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ORIGINAL INVESTIGATION

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Selective processing of food words during insulin-induced hypoglycemia in healthy humans

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Abstract *Rationale:* Hypoglycemia leads to undernutrition of the brain. Favoring selective processing of food stimuli would be an adaptive cognitive strategy. However, hypoglycemia is known to impair several aspects of cognitive function, and it is unknown whether selective cognitive processing of food stimuli occurs during insulin-induced hypoglycemia. *Methods:* In a single-blind repeated measures design, healthy young adults (n=12, six female, mean age 28 years; mean body mass index 22.5 kg/m^2) performed a standard Stroop word-color test, as well as a variant with food words designed to detect selective processing of food cues. Two sessions were scheduled with a 4-week interval. In each session, a hyperinsulinemic clamp method produced a normoglycemic (plasma glucose: 4.7 mmol/l) period, followed on 1 day by a hypoglycemic (2.7 mmol/l) testing period, and on the other day a second normoglycemic testing period (counterbalanced order). *Results:* Color naming verbal reaction time (RT) increased during hypoglycemia (P<0.0001). The extent of the Stroop cognitive interference was independent of plasma glucose level. The key finding is that RT for food words increased more than for non-food control words (P<0.004), and this effect was not predicted by hunger ratings. *Conclusions:* Our data provide new evidence that during hypoglycemia, attention is directed selectively to food-relevant stimuli. The results are discussed in terms of adaptation.

Keywords Hypoglycemia · Plasma glucose · Selective attention · Hunger · Stroop test

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Introduction

Hypoglycemia causes undernutrition of the brain, sometimes leads to dramatic metabolic stress, and generally results in increased hunger (Cox et al. 1993). Another cognitive response could be increased attention to food cues, a strategy potentially requiring activation of fuel-consuming cognitive mechanisms.

Brain fuel depletion (neuroglycopenia) has been shown to impair several aspects of cognitive function and to increase reaction time (RT) (Evans et al. 2000), but data on selective cognitive processing during hypoglycemia are lacking. One method for studying selective attention is the Stroop task. The "emotional" variant of the Stroop task, suitable for examining selective cognitive processing of specific stimuli, has, to the best of our knowledge, never been used during insulin-induced hypoglycemia. The emotional variant of the Stroop task involves a comparison of the time required to speak neutral words with the time required to speak emotionally laden words.

Selective attention to food words has been observed in persons who are fasting, as well as those with tendencies toward eating disorders. Compared to controls, 24-h (Channon and Hayward 1990) but not 6-h (Stewart and Samoluk 1997) food-deprived subjects, as well as persons

reporting chronic dietary restraint (Stewart and Samoluk 1997), showed selective attention to food stimuli. However, other research was less consistent, such as the finding by Green and colleagues (1996) that the hungriest subjects had the smallest impairment in the color-naming of food words. A high caloric preload led to "restrained eaters" manifesting slowed color naming of food words (Ogden and Greville 1993).

The present study examines whether hypoglycemia leads to an adaptive selective attention to food cues, or whether the hypoglycemic cognitive impairment is too severe to allow such selective attention. The possible mediating effect of subjective hunger is also examined. The primary hypothesis was that subjects would take longer to name colors of food words than neutral words during hypoglycemia but not during normoglycemia.

Materials and methods

Subjects

Twelve healthy adult volunteers (six female; mean age 28 years, range 23–35; mean body mass index 22.5 kg/m^2) participated. All were native speakers of German who had normal findings on physical examination, routine blood chemistry and hematology, and standard electrocardiography. The exclusion criteria were current tobacco smoking or sedative use, any sign of illicit drug use, current dieting, or any indication of eating disorder. Subjects read and signed an institutional review board approved informed consent form prior to the beginning of the study. The research was in accordance with the Declaration of Helsinki and was approved by the ethics committee of the Basel University Hospital.

Hypoglycemic clamp and procedure

On the day of medical screening (prior to the first experimental session day), the subjects were familiarized with all of the test procedures.

The two experimental sessions (separated by 4 weeks) were conducted in the psychophysiology laboratory of the Basel University Hospital, according to standard hypoglycemic clamp protocols (DeFronzo et al. 1979; Heine 1993). On both experimental days, subjects entered the facility at 8:00 a.m. They were requested to abstain from food, alcohol, and caffeinated beverages for 12 h.

The hypoglycemic clamp procedure began with the insertion (in the retrograde direction) of an IV catheter into a dorsal vein of the subject's left hand. The subject's hand was then placed in a box heated to 52°C (to open shunt vessels in the hand, yielding venous samples reflective of arterial plasma glucose levels). Another IV catheter was inserted into a cubital vein of the subject's left arm for infusion of insulin and glucose. The subject then had a loading dose of regular human insulin (Actrapid; Novo Nordisk; 0.01 IU/kg body weight), followed by continuous insulin infusion (1 mIU/kg/min). Glucose infusion (20% glucose solution) was started at 2.5 mg/kg per minute and was frequently adjusted throughout the session on the basis of plasma glucose determinations conducted every 5–10 min. Arterialized venous blood samples (1.5 ml) were collected and centrifuged, and then their plasma glucose concentrations were determined with glucose oxidase and a hydrogen peroxide sensor (glucose analyzer2300 STAT Plus, YSI, Yellow Springs, Ohio, USA).

During both experimental sessions, the first (baseline) period targeted plasma glucose at normoglycemic fasting levels (4.7 mmol/l). During the second (target) period of the session, the insulin infusion was increased to 2 mIU/kg per minute and the glucose infusion rate was adjusted in one of the sessions (randomly counterbalanced across subjects) to maintain a normoglycemic level, and in the other session it was reduced to a hypoglycemic plasma glucose level of 2.7 mmol/l. For the hypoglycemic target period, plasma glucose was allowed to drop rapidly by attenuating the glucose infusion rate. Patients were not told of the plasma glucose target level (single blind design). The plasma glucose levels actually attained with the clamp procedures were at or very close to targeted levels: 4.7±0.1 mmol/l during normoglycemic baseline and 4.8±0.1 mmol/l during the normoglycemic target period of the normoglycemic clamp study day; and 4.8±0.1 mmol/l during normoglycemic baseline and 2.7±0.1 mmol/l during the hypoglycemic target period on the hypoglycemic clamp study day (see Fig. 1). The subjects provided a rating of how hungry they felt during the target periods (before test administration) on a 7-point scale (from 0="not hungry at all" to 6="extreme hunger").

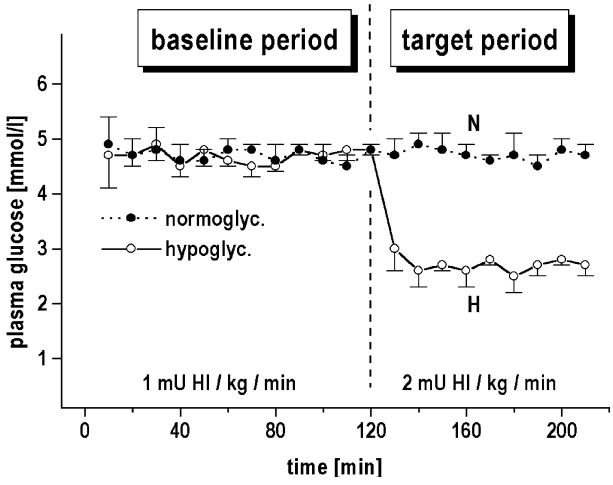

Fig. 1 Timing of testing and hyperinsulinemic clamp effects on plasma glucose. In a cross-over repeated measures design, hyperinsulinemic clamp studies using human insulin (HI) were performed on two occasions, 4 weeks apart. On one occasion, a normoglycemic (plasma glucose: 4.7 mmol/l) baseline (*dark circles*) was followed by a hypoglycemic (plasma glucose: 2.7 mmol/l) target period (*H*). On the other occasion (control condition), the normoglycemic baseline (*open circles*) was followed by a normoglycemic target period (*N*). Means and SEMs are depicted

The subjects had a few practice trials (using the same words as during later testing) of the tests to acclimate to the testing procedure (pre-baseline; data discarded). The baseline period lasted approximately 120 min, and the target period lasted approximately 90 min. As depicted in Fig. 1, testing during the target period began 35 min after target plasma glucose levels were reached in the hypoglycemic target condition, or at a comparable time in the normoglycemic target condition.

Following each session, each subject's plasma glucose level was stabilized, and then they were accompanied during a high carbohydrate lunch. They were paid 500 Swiss Francs for their participation.

Stroop testing

The classic Stroop test requires the subject to name the colors in which words are printed while ignoring the content of the words. The difference between the color naming verbal RT for congruent (the word "blue" written in blue ink) and conflicting (the word "blue" written in yellow ink) color-word combinations provides an index of the degree to which the processing of word content interfered with the color naming task. Based on extensive review of

Stroop testing research, it was inferred (MacLeod 1991) that the Stroop task most likely involves parallel processing of the irrelevant and the relevant aspects of a stimulus. This indicator of cognitive processing bias has also been used successfully with food words to assess selective attention to food cues (Channon and Hayward 1990; Stewart and Samoluk 1997; Braet and Crombez 2003) by comparing response times to food and neutral words.

Our "emotional" version of the Stroop test requires the subject to name as quickly and accurately as possible the color (blue, red, yellow) in which food-relevant (apple, bread, food, hunger, cheese, cake, menu, nut, fruit, pasta, pizza, chicken, juice, sausage), control (car, ball, book, window, flute, violin, hair, trouser, church, song, paper, shoe, pond), and color words (blue, red, yellow) are displayed in German on a gray computer screen. The 120 words are presented in randomized order with an interstimulus interval of 2.5 s (because a pilot study indicated that verbal response onset was unlikely to occur later than 2.5 s after stimulus onset; any later responses were scored as omission errors). The same set of words was used on both study days. Each food and control word was presented once in each color, and each color word was presented 3 times in each color.

The Stroop test dependent variables were verbal RT for the correct responses in the various word categories (RT for false responses was not calculated because of the low frequency of errors).

Verbal responses were assessed with a standard microphone (1 m distance from the subject), amplified, rectified and integrated (time constant: 10 ms), digitized and then recorded for offline analysis (1 kHz, 12-bit resolution). The RT was detected with customized software (the precision of the software was ±2 ms for a 1000 Hz signal during our laboratory testing) in conjunction with manual verification of when the color naming response began (as opposed to an interjection or other sound).

Statistical analysis

Hypoglycemic effects on both standard Stroop (color congruent versus color conflicting word-color combinations) and food Stroop (food words versus control words) RT were analyzed with a three-way repeated ANOVA (word category by clamp condition by order of clamp condition; the first two are within-subjects factors).

Mean±SEM and exact non-adjusted two-tailed *P*-values are reported in the text, and figures. All statistical calculations were performed with SAS software (release 8.0, WinNT, SAS Institute Inc., Cary, N.C., USA).

Results

Stroop testing

As detailed in Fig. 2 (bottom bars), standard Stroop testing showed the usual interference effect [word category main effect: $F(1,10)=65.6$; $P<0.0001$], indicating that the color naming of conflicting word-color combinations had a longer RT than color-naming of congruent combinations. Also as expected (Evans et al. 2000), RT was greater for hypoglycemic than for normoglycemic conditions [clamp condition main effect: $F(1,10)=16.3$; $P<0.002$]. Interestingly, the extent of the Stroop cognitive interference was completely independent of plasma glucose level ["word category by clamp condition" interaction: $F(1,10)=0.0$]. There was no effect of clamp condition order.

As shown in Fig. 2 (top bars), hypoglycemia increased RT for food words as compared to control words, and under normoglycemic conditions, RT for food words did not differ from control (non-food) words ["word category by clamp condition" interaction: $F(1,10)=12.4$, $P=0.005$]. There was no impact of clamp condition order.

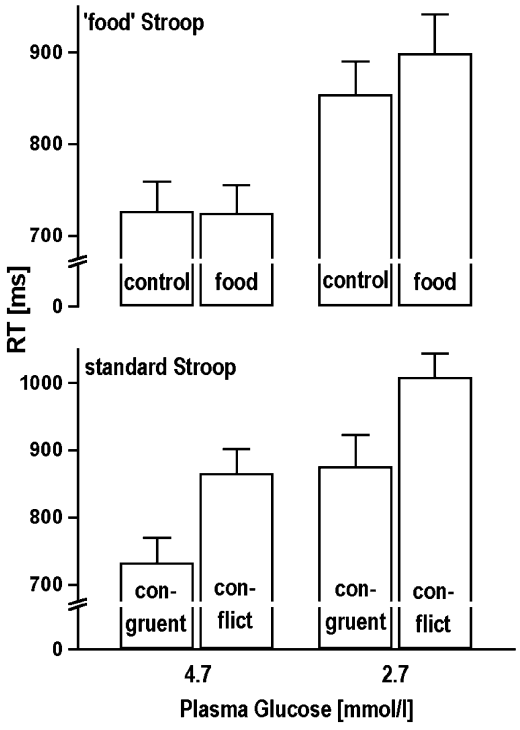

Fig. 2 RT during "food" and standard Stroop testing. During hypoglycemia (plasma glucose: 2.7 mmol/l) but not normoglycemia (plasma glucose: 4.7 mmol/l), color naming of food words takes longer than color naming of control words (see *upper bars*). Such an interaction is not present in the standard Stroop test, for which main effects of word category and clamp condition are present

The above effect was also found when "high glycemic" food words [cake, bread, pizza, pasta; mean RT during normoglycemia: 735±38 ms; during hypoglycemia: 915±46 ms; word category by clamp condition interaction: $F(1,10)=8.8$, $P=0.01$], and "non-high glycemic" food words [all other food words; mean RT during normoglycemia: 721±27 ms; during hypoglycemia: 894±40 ms; word category by clamp condition interaction: $F(1,10)=10.8$, $P=0.008$] were tested separately. Again, there was no impact of clamp condition order.

Other results

Subjects reported feeling much more hunger during the hypoglycemic (4.5±0.2) than during the normoglycemic (2.6±0.3; $P<0.002$) target period. However, the RT difference between food and control words was unrelated to ratings of hunger or body mass index. There were no sex differences.

Discussion

In this study of healthy young adults, the hypoglycemic clamp method impaired cognitive function (RT was prolonged). The magnitude of the Stroop color-naming cognitive interference effect was independent of plasma glucose level, indicating that the Stroop interference effects are present during moderate hypoglycemia. A selective attention to food stimuli (as indicated by an increase in the RT to food stimuli) was caused by hypoglycemia, indicating that with reduced plasma glucose fuel, there is an adaptive attention to food stimuli, rather than an incapacity for selective attention. We infer that given our experimental design, any possible semantic priming effects (Warren 1974) had little or no role in the outcome.

The "emotional" variant of the Stroop task is based on the classic Stroop effect. This classic interference effect (of color naming RT for congruent versus conflicting color-word combinations) was unaltered during hypoglycemia, thereby supporting the use of the "emotional" Stroop variant during hypoglycemia.

The adaptive response of selective attention (some theoretical variants of this concept include enhanced schematic processing of salient material, and changes in focus during threatening conditions) to food cues during hypoglycemia has a special character, as it is not readily explained by other processes. On the one hand, because hunger ratings were not associated with differences in RT prolongation, the selective attention does not appear to be predominantly driven by the emotionally tinged aspect of hunger. On the other hand, the classic Stroop effect does not differ as a function of plasma glucose level, implying that other than a general slowing, the basic process of cognitive interference does not change substantially during the degree of hypoglycemia examined in the present study.

It is likely that survival of the individual and the species was fostered by the ability to direct cognitive resources to food information, thereby selectively increasing the organism's readiness to find and utilize nutrients. Besides hunger, differential attention to food stimuli triggered by hypoglycemia might provide a form of psychological counter-regulation which complements hunger as a motivation to eat.

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References

Braet C, Crombez G (2003) Cognitive interference due to food cues in childhood obesity. J Clin Child Adolesc Psychol 32:32–39

Channon S, Hayward A (1990) The effect of short-term fasting on processing of food cues in normal subjects. Int J Eating Disord 9:447–452

Cox D, Eickhoff K, Gonder-Frederick L, Clarke W (1993) Hunger. a sensitive but nonspecific symptom of hypoglycemia. Diabetes Care 16:1624–1625

DeFronzo R, Tobin J, Andres R (1979) Glucose clamp technique: a method for quantifying insulin secretion and resistance. Am J Physiol 237:E214–223

Evans ML, Pernet A, Lomas J, Jones J, Amiel SA (2000) Delay in onset of awareness of acute hypoglycemia and of restoration of cognitive performance during recovery. Diabetes Care 23:893–897

Green M, Elliman N, Rogers P (1996) Hunger, caloric preloading and the selective processing of food and body shape words. Br J Clin Psychol 35:143–151

Heine R (1993) Methods of investigation of insulin-induced hypoglycemia. In: Frier B, Fisher B (eds) Hypoglycemia and diabetes. Clinical and physiological aspects. Edward Arnold, London, pp 165–175

MacLeod C (1991) Half a century of research on the Stroop effect: an integrative review. Psychol Bull 109:163–203

Ogden J, Greville L (1993) Cognitive changes to preloading in restrained and unrestrained eaters as measured by the Stroop task. Int J Eat Disord 14:185–195

Stewart SH, Samoluk SB (1997) Effects of short-term food deprivation and chronic dietary restraint on the selective processing of appetitive-related cues. Int J Eat Disord 21:129–135

Warren R (1974) Association, directionality, and stimulus encoding. J Exp Psychol 102:151–158