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Persistent blood glucose reduction upon repeated transcranial electric stimulation in men

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ABSTRACT

Background: Transcranial direct current stimulation (tDCS) of the human brain increases systemic glucose tolerance.
Objective/Hypothesis: To investigate whether this effect persists after one week of repeated stimulation. Because systemic glucose uptake relates to brain energy homeostasis, we concomitantly measured cerebral high-energy phosphate metabolites.
Methods: In a sham-controlled crossover design, 14 healthy men were tested under daily anodal tDCS vs. sham for 8 days. Systemic glucose metabolism was examined by concentrations of circulating glucose and insulin. Cerebral energy metabolism – i.e. adenosine triphosphate (ATP) and phosphocreatine (PCr) levels – was assessed by ^{31}phosphorous magnetic resonance spectroscopy.
Results: Blood glucose concentrations were distinctly lower upon tDCS compared with sham stimulation on day 1. This effect persisted on day 8, while serum insulin levels remained persistently unchanged. Transcranial stimulation increased mean levels of ATP and PCr compared with sham on day 1 only. Blood glucose concentrations negatively correlated with PCr content after repeated daily stimulation.
Conclusions: Our data confirm that tDCS reduces blood glucose through an insulin-independent mechanism. This effect persists after 8 days of repeated stimulation and relates to brain energy metabolism. Therefore, transcranial electric stimulation may be a promising non-pharmacological adjuvant option to treat systemic disorders such as glucose intolerance or type 2 diabetes mellitus with a low side-effect profile.

Introduction

The brain is the control organ of systemic glucose and energy metabolism [1–3]. In particular, glucose-sensing neurons in brain areas such as hypothalamus, brain stem and substantia nigra are known to integrate signals of glucose homeostasis and thus directly sense physiological changes in ambient glucose [3]. In turn, the central nervous system regulates peripheral glucose metabolism, e.g. by stimulating hepatic glucose release or pancreatic insulin production [3]. Accordingly, it has been shown that systemic effects on glucose regulation and metabolic functioning can be achieved by influencing the central nervous system in humans, i.e. by anodal transcranial direct current stimulation (tDCS) [4] or intranasal application of insulin [5]. In terms of systemic effects, 20 min of tDCS has been shown to improve glucose tolerance and reduce stress axis activity in human volunteers under experimental gold standard conditions of a euglycemic glucose clamp [4]. In turn, this effect can be attributed to a modified brain energy homeostasis [4].

The aim of the study was to broaden the current insight on tDC stimulation-induced influence on human blood glucose regulation. Against this background, we hypothesized that the acute effects of tDCS can be verified by blood glucose reduction under physiological conditions and persist after repeated stimulation during 8 consecutive days. Due to the known impact of stimulation on neuronal excitation and cerebral energy consumption [2,6] as well as based upon our own previous data [4], we further assumed that blood glucose reduction may be related to brain energy homeostasis. To test these assumptions, we measured circulating concentrations of glucose and insulin, representative stress axis

Abbreviations: tDCS, trancranial direct current stimulation; ATP, Adenosine triphosphate; PCr, Phosphocreatine.

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parameters ACTH and cortisol, as well as cerebral high-energy phosphate – i.e. adenosine triphosphate (ATP) and phosphocreatine (PCr) – content by ^{31}phosphorous magnetic resonance spectroscopy upon 1 and 8 consecutive days of daily anodal tDCS.

Materials and methods

Participants

We examined a homogeneous group of 14 healthy young men (24.8 ± 0.58 years) with a normal body mass (BMI 22.65 ± 0.34 kg/m^2). Subjects had a self-reported regular sleep-wake cycle. Exclusion criteria were acute or chronic internal, neurologic or psychiatric diseases and diabetes mellitus of first-degree family members. We also excluded individuals with alcohol or drug abuse, intake of any kind of medication, as well as shift workers, competitive athletes and persons under acute extraordinary mental or physical strain. Each participant provided written informed consent. The volunteers were asked to fast for 6 h prior to experimental testing (no intake of calorie-containing foods or beverages) and to go to bed no later than 23:00 p.m. before and during the experimental testing period. The study was approved by the ethics committee of the University of Luebeck and carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

Experimental design

The study was performed according to a single-blind, counterbalanced, randomized sham-controlled crossover design. Each subject participated in two blinded 8-day conditions. Experimental conditions comprised the application of daily tDCS or daily sham stimulation for 8 days, respectively. The conditions were separated by a minimum of two weeks. In order to ensure that expectation did not influence the results, after the intervention we asked all participants to estimate in which condition they had just participated. We observed that the correct and incorrect answers were quite balanced. Overall, 8 out of 14 participants correctly recognized tDCS as the real stimulation and 12 correctly identified the sham condition as the sham stimulation (OR for cohort (sham stimulation/real stimulation): 0.222, 95% CI: 0.036–1.390; OR (for cohort treatment = no): 0.417, 95% CI: 0.119–1.458; OR (for cohort treatment = yes): 1.875, 95% CI: 0.960–3.662; Pearson's Chi-Square: P = 0.094; continuity correction: P = 0.209; Fishers exact test P = 0.209). The wash-out interval was 2.5 ± 0.7 weeks on average within a predetermined range of 2–4 weeks. On the days of experimental testing (day 1 and 8), participants were invited to the Department of Neuroradiology at 3:30 p.m. After the determination of body weight by using a medically approved scale (MPS-M, KERN & SOHN GmbH, Balingen, Germany) and placing an intravenous forearm catheter, baseline ^{31}phosphorous-magnetic resonance (^{31}P-MR) spectra were recorded over 10 min and baseline blood samples were taken. For the stimulation procedure, the position of the anodal electrode was defined over the primary motor cortex representation of the left first interdigital muscle (Id1), which had been identified via focal transcranial magnetic stimulation prior to the experiments, as described in previous work [4,7]. The cathodal electrode was placed over the left forehead (supraorbital). Both electrodes (pad size 5*7 cm = 35 cm^2) were soaked with standard saline solution (NaCl 0.9%) and fixed with an elastic strap. A DC-stimulator plus (NeuroConn, GmbH, Illmenau, Germany) delivered 20 min of anodal current flow (1 mA, fade in/out 8s). The procedure was identical during sham stimulation, which was conducted without any current flow and without using the sham mode of the device. Subsequently, a series of five continuous ^{31}P-MR spectroscopy sequences followed (t = −10 min before intervention; t = 30, 40, 50, 60, 70 min after intervention). Meanwhile, three further blood samples were taken (t = 20, 40, 60 min after intervention). Samples to measure blood glucose levels were taken every 5 min throughout the study and concentrations were determined by HemoCue (B-Glucose-Data-Management, HemoCue GmbH, Grossostheim, Germany). Ringer's solution was administered throughout the experiments to ensure fluid and electrolyte supply to participants, as well as ensuring the permeability of the cannula.

Handling and analyses of blood samples

Blood samples were – if necessary – cooled and immediately centrifuged. The supernatants were stored at −80 °C until analyses. Serum insulin, cortisol and plasma ACTH concentrations were measured by commercial enzyme-linked immunoassay (Immulite DPC, Los Angeles, USA; insulin: intra-assay coefficient of variation (CV) < 1.5% and inter-assay CV < 4.9%; cortisol: intra-assay CV < 1.7% and inter-assay CV < 2.8%; ACTH: intra-assay CV < 2.7% and inter-assay CV < 5.4%).

^{31}P-magnetic resonance spectroscopy measurements

^{31}Phosphorus magnetic resonance spectroscopy (^{31}P-MRS) of the cortex was conducted in a 3.0-T magnetic resonance scanner (Achieva 3 T, Philips Medical Systems, Best, Netherlands) by using a doubled-tuned ^{1}H/^{31}P-headcoil (Advanced Imaging Research, Cleveland, Ohio). For sufficient relaxation of the phosphorous metabolites, a repetition time of 4500 ms was chosen with a three-dimensional chemical shift imaging (3D-CSI) sequence (6 × 5 x 3 voxel, 6 kHz bandwidth, 1024 data points, 8:51 min measuring time). Nuclear Overhauser effect [8] and ^{1}H-decoupling during receiving (wideband alternating-phase technique for zero-residual splitting) were applied for improved spectral resolution, ^{1}H-decoupling during excitation by using the second channel of the head coil for transmitting on the ^{1}H-resonance frequencies. To evaluate the spectral data, we applied magnetic resonance user interface with zero filling to 4096 data points, which were apodizing by a 20 Hz Lorenzian filter. Six ^{31}P-MRS sequences were measured as described in the study protocol. Calculation of peak positions and intensities were carried out using the Advanced Method for Accurate Robust and Efficient Spectral fitting (AMARES) algorithm [9]. In order to directly reflect the overall high-energy phosphate turnover [9], we examined the high-energy phosphate compounds ATP (the sum of α-, β- and γ- ATP) and PCr. As a high-energy reservoir, PCr is linked to ATP in a bidirectional way [10]. Catalyzed by creatine phosphokinase, ATP is formed by PCr and vice versa at an ATP-to-PCr molar ratio of 1:1.

Statistical analyses

Data are presented as mean values ± standard error of mean (SEM). Statistical analyses were conducted by Superior Performing Software System Version 20.0 (SPSS Inc., IL, USA) based on analysis of variance (ANOVA) for repeated measurements. Normal distribution of the data was proven by a Shapiro-Wilk test. Correction was made – if necessary – by the Greenhouse-Geisser method. Included factors were 'treatment' (tDCS vs. sham condition) and 'time' (repeated measurements during the experiments). The interaction effect between factors is termed 'treatment by time'. Paired-sample *t*-tests were calculated to compare single time points between conditions and between experimental days. Additionally, bivariate correlation analyses were conducted according to Pearson. All testings comprised n = 15 in each condition. Insulin