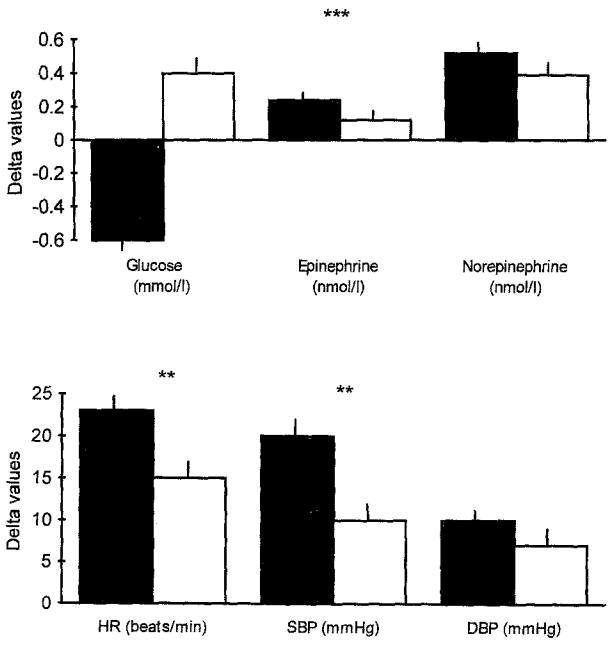

Fig 3. Comparison of groups with increased (■) and decreased/unchanged (□) glucose uptake during MST. SBP, systolic BP; DBP, diastolic BP. **$P < .01$, ***$P < .001$.

when blood glucose concentration was less than 3.8 mmol/L.[34] The mean glucose concentration in our study changed from 4.9 ± 0.1 to 4.5 ± 0.1 mmol/L, and therefore we cannot exclude an effect of relative hypoglycemia on SNS activity. However, we know from this and other studies[35] that subjects' SNS activity increases sharply within seconds after they are informed of a forthcoming stress test, and it seems unlikely that a substantial decrease in glucose concentration could precede this.

Thus, epinephrine seems to have two opposing effects on glucose metabolism in skeletal muscle: by increasing delivery, glucose uptake is facilitated,[31-33] and by impairing cellular uptake itself, net glucose extraction from the circulation may be diminished.[10-13] This may be a sensible physiologic reaction in the "fight or flight" response.[36] This response demands a large increase in blood flow to skeletal muscle, thereby increasing the metabolic demand. It is critical for the organism to maintain euglycemia, since brain function is dependent on a stable glucose supply and tolerates only small variations in blood glucose concentration. The expected decrease in blood glucose concentration when blood flow to skeletal muscle increases may thus be offset by the inhibition of cellular uptake, and a stable blood glucose concentration is maintained.

The brain and heart are the two organs that show the greatest increase in activity during mental stress. In the brain, glucose uptake is regulated by blood glucose concentration and is independent of insulin levels. Since physiologic concentrations of epinephrine do not interfere with this glucose-stimulated uptake,[37] increased cerebral metabolic demands cannot explain the change in overall glucose disposal.[38] At rest, the heart takes only approximately 30% of its nutritional supply from glucose, and during activity this percentage declines as glucose metabolism in the heart is inhibited by increasing lactic acid concentration.[39] During infusion of norepinephrine, there is evidence for decreased rather than increased glycolysis in the heart, together with a greatly increased uptake and oxidation of free fatty acids.[40]

Subjects who showed a decrease in glucose concentration during MST had significantly increased SNS and cardiovascular reactivity to mental stress as compared with the group with unchanged or increased glucose concentration. Although we have no direct measures of peripheral blood flow, this may indicate that this group had an initially larger increase in blood flow to skeletal muscle, explaining the decrease in blood glucose. This is in accordance with the observation that intravenous infusion of epinephrine increases blood flow in the human forearm.[41]

Our period of observation ended after 10 minutes of recovery, at which time blood glucose concentration was normalized although infusion rates of glucose had not been changed. This normalization implies that the initial reduction in glucose concentration was not caused by a spontaneous decrease. Additionally, glucose concentration had been measured 25 times during the clamp before MST, and at no other point in time could such consistent changes be seen. Since the period of observation ended after 10 minutes of recovery, we do not know whether blood glucose continued to increase, and our study therefore does not preclude a more chronic hyperglycemic response to mental stress.

In the control group, ie, when subjects had the clamp procedure simulated with saline, blood glucose concentrations tended to increase, indicating that the decrease observed in the main study was related to the preceding euglycemic clamp and/or hyperinsulinemia. Hyperinsulinemia may antagonize the stimulatory effect of epinephrine on hepatic glucose production. Insulin causes vasodilation when infused intravenously,[42] may increase SNS,[42,43] but usually leaves BP unchanged in short-term studies. Since insulin may already have caused vasodilation before MST, the interaction of hyperinsulinemia and increased epinephrine levels is difficult to ascertain, and we can only speculate that regional differences in blood flow may be involved.

Thus, when mental stress is applied while insulin-mediated glucose uptake is already stimulated, sympathetic overactivity is initially accompanied by increased glucose uptake. This finding is unexpected and cannot be fully explained. The increase in skeletal muscle blood flow during mental stress, with increased substrate delivery to the metabolically active muscle cells, or other unknown interactions between insulin and the SNS may explain the observation.

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