High-Calorie Glucose-Rich Food Attenuates Neuroglycopenic Symptoms in Patients with Addison's Disease

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Context/Objective: Patients with Addison's disease often suffer from fatigue, faintness, lack of concentration, and memory deficits, *i.e.* symptoms reminiscent of those of neuroglycopenia. Suspecting that a lack of central nervous glucose contributes to these symptoms, we examined whether they can be attenuated by the intake of palatable food rich in glucose ("comfort food") in these patients and, furthermore, whether comfort food reduces hypothalamus-pituitary-adrenal axis activity as observed in animal studies.

Design/Setting/Patients/Outcome: Ten Addison patients with primary adrenal insufficiency and acutely discontinued cortisol substitution and 10 matched healthy controls each participated in two experimental sessions in which they were offered a free-choice high-calorie buffet (comfort food) and green salad, respectively, after a mental stress test. Neuroglycopenic and autonomic symptoms, cognitive function (short-term memory, attention), and hormones of the sympathoadrenal system (ACTH, cortisol, catecholamines) were assessed throughout the sessions.

Results: Scores of neuroglycopenic symptoms were persistently higher in Addison patients than in controls and were improved by comfort food in comparison to salad ($P < 0.04$), whereas control subjects did not show such changes. Attention was generally reduced in patients as compared to controls ($P < 0.05$) and was slightly improved by comfort food, as was memory (each $P < 0.07$). Sympathoadrenal hormone concentrations remained unaltered.

Conclusions: High-calorie comfort food reduces symptoms of neuroglycopenia in Addison patients, suggesting that Addison's disease is associated with a deficit in cerebral energy supply that can partly be alleviated by intake of palatable food. It will be important to investigate whether additional oral glucose supply may be helpful in improving patients' well-being. **(*J Clin Endocrinol Metab* 95: 522–528, 2010)**

Patients with Addison's disease often suffer from fatigue, faintness, and deficits in concentration and memory, symptoms that are attributed to a lack of gluco- and mineralocorticoids (1, 2). Similar symptoms are seen in healthy subjects during hypoglycemia-induced neuroglycopenia (3). Addison patients have an increased risk of developing hypoglycemia, probably as a result of increased glucose oxidation and decreased glucose production due to greatly diminished cortisol release, thus leading to improved insulin sensitivity (4). Hypoglycemic episodes accompanied by insufficient brain glucose supply may induce neuroglycopenic states and related symptoms in these patients.

In adrenalectomized rats, free-choice ingestion of sucrose has been shown to reduce the detrimental metabolic effects of cortisol deficiency (5, 6). When healthy rats had access to "comfort food," *i.e.* palatable energy-dense food with high fat and glucose content, they displayed dampened ACTH and corticosterone responses to restraint

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Abbreviation: HPA, Hypothalamic-pituitary-adrenal.

stress (7). In some people, comfort food ingestion is likewise favored in stressful situations, increases well-being, and reduces anxiety (8, 9). These changes probably involve the endogenous opioid system (9, 10). Assuming that unsubstituted Addison patients develop neuroglycopenic conditions, we hypothesized that oral ingestion of free-choice comfort food compensates for neurocognitive and endocrine deficits associated with hypocortisolism. We assessed neurocognitive performance and hypoglycemic counterregulatory hormones in unsubstituted Addison patients and in matched healthy controls over a period of 2 h after ingestion of comfort food or low-calorie green salad.

Subjects and Methods

Subjects

Ten patients suffering from primary adrenal insufficiency [Addison group, five females; age (mean ± SEM), 49.6 ± 3.1 yr; body mass index (BMI), 26.0 ± 1.3 kg/m^2], and 10 age- and BMI-matched healthy subjects (control group, five females; age, 51.3 ± 2.7 yr; BMI, 25.2 ± 1.5 kg/m^2; each $P > 0.69$ for comparison with the Addison group) participated in our study. In the patients, time since diagnosis of Addison′s disease ranged from 1 to 18 yr before study onset. Autoimmunity was the underlying cause of the disease in eight of the patients and bilateral adrenalectomy because of pheochromocytoma and venous thrombosis, respectively, in two patients. Adrenal insufficiency was accompanied by hypothyroidism treated by T_4 substitution in nine patients and by chronic atrophic gastritis in three patients. In all patients, adrenal insufficiency was treated with hydrocortisone [daily dose (mean ± SEM), 26.25 ± 1.46 mg; range, 17.5–30 mg] and fludrocortisone medication (daily dose, 0.08 ± 0.017 mg; range, 0–0.2 mg). Patients and control subjects (except for two men in need of antihypertensive medication and one woman with hypothyroidism treated with T_4 substitution) had no other acute or chronic diseases, no further kind of medication, and no abuse of nicotine, alcohol, or drugs. Each volunteer gave written informed consent before participation, and the study was approved by the local ethics committee.

Experimental design

Each subject participated in two experimental sessions separated by at least 4 wk. In one condition, subjects had free access to a high-calorie buffet (comfort food), consisting of potato chips, peanuts, chocolate, muffins, wine gums, custard, bread rolls, brown bread, cheese, smoked salmon, meat salad, cream cheese, butter, chocolaty hazelnut spread, meatballs, lemonade, drinking chocolate, orange juice, condensed milk, sugar, fruit tea, coffee (decaffeinated), and water (amounting to a total of 8043 offered kilocalories). In the control condition, subjects ingested green salad with a low-calorie dressing and water (amounting to a total of 75 offered kilocalories) to establish a condition with comparable oropharyngeal and gastric stimulation but with very low calorie content and lacking the hedonic value of free-choice comfort food. The order of conditions was balanced across subjects.

On the days of the experiments, patients were allowed to take their hydrocortisone and fludrocortisone medication at 0800 h [hydrocortisone, morning dose (mean ± SEM) 15.25 ± 1.42 mg; range, 10–20 mg; fludrocortisone, morning dose, 0.07 ± 0.011 mg; range, 0–0.1 mg]. All subjects were instructed to have a regular lunch at 1300 h but not to eat afterward. Participants arrived at the medical research unit at 1700 h. The experiments were performed in a sound-attenuated room with the subject resting on a bed with his/her trunk in an almost upright position (~60°). After physical examination, a cannula was inserted into a peripheral vein of the subject's arm. Sessions consisted of a baseline period (1700 to 1810 h), a mental stress test (1810 to 1815 h), a period of food intake (buffet and salad, respectively; 1815 to 1845 h), and a post food intake period (1845 to 2015 h). Attention and memory tests took place during baseline (45 min before food intake) and 90 min after the start of the food-intake period. Blood was sampled at 1730, 1800, and 1815 h during baseline and then, every 15 min until 1945 h with a final blood sampling at 2015 h. Food intake was measured by weighing buffet components before and after meal, and total calorie intake as well as macronutrients were calculated. Patients received their scheduled hydrocortisone dosage after the end of the session.

Because acute mental stress provokes enhanced energy demand, which in turn favors the ingestion of comfort food, we introduced a mental arithmetic stressor. Immediately before being offered the buffet, subjects had to perform the mental arithmetic test of the Trier Social Stress Test, *i.e.* they had to count down from a large prime number in decrements of 13 as quickly and accurately as possible. On every failure, the subject had to restart at the beginning (11). At the end of the session, subjects rated the extent of the perceived stress ("I was stressed during the test situation") on a visual analog scale ranging from 0 to 100.

Neurocognitive tests

Selective attention was tested by means of the Stroop task. The three subtests of the Stroop task were as follows: the first task was to read as fast and correctly as possible color names printed in black ink (word subtest); the second part was to name the ink colors of a series of "X" (color subtest); and the third part was to name the ink color of color names printed in different colors than they denote, *e.g.* "red" printed in blue; interference subtest). For each subtest, a panel was presented showing 30 rows each containing five stimuli that the subject should respond to sequentially. The total number of correct responses within 1 min was determined for each subtest. Different panels were used at each testing, with the order of panels balanced across subjects.

Short-term memory was tested subsequent to the Stroop task by means of a word recall task that had previously been shown to be sensitive to the effects of hypoglycemia (12). Thirty words belonging to three semantic categories (neutral, food-related, and emotional) were presented orally in random order. After a mental arithmetic distraction task of 1 min, the subject was required to write down within 1 min all the words he/she remembered. The number of words correctly recalled was determined in total as well as separately for each semantic category. Different lists were used at each testing, and the order of applied lists was balanced across subjects.

Symptom scales were presented three times, *i.e.* before attention and memory assessments and also 30 min after offering the meal. Subjects rated from zero (not at all) to 9 (severely) the following 11 symptoms that have previously been shown to be increased in hypoglycemia (13): dizziness, tingling, blurred vision, difficulty in thinking, faintness, anxiety, palpitation, hunger, sweating, irritability, and tremor. Consistent with categories

used by previous investigators (3), the first five symptoms are considered neuroglycopenic, and the latter six autonomic.

A mood questionnaire was presented in conjunction with the Stroop task and the memory tests (14). Subjects indicated to which extent from 1 (not at all) to 5 (severely) each of the following 12 adjectives described their current mood: content, rested, restless, unwell, nerveless, calm, tired, well, uneasy, vivid, uncomfortable, and relaxed.

Assays

Blood samples were centrifuged within 1 min after withdrawal, and serum and plasma were kept at −72 C until assay. Serum ACTH, cortisol, C-peptide, and insulin were measured by commercial enzyme-linked immunoassays (all Immulite; Diagnostic Products Corp., Los Angeles, CA) with the following intraassay and interassay coefficients of variation, respectively: cortisol, less than 5.8% and less than 6.3%; C-peptide, less than 7.6% and less than 10.5%; insulin, less than 5.2% and less than 6.1%; and ACTH, less than 6.1% and less than 9.4%. Plasma epinephrine and norepinephrine were measured by standard HPLC with electrochemical detection (Recipe Chemicals + Instruments, Munich, Germany) with the following intraassay and interassay coefficients of variation, respectively: epinephrine, less than 7.6% and less than 4.2%; norepinephrine, less than 6.7% and less than 5.3%.

Statistical analysis

Data are presented as means ± SEM. Analyses are based on ANOVA for repeated measures, including the factors "Food" (comfort food buffet *vs.* salad), "Time" (time points of data collection), and "Group" (Addison group *vs.* control group) with correction of degrees of freedom according to the Greenhouse-Geisser procedure. For pairwise comparisons within one group, Student's paired-samples *t* test was applied. A *P* value <0.05 was considered significant. All calculations were done by SPSS 12.0.0 (SPSS Inc., Chicago, IL).

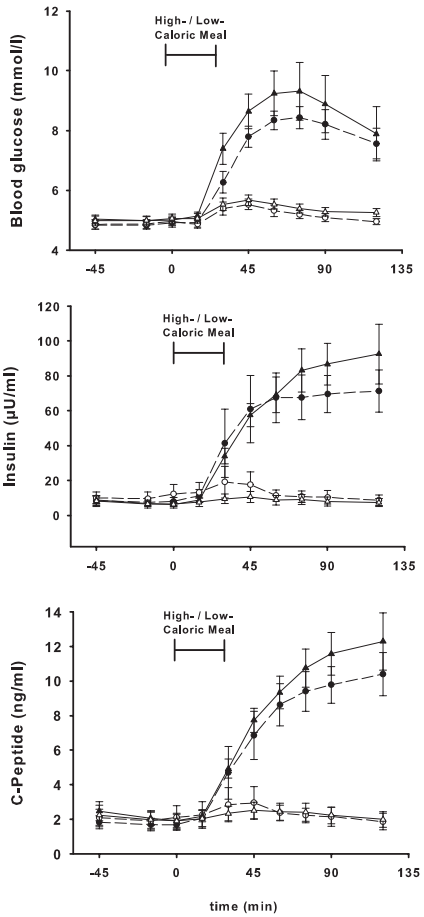

FIG. 1. Plasma concentrations of glucose and serum concentrations of insulin and C-peptide (means ± SEM) before, during, and after ingestion of high-calorie food (comfort food buffet; *black symbols*) and low-calorie food (salad; *white symbols*) in a group of Addison patients (n = 10; *circles*, *dashed lines*) and a group of healthy controls (n = 10; *triangles*, *solid lines*). Food was offered after a baseline period of 45 min, and subjects were free to eat *ad libitum* for 30 min.

Results

Calorie intake, blood glucose levels, and concentrations of insulin

Calorie intake in the comfort food condition was about 20 times higher than in the salad condition in both groups. Calorie intake was not different between groups, equaling 1236 ± 215 kcal in patients and 1516 ± 140 kcal in controls in the comfort food condition ($P = 0.29$, for group main effects) and 65 kcal in both groups in the salad condition ($P = 0.96$). Intake of macronutrients was likewise comparable ($P > 0.15$ for group main effects).

Mean blood glucose levels increased after comfort food ingestion in patients and in controls ($P < 0.001$ for food × time interaction; Fig. 1). Glucose concentrations in patients appeared to increase to a lesser extent than in controls, but this difference failed to reach significance ($P > 0.23$ for group effects). Concentrations of insulin and C-peptide rose after comfort food ingestion in both groups ($P < 0.001$ for food × time) without any group differences ($P > 0.66$ for group effects).

Results of symptom scores, mood ratings, and neurocognitive tests

Sum scores of neuroglycopenic symptoms were persistently higher in Addison patients than controls in both conditions ($P = 0.005$ for group effects; Fig. 2), mainly due to higher ratings of the single symptoms "difficulty in thinking" and "faintness." In contrast to controls, comfort food decreased neuroglycopenic symptoms in Addison patients, with a clear reduction of these symptoms 90 min after comfort food intake (8.2 ± 1.3 *vs.* 10.6 ± 1.2, $P = 0.037$; $P = 0.089$ for food × time × group interaction). Autonomic symptoms were comparable between groups ($P > 0.19$ for group effects) and were dampened by comfort food 30 and 90 min after high-calorie intake in patients ($P < 0.02$) and 90 min after comfort food in controls ($P = 0.008$), mainly by dampening the rating of the single symptom "hunger."

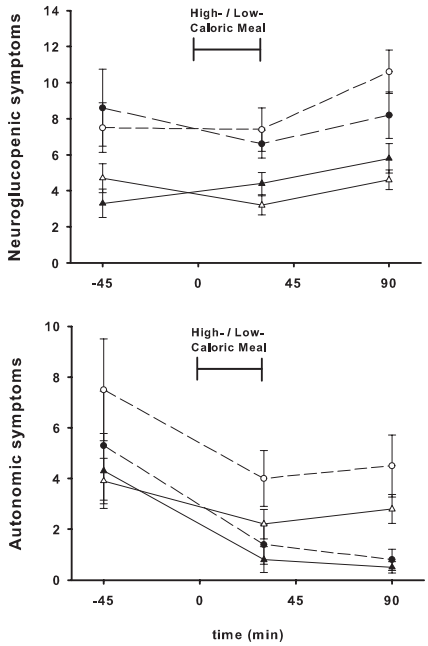

FIG. 2. Rating of symptom scores of neuroglycopenic and autonomic symptoms before and after ingestion of high-calorie food (comfort food buffet; *black symbols*) and low-calorie food (salad; *white symbols*) in a group of Addison patients (n = 10; *circles*, *dashed lines*) and a group of healthy controls (n = 10; *triangles*, *solid lines*). Food was offered after a baseline period of 45 min, and subjects were free to eat *ad libitum* for 30 min.

Ratings of mood were not influenced by calorie condition. Comparing the groups, patients felt more tired and unwell and less vivid than controls in the salad condition ($P < 0.05$ for all). Also, they stated that they felt more restless and less rested, well, and content in the comfort food condition compared with controls ($P < 0.05$ for all).

Comfort food slightly improved performance on the word subtest and the interference test of the Stroop task in the Addison group ($P = 0.13$ and $P = 0.07$ for food main effect, respectively; Table 1), whereas there was no influence of comfort food on any of the subtests in the control group ($P > 0.34$ for food main effect, for all subtests). In the group comparison, patients performed worse than controls in the word reading and in the color naming subtest ($P = 0.013$ and $P = 0.056$ for group effects, respectively).

Comfort food also tended to increase the recall performance of neutral and food-related words in Addison patients ($P = 0.07$ for food main effect and $P = 0.07$ for food × time interaction, respectively). Recall of emotional words in patients and overall wordlist recall in controls were not influenced by food intake ($P > 0.75$ for food main effect, for all subtests), and there were also no differences in the performance between patients and controls ($P > 0.22$ for group effects).

Ratings of the perceived stress during the mental arithmetic test averaged 11.45 ± 2.58 in the Addison group and 10.00 ± 3.83 in the control group (on a scale from 0 to 100) without differences in conditions or groups ($P > 0.47$ for food × group interaction).

Hormonal responses

Concentrations of ACTH and cortisol were not influenced by the type of food in both groups ($P > 0.37$ for

TABLE 1. Stroop task scores and wordlist recall

	High-calorie food (comfort food)	Low-calorie food (salad)	*P* value (ANOVA for food)
Stroop task (attention)			
Addison group			
Word subtest, correct responses	107.0 ± 2.79[a]	103.8 ± 2.96[a]	0.13
Color subtest	77.1 ± 1.72[a]	79.2 ± 1.92	0.27
Interference test	49.7 ± 1.94	47.6 ± 1.44	0.07
Control group			
Word subtest	122.5 ± 2.70	119.7 ± 3.92	0.46
Color subtest	87.0 ± 2.68	86.8 ± 2.96	0.87
Interference test	54.2 ± 2.82	55.3 ± 2.84	0.34
Wordlist (short-term memory)			
Addison group			
Recalled emotional words	2.9 ± 0.43	3.5 ± 0.47	0.88
Recalled neutral words	2.7 ± 0.41	2.3 ± 0.42	0.07
Recalled food words	3.0 ± 0.30	2.9 ± 0.39	0.75
Control group			
Recalled emotional words	4.1 ± 0.41	4.2 ± 0.46	0.89
Recalled neutral words	2.7 ± 0.49	2.7 ± 0.41	1.00
Recalled food words	3.5 ± 0.43	3.5 ± 0.36	0.86

Data are expressed as means ± SEM. Results of the high- and low-calorie food condition were compared by ANOVA and *P* values for main factor "Food" are indicated.

[a] Performance in the word subtest and the color subtest of the Stroop task was significantly impaired in Addison patients compared to controls ($P < 0.05$ for ANOVA Group effects). Baseline values of the Stroop task and the wordlist did not differ between conditions ($P > 0.1$ for all comparisons).

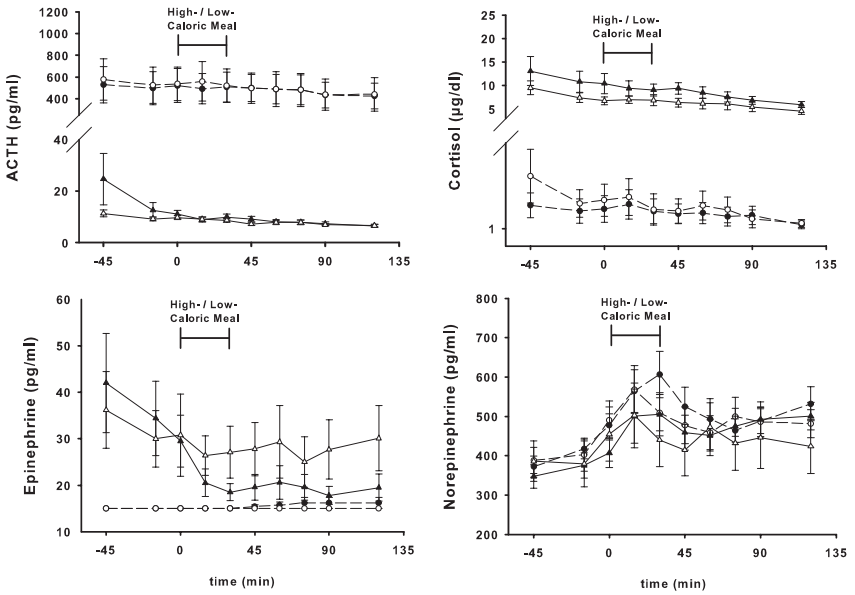

FIG. 3. Plasma or serum concentrations of ACTH, cortisol, epinephrine, and norepinephrine (means ± SEM) before, during, and after ingestion of high-calorie food (comfort food buffet; *black symbols*) and low-calorie food (salad; *white symbols*) in a group of Addison patients (n = 10; *circles*, *dashed lines*) and a group of healthy controls (n = 10; *triangles*, *solid lines*). Food was offered after a baseline period of 45 min, and subjects were free to eat *ad libitum* for 30 min.

respective food × time effects; Fig. 3). As expected, ACTH levels were markedly higher in Addison patients compared with controls ($P = 0.004$), and cortisol levels were likewise significantly lower in patients than controls ($P < 0.001$). Epinephrine levels were very low in patients compared with controls ($P = 0.021$) without any influence of the food in both groups ($P > 0.16$ for food × time). Norepinephrine levels did not differ between conditions or groups ($P > 0.46$ for all comparisons).

Discussion

In our study, Addison patients showed consistently higher neuroglycopenic symptom ratings than healthy control subjects. Moreover, patients displayed reduced attention and impaired mood in comparison to healthy participants. This pattern was partially reversed after free-choice intake of comfort food that in comparison to salad improved neuroglycopenic symptoms and slightly enhanced memory functions and attention without affecting hypothalamic-pituitary-adrenal (HPA) axis activity. Our results suggest that comfort food improves neurocognitive functions independent of HPA axis secretion, possibly by boosting glucose supply to the brain.

There is experimental evidence that a minimal glucocorticoid concentration is required to establish regular secretory activity of the HPA axis (15, 16). In turn, the absence of cortisol leads to severe disintegration of the HPA stress system. We previously hypothesized that normal HPA axis function is necessary for the adequate allocation of glucose to the brain as the final consumer in the energetic supply chain (17, 18). Consequently, cortisol deficiency is expected to induce signs of central nervous energy deficits. Additional glucose supply to the brain might thus attenuate neuroglycopenic symptoms. This is what was observed in the present study.

We further investigated the effects of high-calorie food intake on the HPA axis. Adrenalectomized rats that had access to sucrose displayed normalized values of all metabolic and of most hormonal parameters studied (5, 6). When healthy rats had access to "comfort food," *i.e.* palatable energy-dense food with high fat and glucose content, they displayed dampened ACTH and corticosterone responses to restraint stress (7). In the present study, however, hormonal levels were not influenced by ingestion of high-calorie food. A similar lack of effect on HPA axis activation was observed in previous experiments applying iv glucose infusion in Addison patients (19). In the present study, we changed the design to add the components "oral ingestion," "free-choice," "comfort food," and "mental stress" to the uptake of calories. Oral glucose ingestion reduces hypothalamic activity to a greater extent than iv glucose administration (20), hinting to a critical role of gastrointestinal afferents and psychological aspects in the central processing of glucose uptake. Also, free choice of high-calorie comfort food diminished HPA responses in rats, whereas enforced high-density diets were ineffective and rather stimulated HPA responses (21). Mental stress has been shown to be a suitable trigger of HPA axis activation that could be dampened by comfort food in rats (7). Although we considered all these aspects in our present study, HPA activity was unaffected by free-choice comfort food in our patients.

One explanation for the missing effects of high-calorie food on the HPA axis might be the relatively limited sample size that was due to the general difficulty of enrolling appropriate patients with primary adrenal insufficiency and that might have precluded the detection of more subtle treatment effects. Another explanation may be that the mental stressor used in our study was too mild to impact stress hormones or that subjects were already stressed to some degree because of the laboratory setting so that subtle task-related stress effects were masked. Moreover, in Addison patients, it is possible that ACTH release cannot

be adequately suppressed due to autonomous ACTH production, a phenomenon known to occur in patients with a long history of Addison's disease (22). Our patients had a disease history of at least 1 yr, which is long compared with the animal studies investigating newly adrenalectomized rats. Moreover, whereas food intake lasted 30 min in our study, rats were exposed to comfort food over a period of several days, and importantly, ACTH and cortisol levels were dampened after 10 d but not after 5 d (23), suggesting that longer periods of high-caloric food supply may be necessary to reduce up-regulated ACTH levels.

Interestingly, the quite robust meal-related cortisol peak was absent in our control subjects. It may thus appear a contradiction to the well-investigated cortisol enhancement after food intake, but most studies focused on meal intake at midday, *e.g.* the usual meal time (24). Our buffet was offered at 1800 h, a time where circadian cortisol production is low. This lower production rate seems to correspond with a minor cortisol response showing a large inter- and intraindividual variability (25). Besides, the cortisol peak may be masked or depressed by prior stress-induced rises (26), as is the case with basal cortisol values of our control subjects.

As to catecholamines, epinephrine levels in patients were very low, a finding that was also described by Bornstein *et al.* (27), suggesting that a high intraadrenal glucocorticoid concentration is necessary for adrenal epinephrine synthesis.

Under basal conditions, the Addison patients of our study displayed distinctly increased neuroglycopenic symptoms, supporting the view that unsubstituted Addison patients are in a neuroglycopenic state. This is in line with our initial hypothesis that deficient cortisol may hamper sufficient central nervous energy supply. In accordance, patients with Addison′s disease manifest hypoglycemic symptoms at relatively higher blood glucose levels than healthy humans (28). As we observed in our study, self-rated mood was persistently worse in patients than in controls. Comparable results have been obtained in a recent large cross-sectional study where patients with adrenal insufficiency on standard replacement reported impaired subjective health status, especially fatigue, reduced vitality, and increased anxiety (29). Imperfect replacement strategies with gluco- and mineralocorticoids as well as concomitant therapy with thyroid hormones might also have influenced rated mood in our patients. Impaired attention in comparison to control subjects was another feature of our patients that hints at neuroglycopenic features of Addison's disease. Enhanced activation, concentration, increased arousal, and higher spirits were reported after cortisol infusion in healthy men (30). This suggests that cortisol can induce changes toward euphoric mood, and thus, absent cortisol like in Addison's disease may reduce mood and the ability to concentrate as demonstrated in our subjects.

Importantly, in our study increased neuroglycopenic symptoms were attenuated by oral energy supply, which contrasts to previous experiments where iv infused glucose had no influence on any of the measured parameters (19). This implicates an important role of behavioral factors like the free-choice aspect and hedonic components of food intake like the rewarding quality of high-calorie foods as well as of the gut-brain axis. Free choice of high-calorie food depends on complex decision-making processes in which both the brain stem and the cerebral hemispheres are involved. This active process is essentially different from our infusion experiments in which the participants are passive. The gut-brain axis has also been shown to influence whole body metabolism through the interaction of hypothalamic neuropeptides and gastrointestinal hormones like ghrelin, cholecystokinin, and peptide YY (31). Also, hippocampal activity regulated by the vagus nerve has been demonstrated to modulate eating behaviors mediated by stomach expansion (32). Our results hint at the additional importance of this gut-brain circuitry. Comfort food has been shown to restore the neuroenergetic and hormonal balance in adrenalectomized rats (5, 6). Our finding of a dampening effect on neuroglycopenic symptoms 90 min after ingestion of comfort food may thus reflect a rebalancing effect due to enhanced brain energy supply. Moreover, measures of attention and memory functions were slightly (although not significantly) enhanced by comfort food in comparison to salad ingestion, further buttressing the view that improved cognitive functions due to free-choice high-calorie food intake in Addison patients reflects enhanced energy influx into the brain.

In conclusion, our results suggest the presence of a neuroglycopenic state in Addison patients with symptoms that may in principle be attenuated by comfort food intake. To prove efficacy and efficiency of additional oral glucose supply as a therapeutic adjuvant for improving well-being of the Addison patients, large clinical (multicenter) studies will be important. The relationship between brain energy supply and well-being of patients is important for further understanding and treatment of patients suffering from Addison's disease.

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