Brain Energy Consumption Induced by Electrical Stimulation Promotes Systemic Glucose Uptake

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Background: Controlled transcranial stimulation of the brain is part of clinical treatment strategies in neuropsychiatric diseases such as depression, stroke, or Parkinson's disease. Manipulating brain activity by transcranial stimulation, however, inevitably influences other control centers of various neuronal and neurohormonal feedback loops and therefore may concomitantly affect systemic metabolic regulation. Because hypothalamic adenosine triphosphate–sensitive potassium channels, which function as local energy sensors, are centrally involved in the regulation of glucose homeostasis, we tested whether transcranial direct current stimulation (tDCS) causes an excitation-induced transient neuronal energy depletion and thus influences systemic glucose homeostasis and related neuroendocrine mediators.

Methods: In a crossover design testing 15 healthy male volunteers, we increased neuronal excitation by anodal tDCS versus sham and examined cerebral energy consumption with ^{31}phosphorus magnetic resonance spectroscopy. Systemic glucose uptake was determined by euglycemic-hyperinsulinemic glucose clamp, and neurohormonal measurements comprised the parameters of the stress systems.

Results: We found that anodic tDCS-induced neuronal excitation causes an energetic depletion, as quantified by ^{31}phosphorus magnetic resonance spectroscopy. Moreover, tDCS-induced cerebral energy consumption promotes systemic glucose tolerance in a standardized euglycemic-hyperinsulinemic glucose clamp procedure and reduces neurohormonal stress axes activity.

Conclusions: Our data demonstrate that transcranial brain stimulation not only evokes alterations in local neuronal processes but also clearly influences downstream metabolic systems regulated by the brain. The beneficial effects of tDCS on metabolic features may thus qualify brain stimulation as a promising nonpharmacologic therapy option for drug-induced or comorbid metabolic disturbances in various neuropsychiatric diseases.

Key Words: Adenosine triphosphate, blood pressure, cerebral energy consumption, healthy humans, hormonal regulation, hypothalamus-pituitary-adrenal (HPA) axis

There are various indications that transcranial, and particularly electrical, stimulation of the brain exerts distinct effects on brain functions such as memory consolidation (1), motor learning (2), planning ability (3), or decision making (4) through modulation of local neuronal processes. Clinical options for intervention include forms of electric brain stimulation such as transcranial magnetic (TMS) or transcranial direct current stimulation (tDCS) (5) with beneficial effects in psychiatric and neurological diseases (6). However, because the brain is not simply an isolated organ within the organism but, on the contrary, the superordinate control entity within the hierarchy of all organismic processes, it suggests that electrically evoked potentials in this context may also affect cerebral centers regulating peripheral metabolic systems. Against this background, increasing consensus prevails on the fundamental role of the brain in the control of glucose metabolism (7–9). In a bidirectional manner, efferent and afferent neuronal pathways connect brain centers to peripheral organ function and convey reciprocal feedback signals between brain and periphery to hold the balance of systemic glucose and thereby energy homeostasis. In this context, pharmacologic activation of adenosine triphosphate (ATP)-sensitive potassium (K_{ATP}) channels in the mediobasal hypothalamus have been shown to lower blood glucose levels through inhibition of hepatic gluconeogenesis in rats (8). This finding highlights the importance of ATP, that is, energy, sensing by cerebral K_{ATP} channels for systemic glucose homeostasis. Because K_{ATP} channels are physiologically activated by a drop in available ATP (e.g., under conditions of hypoglycemia) (8), we hypothesized that increased cerebral energy consumption upon neuronal excitation causes a transient ATP decrease (10), which in turn should lead to hypothalamic K_{ATP} channel activation and therefore increased systemic glucose uptake in humans. Transcranial, and particularly electrical, stimulation of the brain represents a good noninvasive option to increase neuronal excitation in humans (5,6). Surprisingly, potential effects of electric brain stimulation on metabolic functions beyond the brain have not been addressed thus far and leave a series of questions in this context unanswered.

Against this background and following our hypothesis, we tested experimentally whether anodal tDCS promotes cerebral energy consumption and therefore systemic glucose uptake in healthy male volunteers. Cerebral energy depletion was assessed by ^{31}phosphorus magnetic resonance spectroscopy (^{31}P-MRS), and overall glucose uptake was measured by hyperinsulinemic-euglycemic clamp, which places plasma glucose concentration under the investigator's control and thus breaks the endogenous glucose-insulin feedback loop. The technique consists of an insulin infusion at a predetermined fixed dosage and a variable glucose infusion rate. Under steady-state conditions of euglycemia, the glucose infusion rate equals glucose uptake, and therefore glucose tolerance, by all tissues in the body (11). Because glucose metabolism is significantly influenced by neurohormonal stress systems, we additionally monitored respective prevalent parameters during the experiments.

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Methods and Materials

Participants

We included 15 healthy men (aged 24.6 ± .69 years, body mass index 23.2 ± .38 kg/m^2) without acute or chronic internal, neurological, or psychiatric disease; nicotine or alcohol abuse; competitive sports involvement; or extraordinary mental or physical strain. The days before experimental testing, participants were instructed to go to bed not later than 11 PM and not to perform exhausting physical exercise. The study was carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association and has been approved by the ethics committee of the University of Lübeck. Each participant gave written informed consent.

Study Design

The study was performed according to a randomized sham-controlled crossover design. On the days of experimental testing, subjects reported to the Department of Neuroradiology at 3:30 PM after fasting for at least 16 hours. Localization of the tDCS site occurred as described in the stimulation protocol. Subsequently, baseline blood samples of glucose, insulin, adrenocorticotropin (ACTH), and cortisol were taken along with a glucose clamp to investigate glucose tolerance (11,12), as previously described (13). After reaching a stable euglycemic plateau between 4.5 and 5.5 mmol/L, baseline ^{31}P-MR spectra were recorded. Subsequently, tDCS was performed. Thereafter, we conducted a second sequence of ^{31}P-MR spectroscopy measurements, and blood was taken again. Because it has been reported that motor cortical excitability upon tDCS lasts for up to 90 min (14,15), we expected a cessation of the stimulatory effects starting 65 min after tDCS. At this time point, we thus began a series of five continuous ^{31}P-MR spectroscopy sequences that ended 105 min after tDCS. Five additional blood samples were taken during this period. To examine delayed tDCS-induced effects on glucose uptake, we continued the glucose clamp for another 2.5 hours and took blood samples at regular intervals of 60 min. After the last spectroscopy sequence, glucose clamping was stopped. Hormone measurements were performed as previously described (16).

Transcranial Direct Current Stimulation Protocol

The applied stimulation protocol is established to cause local effects on cortical excitability for up to 90 min (14,15). The anodal electrode was placed over the primary motor cortex representation of the left first interdigital muscle (Id1), the "hot spot" of which had been identified by focal transcranial magnetic stimulation before the experiment. To localize the point of highest amplitude of the evoked motor action potential in Id1, we applied suprathreshold TM stimulation in a stepwise manner shifting the coil by 1-cm steps over the area right from the vertex. The cathodal electrode was positioned over the left forehead. Both tDCS electrode sheaths were soaked with standard saline solution (NaCl 9%) and fixed by elastic bands. A DC stimulator plus (NeuroConn, Illmenau, Germany) delivered 20 min of anodal stimulation (1 mA, fade in/out 8 sec). For sham stimulation, electrodes were placed at the same sites as for the active stimulation without a current flow.

^{31}P-Magnetic Resonance Spectroscopy Measurements

^{31}P-MR spectra of the motor cortex were taken in a 3.0-Tesla magnetic resonance scanner (Achieva 3T, Philips Medical Systems, Best, the Netherlands) using a double-tuned ^{1}H/^{31}P-headcoil (Advanced Imaging Research, Cleveland, Ohio). To attain sufficient relaxation of the phosphorus metabolites, we chose a repetition time of 4500 msec together with a three-dimensional chemical shift imaging sequence (6 × 5 × 3 voxel, 6-kHz bandwidth, 1024 data points, 8:51 min measuring time). For better spectral resolution ^{1}H-decoupling during excitation, nuclear Overhauser effect (17), and ^{1}H-decoupling during receiving (wideband alternating-phase technique for zero-residual splitting) (18) was applied using the second channel of the head coil for transmitting on the ^{1}H-resonance frequency. Magnetic resonance user interface was used for evaluation of the spectral data. Zero filling to 4096 data points and apodizing by a 20-Hz Lorentzian filter was applied. Peak positions and intensities were calculated with the Advanced Method for Accurate Robust and Efficient Spectral fitting (AMARES) algorithm (19).

Statistical Analyses

Data are presented as mean values ± standard error of mean (SEM). Statistical analysis with Superior Performing Software Systems (SPSS) was based on analysis of variance (ANOVA) for repeated measurements including the factors "treatment" (tDCS vs. sham) and "time" (time points of data collection) and the interaction effect between these factors. We also calculated paired-sample *t* tests to compare single time points between conditions. Moreover, bivariate correlation analyses according to Pearson were conducted. All testings comprised $n = 15$ in each condition, and a p value $< .05$ was considered significant.

Results

Glucose Tolerance and Cerebral High-Energy Phosphate Metabolism

Glucose infusion rates demonstrate that anodal transcranial direct current stimulation of the brain distinctly increases systemic glucose tolerance in healthy male volunteers. Although serum insulin and plasma glucose concentrations did not differ between conditions ($p = .107$ and $p = .326$, respectively), we found that glucose infusion rates displayed a biphasic course upon anodic tDCS compared with the sham condition (Figure 1A). Systemic glucose uptake initially decreased by trend for the first 30 min after tDCS ($p = .077$), which was followed by a significant rise above the infusion rates of the control condition ($p = .012$). This boosting effect on glucose uptake lasted for an overall duration of 60 min ($p = .031$), reached its maximum 200 min after stimulation onset, and ended 40 min thereafter. Comparison of the overall glucose infusion rates throughout the experiments revealed distinctly higher values in the tDCS than in the sham condition ($p = .001$, Figure 1A).

The potential mechanism underlying the observed effects of brain stimulation on systemic glucose homeostasis involves an activation of K_{ATP} channels (8) through a transient drop in cerebral ATP content (20–22). Because our in vivo study in humans does not allow for exploration on a molecular level, we aimed to verify this hypothesis by measurements of the cerebral energy content in the cortex both underneath the stimulation site and in the contralateral hemisphere by ^{31}phosphorus magnetic resonance spectroscopy (^{31}P-MRS). We examined the compounds ATP and phosphocreatine (PCr) reflecting the overall high-energy phosphate turnover (23). PCr represents a high-energy reservoir linked to ATP in a bidirectional reaction in which ATP is formed by PCr and vice versa. In addition to PCr and ATP, the ratios of PCr/inorganic phosphate (Pi) and ATP/Pi were evaluated as an indicator of intracellular energy status (23–25). Results show that the stimulation-induced biphasic effect on systemic glucose tolerance was reflected by the course of the overall brain high-energy phosphate measurements (Figure 1B and 1C). After transcranial stimulation, we observed a drop in the PCr/Pi ratio compared with the sham condition, which became