Acute Psychological Stress Affects Glucose Concentrations in Patients With Type 1 Diabetes Following Food Intake but not in the Fasting State

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OBJECTIVE — To compare the effect of acute psychosocial stress on glucose concentrations in the fasting state and following food intake in patients with type 1 diabetes.

RESEARCH DESIGN AND METHODS — In study 1, 20 patients were exposed to moderate psychosocial stress by means of the Trier Social Stress Test (TSST) in the fasting state. In study 2, the TSST was applied to 20 additional patients 75 min after intake of a standard meal. Glucose concentrations (by continuous glucose monitoring system), blood pressure, and heart rate were monitored on the control day and on the stress testing day.

RESULTS — In both studies, blood pressure increased in response to TSST from 122/77 ± 14/9 mmHg at baseline to a maximum of 152/93 ± 21/13 mmHg ($P < 0.001$), and heart rate increased from 80 ± 11 to 99 ± 19 bpm ($P < 0.001$). In the fasting state (study 1), glucose concentrations remained unchanged during the control day as well as during the stress testing day. In study 2, glucose concentrations were similar on both days before and up to 75 min after the intake of the standard meal. However, a significant delay (of 45 min) in the decrease of glucose concentrations was induced by psychological stress. A two-factor repeated-measures ANOVA revealed a significant difference of glucose concentrations over time ($F = 646.65/P < 0.001$).

CONCLUSIONS — In the postprandial period, acute psychological stress induced a significantly delayed decrease of glucose concentrations, whereas in the fasting state, no effect on poststress glucose concentrations was observed.

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Patients with type 1 diabetes often complain of unexplained glucose excursions. Among other factors, variability in the absorption of insulin preparations and psychological stress may be of importance (2,3). Chronic psychological stress has been associated with higher levels of glycosylated hemoglobin (A1C) (4–6). In contrast, the effect of acute psychological stress on glucose concentrations in patients with type 1 diabetes is less conclusive, with most studies showing no effect and others resulting in increased or even decreased glucose concentrations (5,7–15). In one previous study (5), the stress task was specifically applied in the postprandial state and was considered to have no effect, although the time course of glucose concentrations was altered. An additional study investigated patients on a glucose and insulin infusion in the fasting state. Since the insulin infusion rate was reduced at the beginning of the stress test, glucose concentrations were rising during the stress period, and an impaired insulin sensitivity following mental stress was found (15).

A previous study (16) in healthy men showed a significantly more pronounced cortisol response to psychological stress following an oral glucose load compared with the cortisol response in the fasting state. Since an increase in cortisol levels in patients with type 1 diabetes may cause elevated glucose concentrations, the effect of acute psychological stress on glucose concentrations may critically depend on whether stress is applied in the fasting or fed state. A different metabolic response to stress in the fasting and fed state could explain the different results obtained in clinical trials and contribute to the unpredictable individual glucose response to stress reported by many patients in clinical practice. The aim of our study was therefore to test whether the effect of acute psychosocial stress on glucose concentrations is different in the fasting compared with the fed state.

RESEARCH DESIGN AND METHODS

— Outpatients with type 1 diabetes attending the University Hospital of Zurich for regular visits were invited to participate (patients were not paid). Exclusion criteria were diabetes duration of <3 years, coronary heart disease, uncontrolled hypertension, treatment with β-blocker, adrenal or pituitary

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Abbreviations: CGMS, continuous glucose monitoring system; TSST, Trier Social Stress Test.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

disease, impaired visual acuity, and proliferative diabetic retinopathy. The protocol was approved by the ethics committee of the University Hospital of Zurich, and all patients gave written informed consent.

Study protocol

Two different protocols (studies 1 and 2) were followed. The first 20 patients recruited participated in study 1 and the following 20 patients in study 2. The protocol of study 2 was conducted immediately after the first study. In study 1, the psychological stress test was applied in the fasting state. In study 2, patients underwent the Trier Social Stress Test (TSST) in the postprandial period. Patients were placed in a quiet room and were allowed read. They had the possibility to leave the room and to stay on a balcony. During the preceding control day, the fasting as well as the meal group were monitored under comparable conditions (daytime, measurement of glucose, cortisol, and cardiovascular parameters), without stress application. In both studies, the stress test was performed between 1:30 and 3:30 P.M. Patients were allowed to drink mineral water and were advised to inject their basal insulin as usual (for those patients who had no insulin pump). Capillary blood glucose concentrations were determined in regular intervals.

Study 1: fasting studies

Patients were advised to have breakfast before 8:00 A.M. and arrive at the hospital between 10:00 and 11:00 A.M. At arrival, a capillary blood glucose concentration was determined (Accu-Check Sensor; Roche Diagnostics, Mannheim, Germany), and a continuous glucose monitoring system (CGMS) was placed. At entry, glucose concentrations >9 mmol/l were corrected with short-acting insulin analogues (glucose target 5–8 mmol/l), and glucose concentrations <4 mmol/l were corrected with ingestion of 10 g carbohydrate (Dextroenergen). Subsequently, no additional adjustment with insulin was allowed during the study. Patients were advised to fast until the end of the study (between 4:00 and 6:00 P.M.).

Study 2: standard meal tests

Patients arrived in the hospital between 9:00 and 10:00 A.M. Monitoring and correction of glucose concentrations outside the target range were managed as described above. Seventy-five minutes before the stress test, a standard meal containing 44 g carbohydrate (220 ml Ensure Plus: 53.8% carbohydrate, 29.5% fat, and 16.7% protein) and 6 g glucose (Dextroenergen) were ingested within 10 min. Short-acting insulin was injected at the beginning of the meal; the dose was determined by the patient in knowledge of the carbohydrate content (the same dose was injected at both consecutive days). Subsequently, patients were advised to fast until the end of the study.

Psychological stress test (Trier Social Stress Test)

All subjects were exposed to standardized moderate psychosocial stress by means of the Trier Social Stress Test (TSST) (17). In brief, the TSST consists of a 5-min preparation task, a 5-min speech task where subjects have to introduce themselves and apply for a job, and a 5-min mental arithmetic task in front of an audience consisting of at least two members in white coats. To enhance stress, the session is videotaped, and the audience is trained to appear emotionally neutral. At the beginning of the stress test, subjects are informed that during their performance, nonverbal communication is particularly looked at and analyzed post hoc by means of the tape.

Monitoring

Glucose concentrations were monitored in 5-min intervals by the Medtronic MiniMed CGMS (Medtronic MiniMed; Northridge, CA). Noninvasive ambulatory blood pressure monitoring was carried out with an automatic ambulatory blood pressure monitoring device (Mobil-O-Graf; IEM, Stolberg, Germany), which recorded blood pressure and heart rate by the oscillometric method. Saliva samples were collected for the determination of salivary cortisol. In study 1, the samples were collected twice at baseline and 30, 60, and 90 min after the start of the TSST. In study 2, the exact timing of the saliva samples was −75, −45, −15, +30, +60, and +90 min (meal at −75 min, TSST at 0 min). After collection, samples were stored at a temperature of −20°C before analysis. Cortisol levels were determined by a time-resolved immunoassay with fluorescence detection (16).

Psychometrics tests

To characterize participants in terms of subjects' psychological profile and to detect possible differences between the two groups, several instruments were used. The questionnaires were completed at the beginning of day 1 (control day). To assess symptoms of depression and anxiety, the Hospital Anxiety Depression Scale and the State Trait Anxiety Inventory were used (18,19). Personality traits were assessed with the Freiburger Personality Inventory, which is a 138-item questionnaire covering the following 12 dimensions: life content, social orientation, orientation in terms of achievement, inhibition, arousability, aggressiveness, strain, physical complaints, health concerns, openness, extraversion, and emotionality (20). Furthermore, participants were screened with the Trier Inventory for Chronic Stress, which measures the following six aspects of chronic stress: work overload, worries, social stress, lack of social recognition, work discontent, and intrusive memories. The construct of stress reactivity refers to the disposition of an individual's immediate, intense, and long-lasting answer to a stressor (21). Emotional stress reactivity was measured with the Stress Reactivity Scale, which measures potential reactivity with work overload, social conflicts, social judgment, and failure in the prestress and poststress phase (22). Finally, the Symptom Check List 9, a validated one-dimensional short version of the multidimensional System Check List 90 was used to get an overview of severity of psychological symptoms (23).

Data analysis

Data are presented as means ± SD. Patient characteristics of the study groups were compared using the Mann-Whitney test for ordinal variables (age, BMI, diabetes duration, A1C, total insulin dose, and basal insulin) and Fisher's exact test for categorical variables (sex, retinopathy). T test for independent samples was used to compare the mean values of the questionnaires between study groups. A P value <0.05 was considered statistically significant. A two-factor repeated-measures ANOVA with Greenhouse Geisser correction was performed to determine differences in glucose levels, blood pressure, heart rate, and cortisol concentrations within groups on the 2 study days and over time. To compare the course of glucose concentrations over time versus baseline within days, an ANOVA with re-

Table 1—*Patient characteristics*

	Study 1	Study 2	Total
n	20	20	40
Sex (female/male)	11/9	8/12	19/21
Age (years)	40 ± 13	37 ± 10	38 ± 12
BMI (kg/m^2)	24 ± 3	26 ± 4	25 ± 4
Diabetes duration (years)	16 ± 11	17 ± 10	17 ± 10
A1C (%)	7.7 ± 0.8	7.6 ± 0.7	7.6 ± 0.7
Total insulin dose (units/day)	45 ± 20	53 ± 22	49 ± 21
Basal insulin (units/day)	22 ± 10	24 ± 9	23 ± 9
Retinopathy	6 (30)	5 (25)	11 (28)

Data are means ± SD or *n* (%), unless otherwise indicated.

peated measurements followed by simple contrasts was carried out.

RESULTS

Patients

Patient characteristics and demographic data are summarized in Table 1. A total of 40 patients with type 1 diabetes (21 male and 19 female) participated. No significant differences in patient characteristics were found between the patients of study 1 and those of study 2. All patients had intensified insulin treatment, and 22 (55%) were equipped with an insulin pump. Psychological assessment for stress and psychopathology did not reveal any significant differences between the participants of both studies. The patients participating in studies 1 and 2 were comparable in terms of anxiety, depression, chronic stress proneness, emotional stress reactivity, global severity index of symptoms, and personality traits (data not shown).

Study 1: fasting tests

Blood pressure and heart rate. Profiles of blood pressure and heart rate of all 40 patients are shown in Fig. 1. Whereas blood pressure and heart rate remained unchanged during the control day (*left panels*), a significant increase of all parameters can be seen during the TSST (*right panels*). The two-factor repeated-measure ANOVA showed a highly significant difference of all cardiovascular measurements between the control and stress days ($P < 0.001$) as well as over time ($P < 0.001$), without discriminating the fasting from the meal group (study 1 versus study 2).

In participants of study 1 ($n = 20$), blood pressure increased from 118/78 ± 12/7 mmHg at baseline to a maximum of 149/92 ± 24/14 mmHg 10 min after the start of the TSST ($P < 0.001$), and heart rate increased from 76 ± 10 to 96 ± 19 bpm ($P < 0.001$). Blood pressure and heart rate remained stable for the observed period during the control day (Fig. 1).

Salivary cortisol concentrations

Saliva samples of nine patients were either too small or were insufficient in technical terms (e.g., damage during storage) and therefore did not allow further analysis. In 11 patients, salivary cortisol concentrations significantly increased from 3.5 ± 0.9 nmol/l at baseline (mean of two values before the TSST) to 9 ± 5.5 nmol/l 30 min following the TSST ($P = 0.007$) and 9.7 ± 3.9 nmol/l after 60 min ($P < 0.001$). On the control day, salivary cortisol concentrations were 3.5 ± 1 nmol/l at baseline and 3.1 ± 1.3 nmol/l at 30 and 60 min (mean of both values, P = NS), respectively.

Glucose concentrations

Glucose concentrations measured by the CGMS are shown in Fig. 2*A*. At the time of stress application (0 min), glucose concentrations were 6.8 ± 1.7 and 6.3 ± 2.2 mmol/l on the control and stress days, respectively (P = NS). Moreover, glucose concentrations remained unchanged during the period under observation on the control day (broken line) as well as after stress application (solid line). This was tested by a two-factor repeated-measures ANOVA, which showed no significant differences in glucose concentrations of participants of study 1, neither between the control and stress days nor over time.

Study 2: standard meal tests

Blood pressure and heart rate. In study 2, blood pressure increased from 126/76 ± 16/10 mmHg at baseline to a maximum of 154/93 ± 16/13 mmHg 10 min after the start of the TSST ($P < 0.001$), and heart rate increased from 84 ± 11 to 102 ± 18 bpm ($P < 0.001$). Blood pressure and heart rate remained stable during the observed period on the control day (Fig. 1).

Salivary cortisol concentrations

Again, five saliva samples could not be analyzed for the above-mentioned reasons. In 15 patients, salivary cortisol concentrations increased from 5.5 ± 1.7 nmol/l at baseline (mean of three values before the TSST; higher than the baseline in the fasting state of study 1) to 13.6 ± 10.6 nmol/l 30 min after the start of the TSST ($P = 0.01$) and 10.1 ± 5.5 nmol/l after 60 min ($P = 0.04$). On the control day, salivary cortisol was 5.2 ± 1.8 nmol/l at baseline and 4 ± 1.4 nmol/l at 30 and 60 min (mean of both values, P = NS), respectively. A two-factor repeated-measures ANOVA showed a significant difference between the control and stress days ($F = 36.28/P < 0.001$) as well as a cortisol increase over time after stress application ($F = 9.93/P = 0.001$) in both studies but no discrimination between the fasting and the meal group.

Glucose concentrations

Glucose concentrations of patients participating in study 2 ($n = 20$) are shown in Fig. 2*B*. Baseline glucose concentrations just before intake of the standardized meal (i.e., 75 min before the stress test) on the control and intervention days were almost identical, i.e., 6.8 ± 2.1 and 6.8 ± 1.6 mmol/l, respectively. At the moment of stress application at 0 min, glucose concentrations were 10.4 ± 2.7 mmol/l on the control day and 10.5 ± 2.1 mmol/l on the stress day. The poststress course of glucose concentrations was comparable on both days for the first 30 min, after which a significant delay in the decrease of glucose concentrations became evident under stress conditions compared with the control day. The maximum difference in glucose concentrations between the control and stress days was 1.4 mmol/l 55 and 80 min following the start of stress application. On the control day, glucose concentrations remained significantly increased after meal ingestion during 135

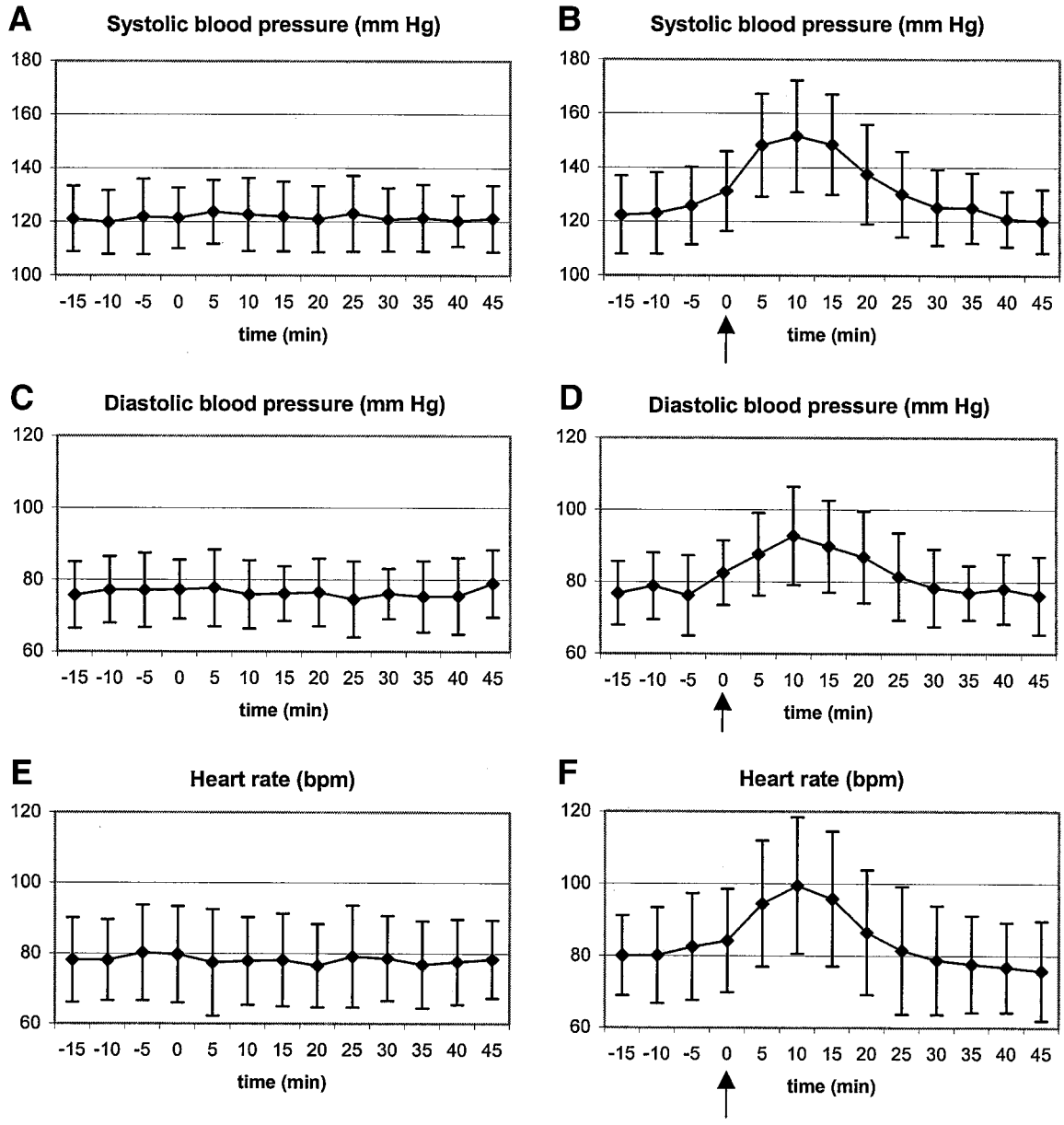

Figure 1—*Blood pressure and heart rate. Blood pressure and heart rate (±SD) in 40 patients with type 1 diabetes on the control day* (A, C, *and* E) *and on the stress day* (B, D, *and* F) *when TSST was applied at the time point 0 min. Onset of stress is indicated by an arrow.*

min (compared with baseline at −75 min), whereas on the stress day, glucose concentrations remained significantly increased for 180 min, i.e., a delay of 45 min was induced by the TSST. A two-factor repeated-measures ANOVA revealed a significant difference over time ($F = 646.65/P < 0.001$) but not between days ($F = 180.12/P = 0.250$). Analysis for interaction of both factors (day × time) was still significant ($F = 34.19/P = 0.015$).

CONCLUSIONS — The present study demonstrates that the effect of acute psychological stress on glucose concentrations in patients with type 1 diabetes critically depends on whether patients are exposed to mental stress in the fasting state or following food intake.

Blood pressure and heart rate promptly increased in response to the TSST in the fasting as well as in the fed state. The immediate cardiovascular response to the psychosocial stress task may be assigned to a release of catecholamines but was not associated with a significant increase in glucose concentrations, neither in the fasting state nor following food intake. However, with a delay of 30 min following the exposure to the TSST, mental stress induced a significant delay of the decrease in postprandial glucose concentrations. No change of glucose concentrations in this time period was observed when the TSST was applied in the fasting state. The time course of glucose concentrations in study 2 closely followed salivary cortisol concentrations (which tended to be higher following food intake than in the fasting state). In an earlier study, Kirschbaum and colleagues (16,24) reported in healthy volunteers

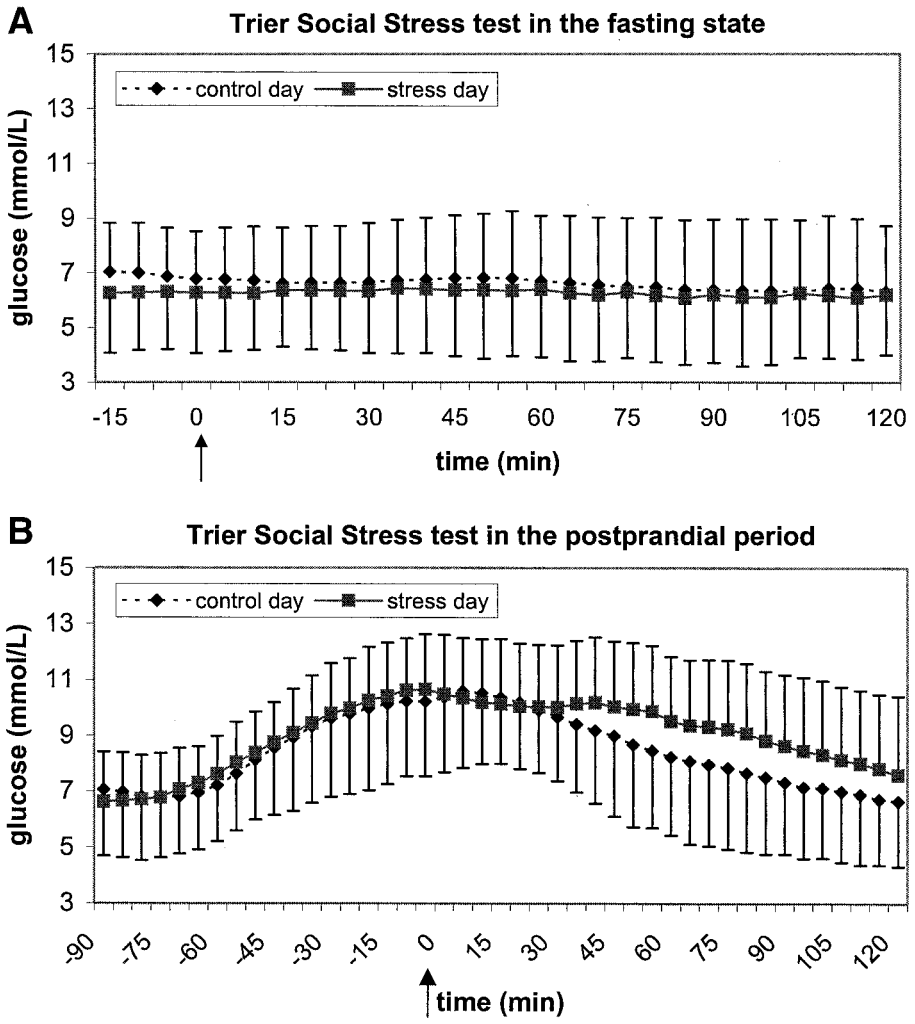

Figure 2—A: *Glucose concentrations in study 1 (in the fasting state). Glucose concentrations (±SD) measured by a CGMS on the control day (broken line) and on the stress testing day (solid line). Onset of stress is indicated by an arrow.* B: *Glucose concentrations in study 2 (following a standard meal). Glucose concentrations (±SD) measured by a CGMS following the intake of a standard meal (containing 50 g carbohydrate) 75 min before the onset of stress (at time point 0 min). Glucose concentrations are shown on the control day (broken line) and on the stress day (solid line). Onset of stress is indicated by an arrow.*

that the TSST induced a significantly more pronounced increase in cortisol secretion when preceded by ingestion of glucose (but not protein or fat) compared with the fasting state. Thus, carbohydrate intake may be permissive or required for a relevant stress-induced hypothalamopituitary adrenal activation, causing a prolonged increase in postprandial glucose concentrations in patients with type 1 diabetes on a given dose of administrated insulin.

Considering that the effect of mental stress on glucose concentrations was modest in absolute terms (compared with the control day, the maximum difference was 1.4 mmol/l at 55 and 80 min following the TSST), one might conclude that acute mental stress does not appear to be responsible for major glucose excursions. However, such an interpretation should be made with caution. The effect of mental stress on postprandial glucose concentrations became apparent with a delay of 30 min after the exposure to the stressor and lasted for ~2 h. In a previous study (15), impaired insulin sensitivity from 1 to 5 h following acute mental stress has been demonstrated. The findings of that study are in agreement with our data. In both studies, the effect of acute mental stress on glucose concentrations became apparent with a delay of 30 min, and the absolute increase in glucose concentrations was similar (1.4 and 1.9 mmol/l). Elevated levels of cortisol following a stressful event may increase insulin resistance and requirements. We therefore conclude that acute mental stress should be accepted as a potential explanation for glucose excursions, particularly in the context of a preceding meal. The exact timing of food and stress required for such an interaction remains to be studied in more detail.

The major limitation of our study is that we determined interstitial glucose concentrations by CGMS but no plasma glucose concentrations. CGMS allowed us to measure interstitial glucose concentration in 5-min intervals without blood sampling and has been shown to reliably estimate blood glucose concentrations in other previous studies (25–27). Since each glucose reading by CGMS depends on the previous results, the time course of glucose excursions is delayed and smoothed. However, the two studies were comparable in terms of the methodology by which glucose concentrations were read. Other limitations are that salivary cortisol was the only stress hormone measured, and a relevant fraction of saliva samples could not be analyzed due to technical reasons. Whether signals from the gastrointestinal tract in response to food intake by nerves or hormones to the brain or whether an increase in ambient glucose concentrations (which may be sensed at the ventromedial hypothalamus) possibly account for the interaction of acute mental stress and food intake cannot be derived from the available data. It may well be that ambient glucose concentrations during mental stress could be crucial for the extent of the metabolic response; clearly, more research is needed in this area. Another limitation of our study is that the stressor applied induced psychosocial stress for a rather short period of time, and effects of longer-lasting or repetitive events on glucose concentrations remain elusive. Further studies should clarify these important issues. In our study, no significant correlation between the results of the psychometric tests and A1C or the response of glucose, blood pressure, heart rate, and cortisol to the TSST was found. A strength of the present study is that an issue of utmost importance for patients and their treating physicians was addressed in a setting

close to clinical practice. To the best of our knowledge, the distinct glucose response to mental stress in the fasting state and following food intake has never been investigated before in patients with type 1 diabetes.

In the fasting state, moderate acute psychological stress had no effect on glucose concentrations, whereas in the postprandial period, a significantly delayed decrease of glucose concentrations became apparent 30 min after the onset of stress. In the light of our findings, patients with type 1 diabetes should anticipate whether they might experience mental stress in the fasting or fed state.

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