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ScienceDirect
Metabolism Clinical and Experimental 58 (2009) 1825–1831
Metabolism
Clinical and Experimental
www.metabolismjournal.com

Effects of glucose infusion on neuroendocrine and cognitive parameters in Addison disease

Johanna Klement[a,*], Christian Hubold[a], Manfred Hallschmid[b], Cecilia Loeck[a], Kerstin M. Oltmanns[b,c], Hendrik Lehnert[a], Jan Born[b], Achim Peters[a]

[a]*Department of Internal Medicine I, University of Luebeck, 23538 Luebeck, Germany*
[b]*Department of Neuroendocrinology, University of Luebeck, 23538 Luebeck, Germany*
[c]*Department of Psychiatry and Psychotherapy, University of Luebeck, 23538 Luebeck, Germany*

Received 7 May 2009; accepted 26 June 2009

Abstract

Sucrose intake has been shown to suppress increased adrenocorticotropic hormone (ACTH) levels in adrenalectomized rats, suggesting that increased cerebral energy supply can compensate for the loss of glucocorticoid feedback inhibition of the hypothalamo-pituitary-adrenal axis. We hypothesized that glucose infusion might acutely down-regulate increased ACTH secretion in patients with Addison disease. We studied 8 patients with primary adrenal insufficiency (Addison group) with short-term discontinuation of hydrocortisone substitution and 8 matched healthy controls in 2 randomized conditions. Subjects received either intravenous glucose infusion (0.75 g glucose per kilogram body weight for 2.5 hours) or placebo. Concentrations of ACTH, cortisol, catecholamines, growth hormone, glucagon, and insulin were measured; and cognitive functions as well as neuroglycopenic and autonomic symptoms were assessed. The ACTH concentrations were not affected by glucose infusion either in the Addison or in the control group. Likewise, concentrations of cortisol, epinephrine, norepinephrine, growth hormone, and glucagon remained unchanged in both groups. Neurocognitive performance and symptom scores were likewise not affected. Independent of glucose infusion, attention of the Addison patients was impaired in comparison with the control group. Our study in patients with Addison disease was not able to support the assumption of a compensatory effect of intravenous glucose infusion on hormonal parameters and neurocognitive symptoms in states of chronic cortisol deficiency. Further studies should examine whether different regimens of glucose administration are more effective.

1. Introduction

Addison disease is characterized by a loss of glucocorticoid and mineralocorticoid function most frequently resulting from autoimmune destruction of the adrenal cortex. Despite cortisol and aldosterone substitution, patients frequently have symptoms such as fatigue, faintness, lack of concentration, and memory deficits [1,2]. These symptoms resemble those of neuroglycopenia [3] and suggest that central nervous glucose deficits may contribute to their development. The release of cortisol may be closely connected to the brain's energy balance as shown in studies with adrenalectomized (ADX) rats [4]. Sucrose-ingested ADX rats were metabolically and hormonally normal in all measured parameters except corticosterone, indicating that sucrose ingestion overcomes some of the deleterious metabolic effects of corticosteroid loss under basal conditions [5]. Moreover, ingestion of sucrose but not of sweet, nonnutritive saccharin solution lowered increased corticotropin-releasing hormone messenger RNA levels in ADX rats, suggesting that the response of the hypothalamus-pituitary-adrenal (HPA) stress axis is modulated by provision of carbohydrate energy sources [4]. On this background, we examined if the infusion of glucose in humans can compensate for a potential energy deficit in the brain, thereby restoring metabolic and neurocognitive effects of hypocortisolism. We compared the effects of glucose infusion in patients with Addison disease with short-term

Institutional Approval: Each volunteer gave written informed consent prior to participation and the study was approved by the local ethics committee of the University of Luebeck.

JK and CH contributed equally to this work.

* Corresponding author. Tel.: +49 451 500 3683; fax: +49 451 500 6595.

E-mail address: Johanna.Klement@uk-sh.de (J. Klement).

0026-0495/$ – see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2009.06.015

discontinuation of their hydrocortisone medication and in healthy controls. Based on the assumption that Addison patients without medication are in a neuroglycopenic state, we examined hypoglycemic counterregulatory hormones and compared cognitive performance of the patients to that of matched healthy controls. We hypothesized that, in the patients, administration of glucose would reduce the increased secretory activity of the HPA axis (particularly adrenocorticotropic hormone [ACTH] concentrations) and improve potentially impaired neurocognitive functions.

2. Subjects and methods

2.1. Subjects

Eight patients with primary adrenal insufficiency (Addison group, 6 women) with a mean ± SEM age of 52.6 ± 3.2 years (range, 39-65 years) and a mean ± SEM body mass index (BMI) of 26.8 ± 1.5 kg/m^2 (range, 23-35 kg/m^2) participated in the experiments. Time of diagnosis ranged from 2 to 22 years before participation in the study. The underlying cause of the disease was autoimmunity or of unknown origin. In 4 patients, adrenal insufficiency was accompanied by hypothyroidism, treated by thyroxin (all euthyroid at the time of experiments); 1 patient was in need of antihypertensive treatment. There were no other acute or chronic diseases and no abuse of nicotine, alcohol, or drugs. Adrenal insufficiency was treated with hydrocortisone (mean ± SEM daily dose, 25.63 ± 1.99 mg; range, 15-30 mg) and fludrocortisone (mean ± SEM daily dose, 0.072 ± 0.013 mg; range, 0-0.1 mg) in all patients. Eight healthy subjects (control group, 6 women) with a mean ± SEM age of 52.1 ± 3.9 years (range, 37-66 years) and a mean ± SEM BMI of 24.5 ± 2.0 kg/m^2 (range, 19-37 kg/m^2) served as controls. None of them had any acute or chronic diseases; any kind of medication; or abuse of nicotine, alcohol, or drugs. There was no significant difference in age (P = .83) and BMI (P = .11) compared with the Addison group. Each volunteer gave written informed consent before participation, and the study was approved by the local ethics committee of the University of Luebeck.

2.2. Experimental design

Each subject participated in 2 experimental sessions, separated by an interval of at least 4 weeks. In one condition, subjects were intravenously infused with glucose solution, whereas in the other condition, they received physiologic saline solution. The study was performed in a randomized single-blinded fashion, and the order of conditions was balanced across subjects.

On the days of the experiments, subjects arrived at the medical research unit at 8:00 AM after an overnight fast of at least 10 hours. Patients with Addison disease had taken their last fludrocortisone medication at 8:00 AM of the previous day and their last hydrocortisone medication at noon on the day before the experiments. 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°). One cannula was inserted into a peripheral vein of the arm, whereas the second one was inserted into an antecubital vein of the contralateral arm. Both cannulas were connected to long thin tubing to enable blood sampling from an adjacent room without the subject's awareness. After physical examination, blood was sampled at 9:00 and 10:00 AM. After this baseline period, glucose infusion was started with a concentration of 0.75 g glucose per kilogram body weight and an infusion rate of 400 mL/h for the next 2.5 hours, resulting in a total infusion volume of 1000 mL. In the placebo condition, 0.9% saline solution was infused. During the infusion period, blood samples were drawn every 20 minutes. At 12:30 PM, the infusion was stopped and patients received their scheduled hydrocortisone dosage. Blood glucose levels (HemoCue, Ängelholm, Sweden), blood pressure, and heart rate were measured at the time of each blood sampling. Blood was centrifuged within 1 minute after withdrawal, and serum and plasma were kept at −72°C until assay.

2.3. Neurocognitive tests

Selective attention was tested using the Stroop test during baseline (t = −30 minutes) and 120 minutes after starting the infusion. The 3 subtests of the Stroop task are as follows: the first task (word-reading subtest) is to read as fast and correctly as possible color names printed in black ink, the second task (color-naming subtest) is to name the ink colors of a series of "X", and the third one (interference subtest) is to name the ink color of color names printed in different colors than they denote, for example, "red" printed in blue. For each subtest, 100 stimuli were presented in an array of 10 lines on a panel. The total number of correct responses within 1 minute 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 during baseline (t = −25 minutes) and 125 minutes after starting the infusion by a word recall task that has previously been shown to be sensitive to the effects of hypoglycemia [6]. Thirty words belonging to 3 semantic categories (neutral, food related, and emotional) were presented orally. After a mental arithmetic distraction task of 1 minute, the subject was required to orally recall within 1 minute 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 scores were presented during baseline (t = −20 minutes) and at 60 and 130 minutes after starting the infusion. Subjects rated from 0 (not at all) to 9 (severely) the following 11 symptoms that have previously been shown to

be increased in hypoglycemia [7]: 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 5 symptoms are considered neuroglycopenic; and the latter 6, autonomic.

2.4. Assays

Serum ACTH, cortisol, C-peptide, insulin, growth hormone (GH), and plasma glucagon concentrations were measured by commercial enzyme-linked immunoassays (all Immulite; DPC, Los Angeles, CA, except glucagon; Adaltis, Montreal, Canada) 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%; GH less than 5.8% and less than 5.5%; glucagon, less than 8.0% and less than 8.2%; ACTH, less than 6.1% and less than 9.4%. Plasma epinephrine and norepinephrine were measured by standard high-performance liquid chromatography 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%.

2.5. Statistical analysis

Data are presented as means ± SEM. Analyses are based on analyses of variance (ANOVA) for repeated measures, including the factors "treat" (glucose infusion vs placebo) and "time" (time points of data collection), with correction according to the Greenhouse-Geisser procedure. The Addison group and the control group were compared by ANOVA with "group" as between-subjects factor. A P value <.05 was considered significant.

3. Results

3.1. Blood glucose and serum insulin levels

In the Addison group as well as in the control group, mean blood glucose levels increased significantly during glucose infusion (each group, $P < .002$ for ANOVA treat main effect, $P < .001$ for time, $P < .001$ for treat × time; Fig. 1). In the Addison group, blood glucose concentrations were lower compared with controls under placebo conditions ($P = .001$, for group main effect) but not in the glucose conditions ($P > .40$).

In both groups, glucose treatment increased concentrations of insulin (each group, $P < .02$ for treat) and C-peptide ($P < .001$) without any differences between groups.

3.2. Hormonal responses

The ACTH levels did not change by glucose infusion compared with placebo in the Addison group ($P > .80$ for treat, Fig. 2) and in the control group ($P > .93$). In the Addison group, plasma ACTH levels were significantly increased as compared with controls ($P < .02$ for group main

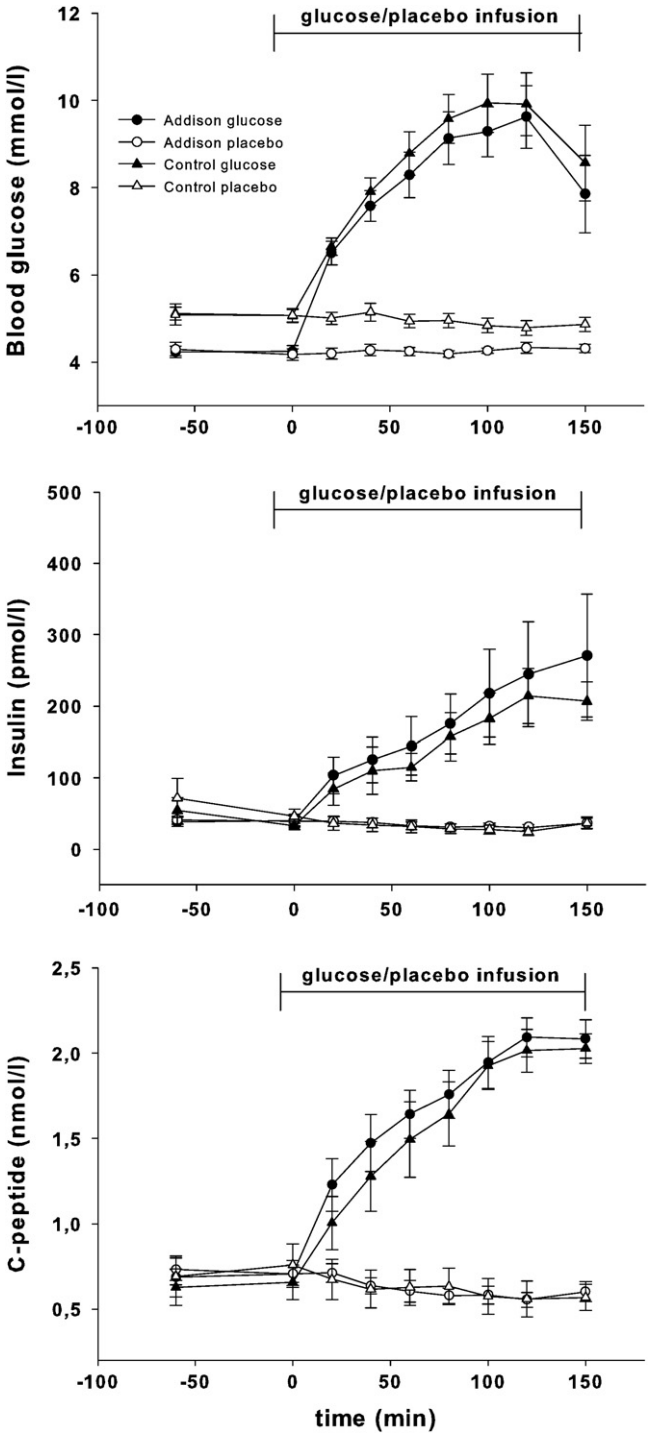

Fig. 1. Blood glucose concentrations and serum insulin and C-peptide levels (means ± SEM) during infusion of glucose (0.75 g/kg body weight) and placebo in a group of Addison patients (n = 8; glucose, black dots; placebo, white dots) and a group of healthy controls (n = 8; glucose, black triangles; placebo, white triangles). Infusions started after a baseline period of 60 minutes with a constant infusion rate of 400 mL/h and were continued for 150 minutes.

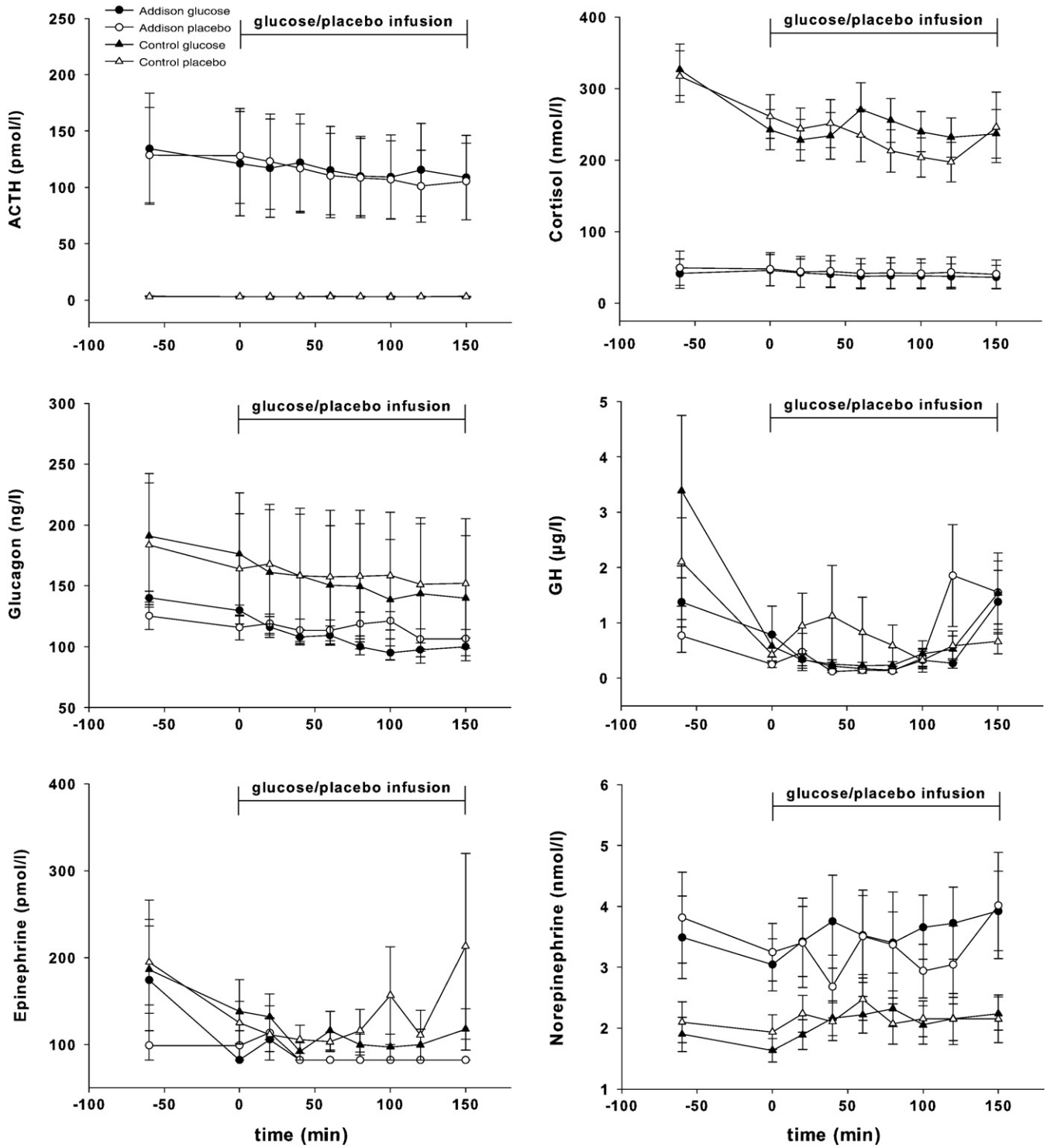

Fig. 2. Plasma or serum concentrations of ACTH, cortisol, glucagon, GH, epinephrine, and norepinephrine (means ± SEM) during infusion of glucose (0.75 g/kg body weight) and placebo in a group of Addison patients (n = 8; glucose, black dots; placebo, white dots) and a group of healthy controls (n = 8; glucose, black triangles; placebo, white triangles). Infusions started after a baseline period of 60 minutes with a constant infusion rate of 400 mL/h and were continued for 150 minutes.

effect). Cortisol concentrations showed a similar pattern without differences between conditions ($P > .31$ for respective treat main effects). As expected, concentrations of cortisol were lower in patients than in controls ($P < .001$).

Concentrations of GH and glucagon did not differ between conditions in the Addison group or in the control group ($P > .78$ for treat, for all comparisons), and concentrations of both hormones were comparable between

Table 1
Neurocognitive tests

Stroop task (attention)	Glucose baseline	Glucose infusion	Placebo baseline	Placebo infusion	*P* value (ANOVA)
Addison group					
Word subtest	103.6 ± 4.26	105.3 ± 4.50	103.0 ± 4.57	101.0 ± 3.65	.066
Color subtest	72.88 ± 4.67	76.3 ± 2.91	71.75 ± 3.49	74.63 ± 3.11	.599
Interference test	45.25 ± 3.74	49.3 ± 3.10	41.00 ± 2.54	48.4 ± 4.10	.212
Control group					
Word subtest	117.4 ± 4.35	120.1 ± 4.97	119.5 ± 9.73	121.38 ± 4.20	.623
Color subtest	86.9 ± 4.51	95.6 ± 3.74	86.9 ± 4.08	94.9 ± 4.41	.860
Interference test	50.6 ± 3.46	60.1 ± 3.08	49.63 ± 3.13	58.8 ± 4.42	.673
Word list (short-term memory)	**Glucose baseline**	**Glucose infusion**	**Placebo baseline**	**Placebo infusion**	***P* value (ANOVA)**
Addison group					
Emotional words	2.9 ± 0.44	2.9 ± 0.58	3.6 ± 0.68	1.9 ± 0.35	.763
Neutral words	3.6 ± 0.80	2.3 ± 0.70	2.8 ± 0.59	3.1 ± 0.81	1.000
Food-related words	3.3 ± 0.59	3.5 ± 0.73	3.3 ± 0.59	3.1 ± 0.72	.670
Control group					
Emotional words	3.3 ± 0.65	3.1 ± 0.61	4.8 ± 0.70	2.9 ± 0.74	.072
Neutral words	3.5 ± 0.50	2.9 ± 0.44	3.3 ± 0.77	3.3 ± 0.94	.912
Food-related words	3.4 ± 0.63	3.9 ± 0.58	4.4 ± 0.73	3.8 ± 0.80	.389

Correct responses of the Stroop task and recalled words of the word list at baseline and during the infusion period are presented (means ± SEM). Results of the glucose and placebo conditions were compared by ANOVA, and *P* values for main factor treat are indicated. Performance in the word subtest and the color subtest of the Stroop task was significantly impaired in Addison patients compared with controls in both conditions ($P < .04$ for ANOVA group effects). There were no significant baseline differences between conditions within one group except for recall of emotional words in controls ($P = .048$).

patients and controls ($P > .37$, for respective group effects). Likewise, concentrations of epinephrine and norepinephrine showed no significant difference between conditions either in the Addison group ($P > .65$ for both hormones) or in the control group ($P > .32$ for both). Comparing the groups, patients revealed persistently higher levels of norepinephrine compared with controls throughout the glucose condition ($P = .029$ for group effect), but did not differ significantly in the placebo condition.

3.3. Neurocognitive functions

Performance on all 3 subtests of the Stroop test was comparable in both conditions in the Addison group and in the control group ($P > .06$ for treat, for all subtests; Table 1). In the group comparison, controls showed a better performance in the word-reading and the color-naming subtest in both treatment conditions ($P < .04$ for all group effects). Short-term memory as assessed by word list recall was not affected by glucose infusion either in the Addison group ($P > .66$ for the treat main effect, for all subcategories) or in controls ($P > .07$ for treat, for all subtests). Word recall was comparable between controls and patients.

Sum scores of autonomic and neuroglycopenic symptoms were also not affected by glucose infusion compared with the placebo condition in both groups ($P > .08$ for treat, for all comparisons; Table 2). In general, symptom scores of the Addison and the control group were well comparable.

4. Discussion

In our study, glucose infusion did not acutely alter secretory activity of the HPA axis or cognitive performance in patients with Addison disease. Compared with healthy control subjects, attention was lower in patients independent of glucose supply.

Table 2
Symptom scores

Symptom scores	Glucose baseline	Glucose infusion	Placebo baseline	Placebo infusion	*P* value (ANOVA)
Addison group					
Neuroglycopenic symptoms	9.9 ± 1.53	9.0 ± 1.35	10.8 ± 1.88	11.8 ± 1.66	.080
Autonomic symptoms	7.0 ± 1.59	5.1 ± 0.92	7.4 ± 1.27	9.1 ± 1.38	.111
Control group					
Neuroglycopenic symptoms	10.3 ± 2.46	9.2 ± 2.29	8.3 ± 1.86	8.9 ± 1.39	.502
Autonomic symptoms	8.1 ± 2.39	6.9 ± 1.32	8.0 ± 1.87	8.5 ± 1.54	.488

Sum scores of autonomic and neuroglycopenic symptoms at baseline and during the infusion period are presented (means ± SEM). Results of the glucose and placebo conditions were compared by ANOVA, and *P* values for main factor treat are indicated. There were no significant baseline differences between conditions within one group.

We were not able to show that intravenous glucose administration influences the secretion of ACTH, cortisol, GH, glucagon, epinephrine, and norepinephrine in patients with Addison disease. This outcome is in contrast to studies where sucrose-ingested ADX rats displayed normal values of all metabolic and of most hormonal parameters studied [5]. However, the studies in rats and the present study in humans differ in several aspects: In rats, sucrose was offered for 4 to 14 days [4,5], whereas here glucose was administered for only a very short 2.5-hour interval. Furthermore, the disintegrated HPA axis activity in Addison patients might have facilitated insulin-dependent pathways resulting in preferential storage of glucose in muscle and fat tissue rather than uptake of the infused glucose into the brain [8]. Importantly, whereas we used an intravenous route of glucose administration, the rat experiments relied on oral ingestion of glucose with a free-choice bottle system. Gastrointestinal afferents and psychologic aspects of ingestion may be decisive factors for the dampening effect of glucose on the neuroendocrine stress system. In a recently published study [9], an oral glucose load reduced hypothalamic activity to a greater extent than the intravenous administration of glucose. Therefore, neuroendocrine signals from the gastrointestinal tract, for example, glucoreceptors, vagal afferents, and gut peptides, might play a critical role in the central nervous processing of glucose uptake. A most important difference is that our patients displayed a history of Addison disease of up to 20 years in comparison with the adrenalectomy in rats that was performed just a few days before the experiments. It might be argued that inadequate ACTH suppressibility possibly due to secondary autonomous ACTH production [10] existed in our patients, which would explain why the patients in contrast to newly ADX animals were not susceptible to the proposed effects of glucose on HPA axis regulation. However, autonomous ACTH production in Addison patients is a very rare phenomenon [11]; and importantly, in clinical routine examinations, 5 of 6 of our patients revealed dynamic ACTH levels susceptible to therapeutic interventions (data not presented). It might also be argued that Addison patients who are known to have an increased risk of hypoglycemic episodes due to diminished cortisol release [12] adapt to recurrent nocturnal hypoglycemic episodes that would influence stress hormone release and their susceptibility to glucose supply, although in our sample of patients, such an assumed counterregulatory adaption appears to be overridden by the main pathologic features of the disease as indicated by high concentrations of ACTH and norepinephrine. Another explanation for our missing effects might be our 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.

In ADX rats, the normalizing effects on the HPA axis of glucose administration may reflect a compensatory influence for lacking glucose supply to the brain, that is, a form of neuroglycopenia. In stressful situations, activation of the HPA axis contributes to the allocation of glucose to the brain [13]. In patients with Addison disease, the derangement of the HPA system may result in diminished brain energy supply and in typical symptoms like faintness, lack of concentration, or memory deficits. In our study, acute glucose infusion apparently was not sufficient to counteract HPA axis dysregulation or effect neurocognitive functions in these patients.

Persistently elevated norepinephrine levels in Addison patients are in line with previous findings in ADX rats, in which adrenalectomy augmented the in vivo release of norepinephrine in the paraventricular nucleus [14].Whereas cortisol treatment abolished this augmentation probably by decreasing the release, turnover, and biosynthesis of norepinephrine in the paraventricular nucleus, our glucose infusion was not able to replace this effect of cortisol.

Impaired attention in Addison patients is possibly due to absent cortisol because extremely high and low levels of cortisol are known to impair cognition [15]. Although there are many studies on cognition and increased cortisol levels in Cushing disease, systematic investigations on cognition and Addison disease are scarce [16]. Simulating adrenal insufficiency by inhibiting cortisol synthesis by metyrapone treatment resulted in impaired long-term declarative memory in young men [17,18], but there are no studies dealing with metyrapone treatment and attention. However, in our Addison patients, only attention is decreased, whereas memory function or subjective symptom ratings did not differ from healthy subjects. We suggest that cognitive functions are influenced depending on the severity of the disease and that attention may be one of the first responding parameters. Interestingly, in a large cross-sectional study, patients with chronic adrenal insufficiency showed impaired subjective health status irrespective of the kind of glucocorticoid replacement regimen [19], indicating a need for improved replacement strategies and possibly additional therapeutic options.

In our study, short-term intravenous glucose administration did not suppress ACTH concentrations or improve attention in Addison patients. To clarify if glucose may still be effective in this context, further studies considering also psychologic and gastrointestinal aspects of ingestion should examine the effects of glucose after oral intake. An easy to use therapeutic option apart from the rather inflexible and occasionally inadequate hydrocortisone substitution would be of greatest clinical value for patients with Addison disease.

Acknowledgment

We thank Kai-Uwe Duysen, Kathleen Kurwahn, and Heidi Ruf for expert technical assistance. This work was supported by the German Research Foundation (DFG).

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