Preserved Hypothermic Response to Hypoglycemia After Antecedent Hypoglycemia

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Hypoglycemia is known to decrease the body temperature and to stimulate counterregulatory hormone secretion. Although it is well established that antecedent hypoglycemia reduces the hormonal response to subsequent hypoglycemia, the effects of antecedent hypoglycemia on the subsequent hypothermic response are obscure. In the present study, body temperature was measured orally during a total of 90 glucose clamp experiments in 45 healthy men. The clamps lasted 6 hours and were performed under 6 different experimental conditions: a euglycemic clamp with a low rate of insulin infusion, 1.5 mU/kg · min (low insulin-eu), a euglycemic clamp with a high rate of insulin infusion, 15.0 mU/kg · min (high insulin-eu), a hypoglycemic clamp with a low rate of insulin infusion, 1.5 mU/kg · min (low insulin-hypo), a hypoglycemic clamp with a high rate of insulin infusion, 15.0 mU/kg · min (high insulin-hypo), and 2 hypoglycemic clamps following an antecedent 2.5-hour hypoglycemia (56 mg/dL) induced by either a low (1.5 mU/kg · min, low insulin-ante-hypo) or a high (15.0 mU/kg · min, high insulin-ante-hypo) rate of insulin infusion. Plasma glucose was maintained normal during the euglycemic clamps and was decreased stepwise during the hypoglycemic clamps (76 → 66 → 56 → 46 mg/dL). During the hypoglycemic clamps, body temperature decreased by 0.26° ± 0.09°C in low insulin-hypo, 0.28° ± 0.09°C in high insulin-hypo, 0.29° ± 0.09°C in low insulin-ante-hypo, and 0.41° ± 0.11°C in high insulin-ante-hypo (all $P < .01$). There were no differences in the hypothermic response to hypoglycemia among the different hypoglycemic conditions ($P > .1$ for all comparisons). In contrast, body temperature remained unchanged during the euglycemic clamps, so the changes in body temperature differed significantly during the euglycemic clamps versus the hypoglycemic clamps ($P < .05$ for all comparisons). The data show that the body temperature decreases during hypoglycemia and this decrease is influenced neither by antecedent hypoglycemia nor by circulating insulin levels.

HYPOTHERMIA forms a basic aspect of the response to hypoglycemia.[1-4] The decrease in body temperature has been proposed to result from an interaction between the thermoregulatory and glucoregulatory systems of the hypothalamus.[5-8] In animals, a lower brain temperature during acute hypoglycemia has been found to limit hypoglycemic neuronal loss.[9] Moreover, a prevention of the normal hypothermic response to severe hypoglycemia resulted in enhanced mortality caused by hypoglycemia.[10] In humans, an elevated body temperature during hypoglycemia has been found associated with a prolonged impairment of consciousness, which persisted even after normalizing the plasma glucose level.[11]

Antecedent hypoglycemia, as well as insulin, has been shown to modulate the counterregulatory hormone response to hypoglycemia. Specifically, insulin has been shown to acutely enhance the counterregulatory hormone response in most[12-15] but not all[16-18] studies. Antecedent hypoglycemia, on the other hand, has consistently been shown to attenuate counterregulatory hormone release during subsequent hypoglycemia.[19-26] However, high levels of insulin during antecedent hypoglycemia have recently been shown to prevent the development of subsequent counterregulatory failure.[27]

The influence of insulin and antecedent hypoglycemia on the hypothermic response to hypoglycemia has not been studied thus far. Here, we report changes in orally measured body temperature during 30 hyperinsulinemic-euglycemic and 60 hyperinsulinemic-hypoglycemic clamps.

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SUBJECTS AND METHODS

Forty-five young healthy men participated in the experiments (mean ± SEM age, 25.8 ± 0.7 years; range, 20 to 30; body mass index, 23.1 ± 0.5 kg/m^2; range, 18.6 to 28.2). Exclusion criteria were chronic or acute illness, current medication of any kind, smoking, alcohol or drug abuse, obesity, and diabetes or hypertension in first-degree relatives. Each subject provided written informed consent, and the study was approved by the local ethics committee.

Body temperature was measured orally during 30 euglycemic and 60 stepwise hypoglycemic clamp experiments lasting 6 hours. Each subject was tested in 2 of a total of 6 clamp conditions performed in a single-blind fashion and in random order with an interval of at least 4 weeks between experiments. The experimental conditions were a euglycemic clamp with a low rate of insulin infusion, 1.5 mU/kg · min (low insulin-eu), a euglycemic clamp with a high rate of insulin infusion, 15.0 mU/kg · min (high insulin-eu), a stepwise hypoglycemic clamp with a low rate of insulin infusion, 1.5 mU/kg · min (low insulin-hypo), a stepwise hypoglycemic clamp with a high rate of insulin infusion, 15.0 mU/kg · min (high insulin-hypo), and 2 stepwise hypoglycemic clamps performed with a low rate of insulin infusion (15.0 mU/kg · min) following an antecedent 2.5-hour hypoglycemia (56 mg/dL) induced by either a low rate of insulin infusion (1.5 mU/kg · min, low insulin-ante-hypo) or a high rate of insulin infusion (15.0 mU/kg · min, high insulin-ante-hypo). Antecedent hypoglycemic clamps were performed about 18 hours beforehand. Results of hormone measurements during these experiments have been published in part elsewhere.[27]

On the day of the antecedent hypoglycemic clamp, the subjects reported to the medical research unit at 1:30 PM. They were instructed not to have breakfast on this day and to fast until the end of the clamp. The experiments were performed in a sound-attenuated room with the subjects sitting with their trunk in an almost upright position (about 60°) and their legs in a horizontal position on the bed. The room temperature was kept between 20° and 22°C by air conditioners. Subjects wore standard pajamas and were covered by a light blanket. A cannula was inserted into a vein on the back of the hand, which was placed in a heated box (50° to 55°C) to obtain arterialized venous blood. A second cannula was inserted into an antecubital vein of the contralateral arm. Both cannulas were connected to long thin tubes, which enabled blood

Table 1. Plasma Glucose (mg/dL) During Baseline, the Hypoglycemic Plateaus of the Stepwise Hypoglycemic Clamps, and the Corresponding Time Intervals of the Euglycemic Clamps (mean ± SEM)

Condition	Baseline	Plateau 1	Plateau 2	Plateau 3	Plateau 4
Low insulin-eu	95.6 ± 1.6	93.7 ± 1.2	94.0 ± 0.9	93.6 ± 1.6	95.4 ± 1.7
High insulin-eu	93.7 ± 1.1	93.3 ± 1.2	95.3 ± 1.1	94.9 ± 1.3	98.6 ± 1.3
Low insulin-hypo	92.2 ± 2.0	73.0 ± 1.5	65.9 ± 0.7	55.0 ± 0.8	45.4 ± 0.4
High insulin-hypo	91.6 ± 0.9	75.5 ± 1.2	64.5 ± 0.5	55.4 ± 0.7	46.1 ± 0.4
Low insulin-ante-hypo	96.4 ± 2.0	76.3 ± 0.7	64.9 ± 0.6	55.9 ± 0.7	46.0 ± 0.5
High insulin-ante-hypo	100.8 ± 1.9	77.4 ± 09	65.0 ± 0.6	56.5 ± 0.6	46.7 ± 0.6

NOTE. Values represent the mean across the respective time intervals.

sampling and adjustment of the rate of dextrose infusion from an adjacent room without the subject's awareness. At 2:00 PM, infusion of insulin (H-insulin; Hoechst, Frankfurt, Germany) began at a continuous rate of either 1.5 or 15.0 mU/min · kg, respectively. The plasma glucose level was measured (Beckman Glucose Analyser; Beckman, Munich, Germany) every 5 minutes, and a variable infusion of 20% dextrose solution was adjusted so that plasma glucose was kept constant at approximately 56 mg/dL.

On the day of the euglycemic and stepwise hypoglycemic clamps, all subjects reported to the medical research unit at 8:00 AM after an overnight fast of at least 10 hours. The setting of these experiments was the same as that of the antecedent hypoglycemic clamps. After a 1-hour baseline period, insulin was infused at a continuous rate of either 15.0 mU/min · kg or 1.5 mU/min · kg for the next 6 hours, respectively. Arterialized blood was drawn at 5-minute intervals to measure plasma glucose, and a 20% dextrose solution was simultaneously infused at a variable rate to control plasma glucose levels. Plasma glucose was kept euglycemic during the euglycemic clamps and reduced in a stepwise manner during the hypoglycemic clamps to achieve 4 respective plateaus of approximately 76, 66, 56, and 46 mg/dL. Each plateau was maintained for a 45-minute period, and the next lower plateau was induced gradually within the next 45 minutes. A semiquantitative symptom questionnaire, including the symptoms "sweating" and "feelings of warmth," was administered every 15 minutes. Subjects were asked to rate the intensity of these symptoms between 0 (none) and 4 (severe). Blood samples were collected every 30 minutes and immediately centrifuged, and the supernatants were stored at −24°C until assay. Serum insulin, epinephrine, and norepinephrine levels were measured as previously described.[28]

Body temperature was orally measured (Digital Thermometer; Hartmann, Heidenheim, Germany) twice at every plateau of the hypoglycemic clamp and at the corresponding time points during the euglycemic clamps. The mean difference between the 2 temperature measurements at each time point, ie, a total of 450 measurements in duplicate, was 0.03°C with a standard deviation (SD) of 0.02°C. To determine the reproducibility and variability of the oral temperature measurement, 10 subsequent measurements were made in 2 subjects. This test had a coefficient of variation less than 0.08% (mean ± SD, 36.542° ± 0.028°C and 36.352° ± 0.029°C). A previous study by Fallis et al[29] determining the accuracy of oral temperature measurement reported a high correlation between oral and pulmonary artery (r = .92 to .96) temperature measurements in subjects with and without an endotracheal tube.

Statistical analysis was performed with the SPSS Statistics Program Version 6.0 (SPSS, Chicago, IL). A sample size of 15 subjects in each experimental condition provided a statistical power of .83 to detect differences in body temperature between baseline and hypoglycemia that were smaller than 0.15°C given a SD of 0.20°C. All values are presented as the mean ± SEM. Values were calculated for the baseline period, the hypoglycemia plateaus, and the corresponding time intervals during euglycemic clamps. A paired Student's t test was used to assess the effects of the clamps with reference to the respective baseline. Analyses of covariance (ANCOVAs) were performed to compare body temperature among the experimental conditions, with baseline values serving as a covariate. Moreover, changes in body temperature and other variables obtained at the final hypoglycemic plateau were expressed as a difference versus baseline, and these values were subsequently subjected to correlation analysis (Pearson's correlation). A P value less than .05 was considered statistically significant.

RESULTS

Antecedent Hypoglycemic Clamp

During both the high-rate and low-rate insulin infusion, plasma glucose decreased to about 56 mg/dL within the first 30 minutes and was then maintained at this level until the end of the clamp. Mean serum insulin concentrations were approximately 40-fold higher (3,603 ± 309 *v* 87 ± 3 μU/mL) during the high-rate versus low-rate insulin infusion.

Six-Hour Euglycemic and Stepwise Hypoglycemic Clamps

Plasma glucose and serum insulin levels measured during the experiments are summarized in Tables 1 and 2, respectively. Body temperature decreased during all hypoglycemic clamp conditions, but was unaltered during both of the euglycemic clamp conditions (Table 3). The decrease in body temperature did not differ between the low and the high insulin-hypo condition ($F[1,27] = 0.117$, $P = .735$). The low insulin-ante-hypo condition had no effect on the hypothermic response to

Table 2. Serum Insulin (μU/mL) During Baseline, the Hypoglycemic Plateaus of the Stepwise Hypoglycemic Clamps, and the Corresponding Time Intervals of the Euglycemic Clamps (mean ± SEM)

Condition	Baseline	Plateau 1	Plateau 2	Plateau 3	Plateau 4
Low insulin-eu	7.5 ± 0.6	101.8 ± 5.6	100.5 ± 5.6	104.1 ± 4.8	104.5 ± 5.3
High insulin-eu	7.5 ± 0.6	3,155.0 ± 214.3	4,068.2 ± 240.9	4,709.2 ± 287.0	4,746.6 ± 263.3
Low insulin-hypo	7.7 ± 0.6	90.2 ± 5.5	89.3 ± 3.9	91.2 ± 5.8	88.7 ± 6.8
High insulin-hypo	6.7 ± 0.6	3,132.6 ± 168.1	4,176.4 ± 297.8	4,328.0 ± 250.6	4,613.5 ± 263.3
Low insulin-ante-hypo	10.5 ± 1.1	92.3 ± 3.4	97.5 ± 6.4	90.0 ± 4.4	92.5 ± 6.1
High insulin-ante-hypo	10.3 ± 0.7	99.5 ± 3.9	95.8 ± 3.5	94.5 ± 4.7	98.6 ± 4.8

NOTE. Values represent the mean across the respective time intervals.

Table 3. Core Body Temperature (°C) During Baseline, the Hypoglycemic Plateaus of the Stepwise Hypoglycemic Clamps, and the Corresponding Time Intervals of the Euglycemic Clamps (mean ± SEM)

Condition	Baseline	Plateau 1	Plateau 2	Plateau 3	Plateau 4
Low insulin-eu	36.30 ± 0.05	36.16 ± 0.05	36.21 ± 0.05	36.26 ± 0.05	36.25 ± 0.06
High insulin-eu	36.36 ± 0.07	36.23 ± 0.07	36.24 ± 0.08	36.31 ± 0.08	36.29 ± 0.07
Low insulin-hypo	36.25 ± 0.05	36.23 ± 0.07	36.27 ± 0.06	36.13 ± 0.06	35.99 ± 0.11*
High insulin-hypo	36.32 ± 0.06	36.25 ± 0.07	36.20 ± 0.08	36.21 ± 0.07	36.04 ± 0.06*
Low insulin-ante-hypo	36.36 ± 0.05	36.26 ± 0.05	36.27 ± 0.04	36.17 ± 0.09	36.07 ± 0.06*
High insulin-ante-hypo	36.33 ± 0.07	36.27 ± 0.08	36.29 ± 0.05	36.11 ± 0.08	35.93 ± 0.08*

NOTE. There were no significant differences among the hypoglycemic clamp conditions and among euglycemic conditions.

*$P < .01$ *v* baseline by paired *t* test, $P < .05$ *v* low insulin-eu by ANCOVA with baseline values as a covariate, and $P < .05$ *v* high insulin-eu by ANCOVA with baseline values as a covariate.

hypoglycemia as compared with the low insulin-hypo (F[1,27] = 0.316, $P = .579$) and high insulin-hypo (F[1,27] = 0.236, $P = .631$) condition. In the high insulin-ante-hypo condition, the decrease in body temperature was more pronounced versus the low insulin-ante-hypo (F[1,27] = 2.601, $P = .118$), low insulin-hypo (F[1,27] = 2.127, $P = .177$), and high insulin-hypo (F[1,27] = 1.339, $P = .257$) condition, although these differences did not reach statistical significance.

To determine the glycemic threshold for the decrease in body temperature, 2 different methods were used: (1) determining the glycemic plateau at which changes in body temperature first reached statistical significance with reference to the baseline values, and (2) comparing the changes in body temperature during the hypoglycemic plateaus versus the corresponding time intervals of the euglycemic clamps. Using both methods, we found body temperature to be significantly reduced only at the last hypoglycemic plateau in all hypoglycemic conditions, suggesting the glycemic threshold for the decrease in body temperature to be between the third and fourth glycemic plateau, ie, when plasma glucose was between 56 and 46 mg/dL.

During all hypoglycemic conditions, self-rated symptoms of sweating and warmth increased, but the increase in the sweating score tended to be reduced in both ante-hypo conditions compared with the low insulin-hypo condition (both $P < .1$). Plasma norepinephrine and epinephrine concentrations increased during all hypoglycemic clamp conditions, but the increase in norepinephrine was significantly reduced in the low insulin-ante-hypo condition as compared with the other hypoglycemic conditions ($P < .05$ for all comparisons). The increase in epinephrine tended to be reduced after both the high and low antecedent hypoglycemia. Notably, plasma norepinephrine and the sweating score increased (both $P < .05$) during the euglycemic clamps when insulin was infused at the high rate, but not when it was infused at the lower rate (Table 4).

Correlation analyses of the pooled data for all hypoglycemic conditions showed that the decrease in body temperature was inversely correlated with a feeling of warmth, the sweating score, and catecholamine levels. Changes in sweating were positively correlated with changes in the warmth score and in catecholamines. But there was no correlation between changes in the warmth score and in catecholamines (Table 5).

DISCUSSION

Consistent with previous studies,[1-3,8] the present data show a decline in body temperature during hypoglycemia. The novel finding reported here is that the hypoglycemia-induced decrease in body temperature is not influenced by circulating insulin levels or by antecedent hypoglycemia, both of which are known to modulate counterregulatory hormone release.

The most notable finding is the resistance of the hypothermic response to the effects of antecedent hypoglycemia. Glucose counterregulation, as well as hypoglycemia awareness, have frequently been shown to be impaired after antecedent hypoglycemia,[19-25] suggesting a central nervous adaptation to hypoglycemia. Also, hypoglycemia-induced cognitive dysfunction is reduced after antecedent hypoglycemia.[19,30-32] On this background, the present findings suggest that the hypothermic response to hypoglycemia is not directly related to the hormonal, symptomatic, and cognitive responses to hypoglycemia.

In the present study, the antecedent hypoglycemia was mild, and it was only a single episode of antecedent hypoglycemia. Thus, with more severe and more frequent antecedent hypoglycemic episodes, an attenuating influence on the hypothermic

Table 4. Changes (4 plateau values − baseline values) in Body Temperature, Symptom Score, and Catecholamine Concentration During the Clamps (mean ± SEM)

Variable	Low insulin-eu	High insulin-eu	Low insulin-hypo	High insulin-hypo	Low insulin-ante-hypo	High insulin-ante-hypo
Temperature (°C)	−0.05 ± 0.08	−0.07 ± 0.08	−0.26 ± 0.09*†	−0.28 ± 0.09*†	−0.29 ± 0.09*†	−0.41 ± 0.11*†
Warmth score	−0.07 ± 0.11	−0.03 ± 0.09	+0.82 ± 0.29*†	+0.92 ± 0.28*†	+0.45 ± 0.22*†	+0.61 ± 0.35*†
Sweating score	−0.03 ± 0.07	+1.35 ± 0.25*†	+2.39 ± 0.34*†	+1.74 ± 0.29*†	+1.67 ± 0.26*†‡	+1.56 ± 0.28*†‡
Norepinephrine (pg/mL)	+14.5 ± 15.2	+58.6 ± 14.9*†	+211.4 ± 40.1*†	+256.3 ± 29.2*†	+117.9 ± 20.8*†§	+188.6 ± 23.9*†‖
Epinephrine (pg/mL)	+0.1 ± 3.5	+28.4 ± 17.0	+872.1 ± 149.7*†	+792.0 ± 87.8*†	+572.8 ± 90.0*†‡	+585,7 ± 78,7*†

*$P < .05$ for changes during the clamp (4 plateaus *v* baseline).

†$P < .05$ *v* low insulin-eu.

‡$P < .1$, §$P < .05$ *v* low insulin-hypo.

‖$P < .05$ *v* low insulin-ante-hypo.

Table 5. Correlations Between the Changes (4 plateaus − baseline) in Body Temperature, Symptom Scores, and Catecholamine Concentrations

	Δ Temperature	Δ Warmth	Δ Sweating	Δ Norepinephrine
Δ Warmth	−.31†			
Δ Sweating	−.43‡	.52‡		
Δ Norepinephrine	−.28*	.17	.33†	
Δ Epinephrine	−.40‡	.17	.40‡	.62‡

NOTE. Data are pooled across all 60 hypoglycemic clamps.
*$P < .05$.
†$P < .01$.
‡$P < .001$.

response to hypoglycemia may still develop. However, the antecedent hypoglycemia in the present study proved sufficient to reduce the release of norepinephrine and other counterregulatory hormones[27] during subsequent hypoglycemia. Thus, the hypothermic response to hypoglycemia seems distinctly less sensitive to antecedent hypoglycemia than neuroendocrine counterregulation. Considering the protective function of hypothermia for the brain during severe hypoglycemia,[9,10] a preserved hypothermic response would be crucial.

Although glycemic thresholds for glucose counterregulation, symptomatic responses, and cognitive dysfunction during hypoglycemia have been well defined in previous studies,[33] the glycemic threshold for the hypothermic response has not been determined thus far. From the present data, one may estimate the glycemic threshold for the decrease in body temperature to be between 56 and 46 mg/dL. However, since it is not known how much time is required to obtain a steady-state change in body temperature during hypoglycemia, it is still possible that the duration of the hypoglycemic plateaus in the present study was not sufficient to reach steady state with regard to the temperature decrease. Therefore, the glycemic threshold for the hypothermic response to hypoglycemia could also be lower, ie, at a higher plasma glucose, than estimated in the present data.

Another remarkable finding is that despite the decrease of body temperature, subjects felt warmer at the end of the hypoglycemic clamp than during the baseline period. Correlation analysis, in fact, confirmed an inverse relation between the change in body temperature and feelings of warmth during the hypoglycemic clamps. The phenomenon of an inverse relationship between thermal perception and changes in body temperature is well known in association with fever. The present finding of a likewise inverse relationship between thermal perception and changes in body temperature during hypoglycemia may hint at a central nervous regulation of body temperature during hypoglycemia by means of a thermoregulatory setpoint shift toward a lower body temperature. Consistent with this hypothesis, Passias et al[8] previously reported that even mild hypoglycemia (~50 mg/dL) causes a 0.60°C decrease in the body temperature threshold for shivering and also a decrease in thermal perception during exogenous cooling.

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