Acute, same-day effects of antecedent exercise on counterregulatory responses to subsequent hypoglycemia in type 1 diabetes mellitus

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Sandoval, Darleen A., Deanna L. Aftab Guy, M. Antoinette Richardson, Andrew C. Ertl, and Stephen N. Davis. Acute, same-day effects of antecedent exercise on counterregulatory responses to subsequent hypoglycemia in type 1 diabetes mellitus. Am J Physiol Endocrinol Metab 290: E1331–E1338, 2006. First published January 31, 2006; doi:10.1152/ajpendo.00283.2005.—Exercise-induced hypoglycemia can occur within hours after exercise in type 1 diabetes mellitus (T1DM) patients. This study tested the hypothesis that an acute exercise bout causes (within hours) blunted autonomic and metabolic responses to subsequent hypoglycemia in patients with T1DM. Twelve T1DM patients (3 W/9 M) were studied during a single-step, 2-h hyperinsulinemic (572 ± 2.9 pmol/l) hypoglycemic (2.8 ± 0.1 mmol/l) clamp 2 h after either a hyperinsulinemic euglycemic (AM EUG) or hypoglycemic clamp (AM HYPO) or after sitting in a chair with basal insulin infusion (AM CON) or 90 min of moderate-intensity exercise (50% VO2max, AM EX). Both AM HYPO and AM EX significantly blunted epinephrine responses and muscle sympathetic nerve activity responses to subsequent hypoglycemia compared with both control groups. Endogenous glucose production was significantly lower and the exogenous glucose infusion rate needed to maintain the hypoglycemic level was significantly greater compared with both control groups. Exercise-induced hypoglycemia has been reported to occur within 2 h after exercise.

Although acute exercise-induced hypoglycemia in T1DM may at least partially stem from iatrogenic causes (i.e., in balance of subcutaneous insulin and metabolic needs), we (13) have demonstrated that morning hypoglycemia could acutely reduce neuroendocrine and symptom responses to subsequent, same-day, afternoon hypoglycemia in nondiabetic individuals. Despite the blunted neuroendocrine responses, the morning hypoglycemia caused an insulin-resistant state in the afternoon that resulted in significantly reduced rates of glucose oxidation and glucose flux. The increased insulin resistance in the afternoon appeared to offset and partially compensate for the blunted neuroendocrine response by limiting increases in glucose utilization during afternoon hypoglycemia. However, it remains unknown whether in T1DM blunted counterregulation could also be a mechanism responsible for causing acute (within hours) exercise-induced hypoglycemia. Furthermore, the effects of morning exercise on metabolic counterregulatory responses occurring during same-day hypoglycemia in T1DM are unknown. Antecedent exercise may be additionally problematic, as exercise is known to acutely increase insulin sensitivity. Thus the scenario could arise in T1DM that hypoglycemia occurring after exercise could be characterized not only by blunted neuroendocrine responses but also by the ablation of the protective effect of posthypoglycemic insulin resistance. This would result in increased glucose utilization during the subsequent hypoglycemia and consequently cause lower glycemic levels. Thus the aim of this study was to determine the acute effects of morning exercise or moderate hypoglycemia (2.9 mmol/l) on autonomic, neuroendocrine, and metabolic responses during same-day, subsequent afternoon hypoglycemia in T1DM patients.

RESEARCH DESIGN AND METHODS

Subjects

We studied 12 patients with T1DM (9 male/3 female; age 30 ± 2 yr; body mass index 25 ± 1 kg/m2; HB A1c 8 ± 0%, normal range 4.0–6.5%) and duration of diabetes (18 ± 3 yr). None of the patients reported a history of hypoglycemic unawareness, and all received insulin as their only medication. No patient had any clinical evidence of autonomic neuropathy or any other tissue specific complication of diabetes. All patients had normal blood count, plasma electrolytes, and liver and renal function. Studies were approved by the Vanderbilt University Human Subjects
Institutional Review Board, and all subjects gave informed written and verbal consent.

Preliminary Exercise Testing

At least 2 wk before the initial study, subjects performed an incremental exercise test on a stationary cycle ergometer to determine maximum oxygen consumption ($V_{\text{O}_2 \text{max}}$). Expired gases were collected and analyzed using computerized open-circuit indirect calorimetry (ParvoMedics, Sandy, UT). $V_{\text{O}_2 \text{max}}$ was determined when at least two of the following three criteria were met: 1) the subject was too tired to continue, 2) the respiratory exchange ratio was greater than 1.0, or 3) the oxygen consumption plateaued with an increase in workloads. Subjects studied ranged from sedentary to recreationally active (average $V_{\text{O}_2 \text{max}}$ 31 ± 3 ml·kg$^{-1}$·min$^{-1}$, range 18–48 ml·kg$^{-1}$·min$^{-1}$).

Experimental Design

Subjects underwent randomized, single-blind studies consisting of one episode of hyperinsulinemic (9 pmol/kg·min) hypoglycemia ($2.8 \pm 0.1$ mmol/l) 2 h after either a hyperinsulinemic euglycemic clamp (AM EUG) or a hyperinsulinemic hypoglycemia clamp (AM HYPO) or sitting in a chair with basal insulin infusion (1 U/h; AM CON) or after 90 min of moderate-intensity exercise (50% $V_{\text{O}_2 \text{max}}$, AM EX). All study patients were asked to avoid any exercise and consume their usual weight-maintaining diet for 3 days before each study. All patients performed intensive home blood glucose monitoring (before each meal, at bedtime, and on two occasions at 3:00 AM) for 2 wk before a study. An experiment was not conducted if blood glucose readings fell below 3.9 mmol/l. On the day preceding an experiment, intermediate or long-acting insulin was discontinued and replaced by injections of regular insulin before breakfast and lunch. Each subject was admitted to the Vanderbilt General Clinical Research Center (GCRC) at 5:00 PM on the evening before an experiment. At that time, two intravenous cannulae were inserted under 1% Lidocaine as a local anesthesia. One cannula was placed in a retrograde fashion into a vein on the back of the hand. This hand was placed in a heated box (55–60°C) so that arterialized blood could be obtained (1); the other cannula was placed in the contralateral arm for infusions. Patients then received an evening meal, and a continuous low-dose infusion of insulin was started to normalize plasma glucose.

The insulin infusion was adjusted overnight to maintain blood glucose between 4.4 and 7.2 mmol/l.

After an overnight 10-h fast, at ~10:00 AM and after a 30 min basal period, subjects were randomized to be studied under one of the four protocols (AM EUG, AM HYPO, AM CON, or AM EX). The AM EUG and AM HYPO clamp experiments involved a standardized hyperinsulinemic euglycemic or hypoglycemic glucose clamp. An insulin infusion solution was prepared with normal saline containing 3% (vol/vol) of the subject’s own plasma. At time 120 min, a primed constant (9.0 pmol·kg$^{-1}$·min$^{-1}$) infusion of insulin (Eli Lilly, Indianapolis, IN) was started via a precalibrated infusion pump (Harvard Apparatus, South Natick, MA) and continued until 240 min. The rate of fall of glucose was controlled (0.06 mmol/min), and for AM HYPO the glucose nadir (2.9 mmol/l) was achieved using a modification of the glucose clamp technique (14). During the clamp periods, plasma glucose was measured every 5 min, and a 20% dextrose infusion was adjusted so that plasma glucose levels were held constant ($5.1 \pm 0.1$ mmol/l for EUG and $2.8 \pm 0.1$ mmol/l for HYPO). Potassium chloride (20 mmol/l) was infused during the clamp to reduce insulin-induced hypokalemia.

For the AM CON studies subjects sat in a chair, and for the AM EX studies subjects exercised on an upright cycle ergometer (Medical Graphics, Yorba Linda, CA) and pedaled at 60–70 rpm for 90 min. During exercise and while resting in the chair (control subjects), insulin was infused at 1 U/h, and potassium chloride was infused at a rate of 5 mmol/h. Plasma glucose was measured every 5 min during both exercise and control periods and was maintained at 5.1 ± 0.1 mmol/l with a 20% dextrose infusion.

After the morning procedures, at 240 min (Fig. 1), a primed (18–μCi) infusion of 0.18 μCi/min) of HPLC-purified [3-3H]glucose (PerkinElmer Life Sciences, Boston, MA; 11.5 mCi·mmol$^{-1}$·1$^{-1}$) was administered via a precalibrated infusion pump (Harvard Apparatus). Also at that time, the microneurography procedure (described below) was started. At 360 min, a hyperinsulinemic hypoglycemic clamp (using identical clamping procedures described above) was performed on all subjects.

Direct Measurement of Muscle Sympathetic Nerve Activity

Muscle sympathetic nerve activity (MSNA) was recorded in the present study, as this has been demonstrated to reflect increased sympathetic activity during insulin-induced hypoglycemia (9, 10, 12, 17, 18). MSNA was measured from the peroneal nerve at the level of the fibular head or popliteal fossa, and the data were processed as described previously (32).

Tracer Calculations

Rates of glucose appearance ($R_{\text{a}}$), endogenous glucose production (EGP), and glucose utilization were calculated according to the methods of Wall et al. (35). EGP was calculated by determining the total $R_{\text{a}}$ (this comprises both EGP and any exogenous glucose infused to maintain the desired hypoglycemia) and subtracting it from the amount of exogenous glucose infused. It is now recognized that this approach is not fully quantitative, because underestimates of total $R_{\text{a}}$ and rate of glucose disposal ($R_{\text{d}}$) can be obtained. The use of a highly purified tracer and taking measurements under steady-state conditions (i.e., constant specific activity) in the presence of low glucose flux eliminates most, if not all, of the problems. In addition, to maintain a constant specific activity, isotope delivery was increased commensurate with increases in exogenous glucose infusion. During this study, only glucose flux results from the steady-state basal and the final 30-min periods of the hypoglycemic clamps are reported.

Analytical Methods

Plasma glucose concentrations were measured in triplicate using the glucose oxidase method with a glucose analyzer (Beckman, Fullerton, CA). Blood for hormones and intermediary metabolites was drawn twice during the control period and every 15 min during the experimental period. Catecholamines were determined by HPLC (4) with an interassay coefficient of variation (CV) of 12% for both epinephrine and norepinephrine. We made two modifications to the procedure for catecholamine determination: 1) we used a five-point rather than a one-point standard calibration curve; and 2) we spiked the initial and final samples of plasma with known amounts of epinephrine and norepinephrine so that accurate identification of the relevant catecholamine peaks could be made. Insulin (36) (CV = 11%), cortisol (Clinical Assays Gamma Coat Radioimmunoassay Kit; interassay CV = 6%), growth hormone (25) (interassay CV = 8%), and pancreatic polypeptide (23) (interassay CV = 8%), and glucagon (Linco Research, St. Louis, MO; interassay CV = 15%) were all measured using radioimmunoassay techniques. Lactate, glyceral, alanine, and β-hydroxybutyrate were measured on deproteinized whole blood, using the method of Lloyd et al. (29). Nonesterified fatty acids (NEFA) were measured using the WAKO kit adopted for use on a centrifugal analyzer (24).

Cardiovascular parameters (heart rate and systolic, diastolic, and mean arterial pressure) were assessed every 10 min and measured manually during exercise and control periods and noninvasively by a Dinamap during all hyperinsulinemic clamp periods (Critikon, Tampa, FL). Symptoms of hypoglycemia were assessed every 15 min during the hypoglycemic clamps by use of a previously validated semiquantitative questionnaire (6). Each subject was asked to rate
symptoms of tiredness, confusion, hunger, dizziness, difficulty thinking, blurred vision, sweatiness, tremor, agitation, heat/thirst, and palpitations. The score for the first six symptoms was summed for neuroglycopenic and for the last five symptoms for autonomic symptom scores.

Expired gases were collected and analyzed during the basal period and the final 15 min of each experimental period (morning and afternoon) using computerized open-circuit indirect calorimetry (TrueOne 2400; ParvoMedics, Sandy, UT). Whole body fat and carbohydrate oxidation was calculated using the equations of Frayn (16) after correction for protein oxidation. Nonoxidated glucose disposal was calculated by subtracting oxidative glucose disposal from glucose Rd.

Statistical Analysis

Data are expressed as means ± SE and were analyzed using standard parametric, two-way analysis of variance (ANOVA) and with repeated measures where appropriate. A Tukey’s post hoc analysis was used to delineate statistical significance. \( P < 0.05 \) was accepted as statistical significance.

RESULTS

AM Results

Subjects performed a relative exercise intensity of 54 ± 1% \( \text{V} \text{O}_2 \text{max} \) for the AM EX group. Exercise caused heart rate to increase from 76 ± 2 to 130 ± 7 beats/min and systolic blood pressure to increase from 108 ± 3 to 134 ± 6 mmHg, whereas diastolic blood pressure did not change. During morning hypoglycemia, heart rate increased by 12 ± 6 beats/min and systolic blood pressure increased by 6 ± 3 mmHg, whereas diastolic blood pressure did not change. There were no significant cardiovascular changes during morning procedures in the AM EUG or AM CON groups.

Morning glucose levels were similar to baseline during the final 30 min of the exercise (5.2 ± 0.1 mmol/l), control (5.2 ± 0.2 mmol/l), and euglycemic clamp (5.1 ± 0.1 mmol/l) periods and reached a nadir of 2.8 ± 0.1 mmol/l during morning hypoglycemia (Fig. 2). Similarly, morning insulin levels were similar to baseline (64 ± 10 pmol/l) during the final 30 min of the AM EX (75 ± 6 pmol/l) and CON (70 ± 11 pmol/l; Fig. 2). Insulin levels reached 573 ± 49 pmol/l during AM EUG and 574 ± 31 pmol/l during AM HYPO (Fig. 2).

Epinephrine responses were lower (928 ± 144 vs. 1,538 ± 146 pmol/l, \( P < 0.05 \)) and norepinephrine responses were higher (4.7 ± 0.6 vs. 1.5 ± 0.2 pmol/l, \( P < 0.05 \)) during the final 30 min of the morning exercise bout compared with the morning hypoglycemic clamp. Plasma cortisol increased by similar amounts by the final 30 min of exercise and hypoglycemia (649 ± 88 and 742 ± 206 nmol/l, respectively). Lactate increase with morning exercise was significantly greater than with morning hypoglycemia (1.6 ± 0.2 vs. 1.2 ± 0.1 mmol/l, \( P < 0.05 \)). **β-Hydroxybutyrate did not increase significantly during morning procedures in any group. None of the counterregulatory hormones or metabolites increased over baseline**
in either the AM EUG or AM CON groups during the morning experimental periods.

**PM Results**

*Glucose and insulin levels.* During the afternoon hypoglycemic clamp, steady-state plasma glucose (2.8 ± 0.1, 2.8 ± 0.1, 2.7 ± 0.1, and 2.8 ± 0.1 mmol/l) and insulin levels (571 ± 43, 579 ± 43, 557 ± 84, and 597 ± 57 pmol/l) were similar between the AM EUG, AM HYPO, AM CON, and AM EX groups, respectively (Fig. 2).

*Counterregulatory hormone levels.* Epinephrine response to hypoglycemia was significantly lower in AM HYPO and AM EX vs. AM EUG and AM CON (1,719 ± 247 and 1,528 ± 424 vs. 2,278 ± 191 and 1,959 ± 533 pmol/l, *P* < 0.05, respectively; Fig. 3). Norepinephrine (Fig. 3), pancreatic polypeptide, growth hormone, cortisol, and glucagon responses to hypoglycemia were similar between the four groups (Table 1).

**Glucose Kinetics**

Glucose specific activity (dpm/mmol) did not change significantly during either the control period or the final 30 min of the hypoglycemic clamp (CV = 4 and 5% for basal and final 30 min of hypoglycemia; Table 2). Endogenous glucose production was significantly lower during the final 30 min of hyperinsulinemic hypoglycemia in AM EX compared with AM CON and AM EUG (1.5 ± 0.5 vs. 4.2 ± 1.5 and 3.4 ± 0.7 μmol·kg⁻¹·min⁻¹, *P* < 0.05; Fig. 4). As a consequence, the exogenous glucose infusion rate needed to maintain the hypoglycemic level of 2.8 mmol/l was significantly greater in AM EX compared with AM CON (20 ± 3 vs. 12 ± 2 μmol·kg⁻¹·min⁻¹, *P* < 0.05; Fig. 4). Glucose Rd was significantly lower in AM HYPO than in AM EUG, AM CON, and AM EX (12 ± 2 vs. 23 ± 4, 17 ± 2, and 22 ± 2 μmol·kg⁻¹·min⁻¹, respectively, *P* < 0.05; Fig. 4). Indirect
calorimetry data indicated that both the basal and final 30-min period (P < 0.05; Table 3) fat oxidation rates were significantly greater in AM EX and AM HYPO compared with AM EUG. Final 30-min nonoxidative glucose disposal rates were also significantly greater in AM EX compared with all other groups (1.6 ± 0.5 vs. 0.7 ± 0.4, 0.3 ± 0.2, and 0.7 ± 0.3 mg·kg⁻¹·min⁻¹ for AM EX vs. AM EUG, AM HYPO, and AM CON, respectively, P < 0.05).

**Intermediary Metabolism**

Basal NEFA (527 ± 66 and 512 ± 113 vs. 200 ± 44 and 202 ± 81 μmol/l, P < 0.05) and glycerol (111 ± 23 and 86 ± 14 vs. 57 ± 11 and 67 ± 14 μmol/l, P < 0.05) levels were significantly greater after AM HYPO and EX compared with both AM EUG and AM CON (Fig. 5). However, by the end of the afternoon hypoglycemia, values for both NEFA and glycerol were similar between groups. Lactate levels significantly increased with hyperinsulinemic hypoglycemia similarly among the three groups (Table 4). Basal β-hydroxybutyrate levels were also greater after AM HYPO and EX compared with AM EUG and CON groups (0.23 ± 0.05 and 0.36 ± 0.08 vs. 0.05 ± 0.01 and 0.10 ± 0.04 mmol/l, P < 0.05; Table 4). However, by the end of the hyperinsulinemic hypoglycemic clamp, β-hydroxybutyrate levels were similar among the groups. Basal and final 30-min alanine levels during the afternoon hypoglycemic clamp were similar among the groups (Table 4).

**Cardiovascular and Symptomatic Responses**

Heart rate significantly increased with hyperinsulinemic hypoglycemia in all groups (Table 4). However, systolic blood pressure, mean arterial pressure, and diastolic blood pressure did not change with hyperinsulinemic hypoglycemia in any group (Table 4). Total hypoglycemic, autonomic, and neuroglycopenic symptom scores were similar among the groups (Table 4).

Table 2. Glucose specific activity for basal and final 30-min periods during afternoon hyperinsulinemic hypoglycemia in the 4 experimental groups

<table>
<thead>
<tr>
<th>Time, min</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>AM EUG</td>
<td>363±94</td>
<td>374±35</td>
<td>377±36</td>
<td>297±20</td>
<td>292±21</td>
<td>296±22</td>
</tr>
<tr>
<td>AM HYPO</td>
<td>467±69</td>
<td>475±63</td>
<td>439±47</td>
<td>369±27</td>
<td>360±29</td>
<td>355±30</td>
</tr>
<tr>
<td>AM CON</td>
<td>427±36</td>
<td>435±20</td>
<td>413±26</td>
<td>229±33</td>
<td>237±37</td>
<td>242±38</td>
</tr>
<tr>
<td>AM EX</td>
<td>393±62</td>
<td>390±54</td>
<td>392±52</td>
<td>303±26</td>
<td>302±24</td>
<td>300±20</td>
</tr>
</tbody>
</table>

Values are means ± SE.

MSNA

MSNA significantly increased with hypoglycemia in AM EUG and AM CON (P < 0.05) but failed to increase during hypoglycemia in both AM EX and AM HYPO (Fig. 6).

**DISCUSSION**

We have previously reported in nondiabetic individuals that posthypoglycemic insulin resistance could provide a protective mechanism against repeated hypoglycemia by compensating for the blunted neuroendocrine/autonomic nervous system responses (13). The current study extends those findings by demonstrating in T1DM that both morning exercise and hypoglycemia can blunt the key counterregulatory mechanism of epinephrine but not symptom responses during afternoon hypoglycemia.
compared with the hypoglycemia induced decreased Rd) sug-

significance, although it should be noted that norepinephrine
these patients.
remove three primary, critical defenses against the stress in

ity of T1DM to regulate insulin levels during hypoglycemia

MSNA) occurring after morning exercise or hypoglycemia

that the reduced sympathetic nervous drive (epinephrine and

is an important defense against falling glycemia. Of concern is

the morning stress. Nevertheless, preservation of symptoms

addition, it is also possible that we did not have enough

plex, and it is not uncommon to see a dissociation between

Regulation of symptomatic responses to hypoglycemia is com-

crine responses) but not all (i.e., preservation of symptoms)

shorter duration) resulted in blunting of some (i.e., neuroendo-

glycemia. This current finding is consistent with previous work
demonstrating that a lower “dose” of hypoglycemia (i.e., shorter duration) resulted in blunting of some (i.e., neuroendocri
ne responses) but not all (i.e., preservation of symptoms) coun-
terregulatory responses to subsequent hypoglycemia (9). Regu-
lation of symptomatic responses to hypoglycemia is com-
plicated, and it is not uncommon to see a dissociation between sympathe
cic drive and autonomic symptoms (9, 11, 17, 32). In addition, it is also possible that we did not have enough statistical power to detect a difference in symptom scores after the morning stress. Nevertheless, preservation of symptoms has clinical relevance, as symptom awareness of hypoglycemia is an important defense against falling glycemia. Of concern is that the reduced sympathetic nervous drive (epinephrine and MSNA) occurring after morning exercise or hypoglycemia combined with absent glucagon responses (20) and the inability of T1DM to regulate insulin levels during hypoglycemia remove three primary, critical defenses against the stress in these patients.

Plasma norepinephrine responses were numerically smaller following morning exercise, but this did not reach statistical significance, although it should be noted that norepinephrine levels are influenced by large changes in clearance at several differencing tissues (i.e., liver, gut, and synaptic cleft). This makes changes in plasma norepinephrine a relatively small experimental signal to measure during hypoglycemia. Thus it is possible that a larger sample size may have demonstrated significantly reduced norepinephrine responses following morning exercise.

The blunted epinephrine responses following morning exercise appeared to have a significant effect on altering glucose kinetics during afternoon hypoglycemia. In longer-duration T1DM individuals (and thus greater insulin deficiency), epinephrine is the primary mechanism to acutely increase EGP during hypoglycemia. Additionally, epinephrine also plays a major role by limiting peripheral glucose uptake by directly inhibiting hexokinase activity and glucose phosphorylation and indirectly increasing free fatty acid levels (2, 26). Thus the blunted epinephrine responses following afternoon hypoglycemia following morning exercise would be expected to be a major factor for the reduced EGP. Interestingly, despite similarly blunted epinephrine responses in AM HYPO, EGP was not reduced compared with AM EUG. This may be explained by a relative induction of hepatic insulin resistance following the morning episode of hypoglycemia.

The enhanced lipolysis (as indicated by NEFA and glyc-
erol levels) and fat oxidation rates (as indicated by the indirect calorimetry and β-hydroxybutyrate data) occurring following morning exercise and hypoglycemia also appeared to influence glucose kinetics during afternoon hypo-

Table 3. Indirect calorimetry and metabolite responses to afternoon hyperinsulinemic hypoglycemia in the 4 experimental groups

<table>
<thead>
<tr>
<th></th>
<th>Fat Disposal, mg·kg⁻¹·min⁻¹</th>
<th>Lactate, mmol/l</th>
<th>β-Hydroxybutyrate, mmol/l</th>
<th>Alanine, mmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>AM EUG Basal</td>
<td>0.4±0.1*</td>
<td>0.6±0.1</td>
<td>0.9±0.3</td>
<td>0.25±0.02</td>
</tr>
<tr>
<td>AM EUG Final 30 min</td>
<td>0.3±0.1*</td>
<td>1.1±0.1†</td>
<td>1.0±0.3</td>
<td>0.24±0.02</td>
</tr>
<tr>
<td>AM HYPO Basal</td>
<td>0.7±0.2†</td>
<td>0.7±0.1</td>
<td>0.13±0.03</td>
<td>0.27±0.04</td>
</tr>
<tr>
<td>AM HYPO Final 30 min</td>
<td>0.4±0.1†</td>
<td>1.1±0.1†</td>
<td>0.31±0.06</td>
<td>0.26±0.02</td>
</tr>
<tr>
<td>AM CON Basal</td>
<td>0.5±0.2†</td>
<td>0.5±0.1</td>
<td>0.6±0.1</td>
<td>0.21±0.01</td>
</tr>
<tr>
<td>AM CON Final 30 min</td>
<td>0.3±0.1†</td>
<td>0.9±0.1†</td>
<td>0.7±0.2</td>
<td>0.2±0.01</td>
</tr>
<tr>
<td>AM EX Basal</td>
<td>1.0±0.1</td>
<td>0.7±0.1</td>
<td>0.13±0.03</td>
<td>0.23±0.03</td>
</tr>
<tr>
<td>AM EX Final 30 min</td>
<td>0.7±0.1</td>
<td>0.9±0.1†</td>
<td>0.31±0.06</td>
<td>0.20±0.02</td>
</tr>
</tbody>
</table>

Values are means ± SE. *P < 0.05 vs. corresponding time point in AM HYPO and AM EX. †P < 0.05 vs. corresponding time point in AM EX. ⁡P < 0.05 final 30 min vs. basal time points.

Fig. 5. Free fatty acid and glycerol levels during the afternoon hyperinsuline-
ic (9 pmol·kg⁻¹·min⁻¹) hypoglycemic clamp in T1DM subjects who underwent a hyperinsulinemic euglycemia (AM EUG), hypoglycemia (AM HYPO), control (AM CON), or moderate-intensity exercise (AM EX) in the morning. Values are means ± SE. *P < 0.05, AM HYPO vs. AM EUG and AM EX vs. AM CON.
glycemia. Elevations of NEFA have been shown to reduce glucose utilization during hypoglycemia in nondiabetic volunteers (15). In fact, glucose $R_d$ was reduced following AM HYPO compared with all other groups but was similar to control groups during afternoon hypoglycemia following AM EX. Of note, there were significantly greater reductions in both NEFA and glycerol during afternoon hypoglycemia following AM HYPO or AM EX, indicating a greater utilization over production of these substrates. Thus the enhanced fat metabolism appeared to cause a degree of insulin resistance after AM HYPO, whereas, after AM EX, glucose $R_d$ was similar to control studies due to the actions of exercise to enhance glucose $R_d$ (27), thereby offsetting the effects of fat to reduce insulin sensitivity.

Ninety minutes of prolonged moderate exercise were used in the present study. This model of exercise is representative of a variety of physical activities typically undertaken by individuals with T1DM (e.g., soccer, tennis, cycling). Whether differing durations or greater intensities of antecedent exercise may influence subsequent counterregulatory responses to hypoglycemia in T1DM needs to be determined. Changes in these parameters (i.e., differences in duration and work intensities) appear to influence responses to subsequent hypoglycemia in nondiabetic individuals, as other studies examining same-day effects of prior exercise on subsequent counterregulatory responses to hypoglycemia have shown divergent results. For example, prolonged exercise in dogs reduced counterregulatory responses to immediate subsequent glucoprivation (28) but not in response to subsequent hyperinsulinemic hypoglycemia (27). In nondiabetic humans, one bout of prolonged exercise (60 min at 60% $V_{O2\text{max}}$) had no effect on counterregulatory responses to subsequent (90 min postexercise) hypoglycemia (31). In addition, the results of both the present study and our previous 2-day study where exercise occurred almost 24 h earlier (33) showed that antecedent exercise blunted epinephrine, MSNA, and EGP responses to subsequent hypoglycemia. In contrast, in the current study, fat metabolism and nonoxidative glucose disposal were all increased after prior exercise, whereas in the 2-day study fat metabolism was reduced and glucose $R_d$ and oxidative glucose disposal were significantly greater during day 2 hypoglycemia compared with the control group. Thus our current and previous data, together with the contrasting data summarized here (27, 31) suggest that duration, volume, intensity, and time elapsed after prior exercise may all influence metabolic counterregulatory responses to subsequent hypoglycemia.

In summary, the combined effects of exercise on the sympathetic nervous system and metabolic responses to subsequent hypoglycemia suggest that, acutely, exercise is a potent risk factor for hypoglycemia in T1DM. It would seem that, after prolonged moderate exercise in T1DM patients, a time course of autonomic nervous system and metabolic changes are activated that contribute to exercise-induced hypoglycemia. These physiological counterregulatory deficits are apparent within hours after morning exercise or hypoglycemia and persist for at least 24 h. These data underscore the importance of strict glucose monitoring and adjustments of insulin replacement doses after exercise in T1DM patients in order for them to enjoy the benefits of exercise without an increased risk of subsequent hypoglycemia.

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