

COMMENTARY ON: Double transcranial direct current stimulation of the brain increases cerebral energy levels and systemic glucose tolerance in men. Wardzinski EK, Friedrichsen L, Dannenberger S, Kistenmacher A, Melchert UH, Jauch-Chara K, Oltmanns KM. *J NEUROENDOCRINOL* 2019;31:e12688.

Juan N. Andino and Melissa J. Chee

Department of Neuroscience, Carleton University, Ottawa ON Canada

Transcranial direct current stimulation (tDCS) is a non-invasive approach to pass electrical current to localized cortical areas in the brain, and it is currently used as a non-pharmaceutical therapy to treat psychiatric and neurological disorders, including depression, anxiety, and chronic pain^{1,2}. In depressed patients, concurrent tDCS treatment can also lower blood glucose and cortisol levels^{3,4}. This work sets the stage for tDCS treatment to improve glucose tolerance, thus expanding its therapeutic potential in diabetic patients. It may also improve the stress axis, thus lowering blood pressure in patients who are also hypertensive. This study by Wardzinski et al characterized tDCS-mediated regulation of blood glucose and elucidated the optimal conditions to maximize the beneficial effects of tDCS.

The Oltmanns laboratory has previously showed that tDCS can be a hormone and energy regulator in healthy adult males^{5,6}. They performed hyperinsulinaemic-euglycaemic glucose clamps and measured the glucose infusion rate to determine systemic glucose tolerance. During this procedure, glucose infusion rates increase with glucose uptake at insulin-sensitive organs in the body so that blood glucose concentration would remain clamped at a constant level throughout. In effect, an increase in glucose infusion rates reflect an increase in glucose uptake and an improvement in glucose tolerance. They showed that a single tDCS (tDCS-1) improved systemic glucose tolerance, brain energy levels (i.e. ATP and phosphocreatine), and decreased serum cortisol levels without inducing any insulin spikes or dips. Additionally, tDCS-1 effects lasted at least 115 minutes⁵. Based on these findings, they then determined the cumulative effect of tDCS-1 treatment and found that tDCS-1 administered daily for eight consecutive days did not further improve glucose tolerance⁶. While this result showed that tDCS-1 improvements were not cumulative from one day to the next, the possibility remained that two consecutive tDCS applied within a critical time interval could further improve glucose uptake.

In this current study, Wardzinski and colleagues applied two consecutive tDCS, tDCS-1 and tDCS-2, to elucidate the conditions that may prolong and improve the beneficial effects of brain stimulation on glucose tolerance, cerebral phosphate levels, and the stress axis. Prior results showed that tDCS altered glucose absorption for 55 minutes but changes in brain phosphate levels were longer lasting (~115 minutes), thus the authors selected an inter-stimulation duration of 115 minutes. This question offered three potential answers with regards to the inter-

stimulation period. In the first possible outcome, tDCS-2 does not alter glucose uptake, thus additional tDCS within a 24-hour period does not produce improve metabolic benefits. In a second possible outcome, tDCS-2 could have a smaller effect in duration or magnitude than tDCS-1, which would indicate a desensitization effect. Here, Wardzinski and colleagues conferred a third possible outcome and showed that tDCS-1 and tDCS-2 similarly increased glucose uptake and brain ATP levels. Although tDCS-2 produced further reductions in cortisol levels, it is not clear if tDCS-2 produced a greater improvement in glucose absorption than tDCS-1. It appears that tDCS-mediated effects on glucose uptake and the stress axis occur and recover over different time periods, but while the effects on the stress axis can be amplified, that on blood glucose or brain phosphate levels do not.

These results show that consecutive tDCS treatments could be effective at improving glucose uptake, lowering blood glucose, increasing brain phosphate levels, and reducing stress hormone levels. They provide supporting evidence to test the efficacy of multiple recurring tDCS over a prolonged treatment period. Wardzinski showed that the increased glucose absorption rate may be constant from the tDCS-1 to tDCS-2 without producing untoward hypoglycemic effects. It would be interesting to determine if multiple, consecutive tDCS applied over a 24-hour period would continue to be effective at improving glucose tolerance. Additional studies involving daily sessions comprising multiple tDCS treatments would be required to test the safety and efficacy of this technology to control blood glucose, and this work by Wardzinski and colleagues provides a strong foundation to test these parameters.

References

1. Bikson M, Paneri B, Giordano J. The off-label use, utility and potential value of tDCS in the clinical care of particular neuropsychiatric conditions. *J Law Biosci.* 2016; **3**(3):642–646.
2. Lefaucheur J-P et al. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). *Clin Neurophysiol.* 2017; **128**(1):56–92.
3. Rasmussen KG, Ryan DA. The effect of electroconvulsive therapy treatments on blood sugar in nondiabetic patients. *J ECT.* 2005; **21**(4):232–234.
4. Ghanizadeh A, Issaee M, Sigaroody MO, Kaviani K. The effect of electroconvulsive therapy on blood glucose, creatinine levels, and lipid profile and its association with the type of psychiatric disorders. *Neurochem Int.* 2012; **61**(7):1007–1010.
5. Binkofski F, Loebig M, Jauch-Chara K, Bergmann S, Melchert UH, Scholand-Engler HG, Schweiger U, Pellerin L, Oltmanns KM. Brain energy consumption induced by electrical stimulation promotes systemic glucose uptake. *Biol Psychiatry.* 2011; **70**(7):690–695.
6. Kistenmacher A, Manneck S, Wardzinski EK, Martens JC, Gohla G, Melchert UH, Jauch-Chara K, Oltmanns KM. Persistent blood glucose reduction upon repeated transcranial electric stimulation in men. *Brain Stimul.* 2017; **10**(4):780–786.