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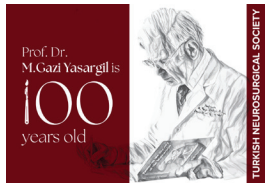

Therapeutic Effects of tDCS on Calcium and Glutamate Excitotoxicity in a Cerebral Ischemia–Reperfusion Rat Model

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ABSTRACT

AIM: To investigate the therapeutic effects of transcranial direct current stimulation (tDCS) on calcium and glutamate excitotoxicity caused by ischemia–reperfusion (IR).

MATERIAL and METHODS: The IR model was generated by transient middle cerebral artery occlusion. tDCS treatment was applied at 1 mA for 30 min daily at the 2nd, 24th, and 48th h of IR. The motor and cognitive functions and the concentrations of Ca^{2+}, glutamate, and N-methyl-D-aspartate receptor (NMDAR) in the hippocampus tissues were evaluated.

RESULTS: Results showed a reduction in motor and cognitive functions in the IR group compared with that in the sham group, whereas these functions increased in the IR+tDCS group compared with those in the IR group. Ca^{2+}, glutamate, and NMDAR concentrations were higher in the IR group than in the sham group but lower in the IR+tDCS group than in the IR group.

CONCLUSION: These results suggest that tDCS treatment improves motor and cognitive dysfunctions after IR and exerts therapeutic effects on learning and memory through the regulation of Ca2+ and glutamate excitotoxicity.

KEYWORDS: Excitotoxicity, Glutamate, Ischemia–reperfusion, tDCS

ABBREVIATIONS: IR: Ischemia/reperfusion, **tDCS:** transcranial direct current stimulation, **NMDAR:** N-methyl-D-aspartate receptor

INTRODUCTION

The brain, which accounts for approximately 2% of our body weight, consumes 25% of glucose, 20% of blood flow, and 25% of total oxygen. The primary energy source of our brain is adenosine triphosphate (ATP) (2). Blockage of the cerebral artery supplying the brain causes insufficient blood flow to the center and surrounding area supplied by the artery (2). Ischemia in the brain causes disruption

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of Na^+/K^+ ATPase activity due to ATP deficiency, change in membrane potential, depolarization of neurons, and release of neurotransmitter substances from neurons. Consequently, there occurs an excessive release of glutamate and aspartate into the extracellular space (2). However, the reuptake of glutamate and aspartate into the cell does not occur because the involved mechanism is energy-dependent, which exerts an excitotoxic effect. Furthermore, this situation triggers the continuous stimulation of neurons and Ca^{2+} uptake into the cell. Increased glutamate concentrations in the synaptic gap causes overstimulation of postsynaptic glutamate receptors, especially N-methyl-D-aspartate receptors (NMDARs) (35). Overactivation of NMDARs intakes more calcium ions into the cell and activates enzymes such as protease, nuclease, and caspase, leading to neuronal death in the postsynaptic region (35).

It is essential to treat stroke because of its adverse effects on the individual, family, and society in terms of psychology, community, and economy. The primary purpose of stroke treatment is to ensure that the brain region that cannot be supplied with blood is resupplied with blood and receives the essential nutrients to prevent secondary damage that may occur after ischemia and to accelerate treatment (2). In the clinic, antiaggregant, anticoagulant, thrombolytic, antiedema, and neuroprotective medications are frequently used for stroke treatment. Antiaggregants are drugs that inhibit the aggregation of platelets. Although there are studies on drug treatment for cognitive impairment after cerebral ischemia, neuromodulation by transcranial direct current stimulation (tDCS) has recently been widely used. tDCS is a noninvasive technique that causes changes in membrane potential through the modulation of Na^+ and Ca^{2+} channels by transmitting subthreshold electrical activity to the brain. tDCS is effective on voltage-gated calcium channels, AMPA, and NMDA (23-25). tDCS modulates the membrane potential mediated by the GABAergic and glutamatergic pathways (2). Regulation of these ion channels occurs through the regulation of Na^+ and Ca^{2+} ion transients involved in processes such as cell stimulation, cell death, and apoptosis (2,4). This study was conducted to investigate the therapeutic effects of tDCS on motor and cognitive function impairment caused by calcium and glutamate excitotoxicity in an ischemia–reperfusion model. In addition, cognitive function was evaluated.

MATERIAL and METHODS

All animal use and experimental protocols were approved and implemented by Erciyes University (22/212). A total of 30 male Wistar albino rats weighing 290–300 g were divided into sham, IR, and IR+tDCS groups (Figure 1). The IR model was generated through a 90-min middle cerebral artery occlusion (MCAO), which was used in our previous study and that of Longa et al. (2,18). tDCS treatment was administered as anodal 1 mA for 30 min and 2 days under isoflurane anesthesia (Figure 2) using the Gün medical device. Motor function

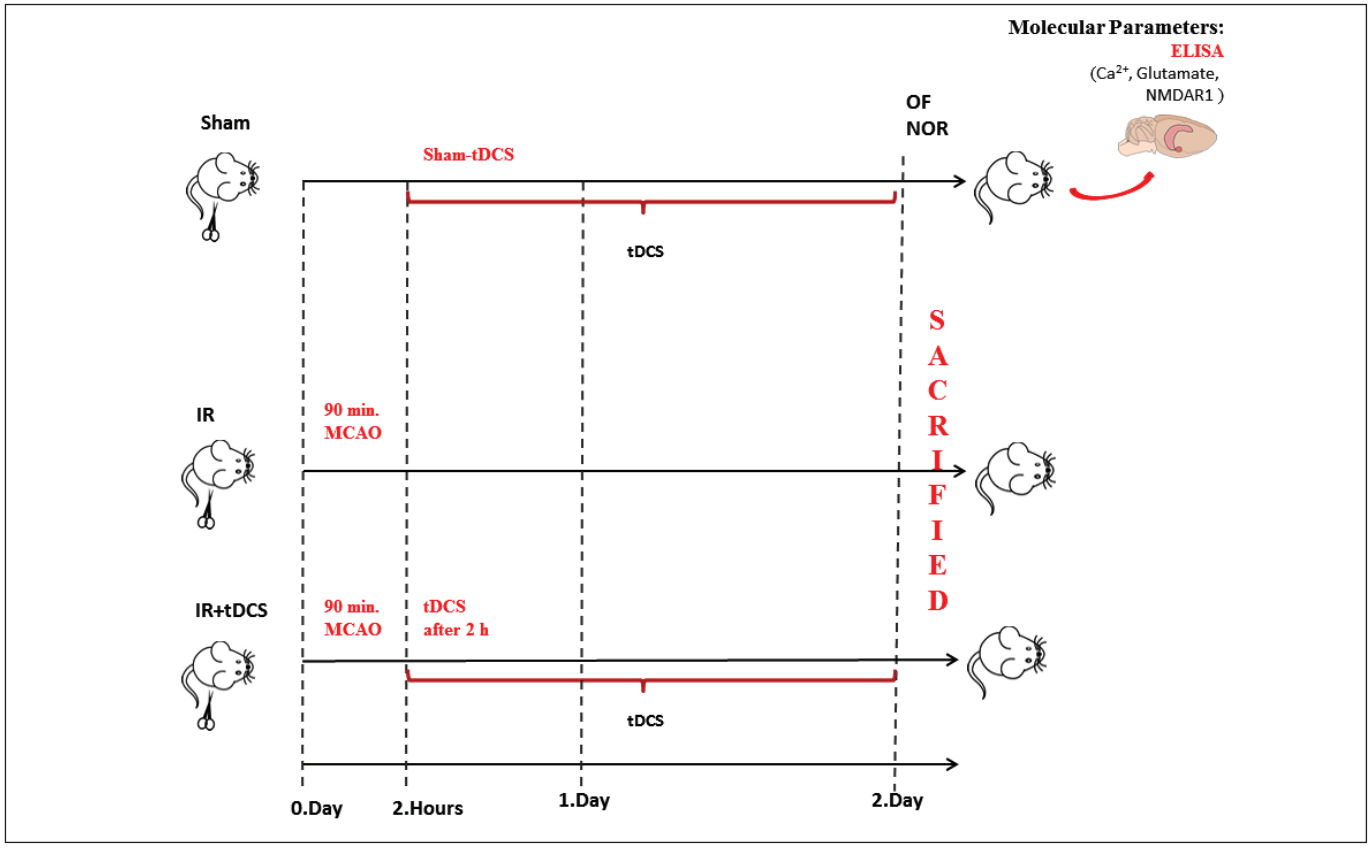

Figure 1: Experimental protocol.

Table I: Behavior Results of Experimental Groups

	Sham		IR		IR+tDCS	
	Mean	**SEM**	**Mean**	**SEM**	**Mean**	**SEM**
Body weight (gr)	298.00	5.60	275.00	4.80	281.00	5.00
mNSS test score	3.80	0.40	**9.30****	0.90	**7.40**#	**0.70**#
Total Distance (cm)	1289.79	91.97	**786.84****	30.84	**1052.53**#	**38.34**#
Velocity (cm/s)	4.25	0.22	**2.96****	0.10	**3.75**#	**0.16**#
Discrimination index (%)	72.00	1.69	**41.00****	4.60	**60.00**#	**2.32**#
Exploration time of the novel object (s)	40.67	1.18	**29.00****	2.51	**34.00**#	**1.84**#

***p<0.01 compared to sham, #p<0.05, ## p<0.01 compared to IR, one-way ANOVA test, followed by Tukey post hoc test. All data are presented as means ± SEM, n=10 for each group)*

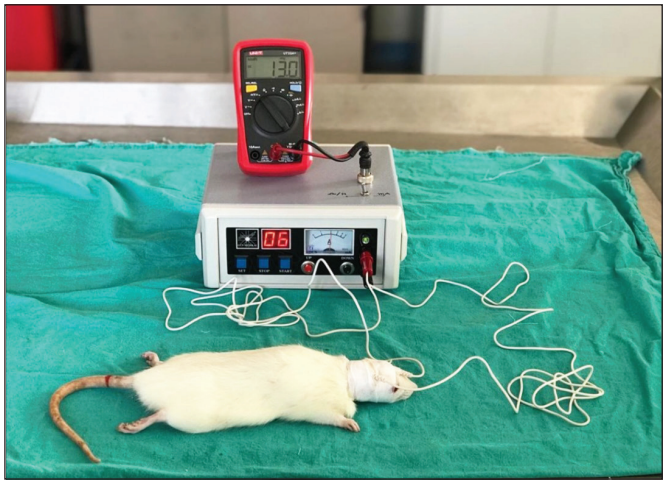

Figure 2: tDCS treatment application.

and cognitive function were evaluated using the open field (OF) and novel object recognition (NOR) tests, respectively. The concentrations of Ca^{2+}, glutamate, and NMDAR1 in the hippocampus tissue were analyzed by ELISA.

Assessment of Neurological Severity Score (NSS)

Rats were subjected to a modified NSS test, which is similar to the sensory, motor, reflex, and balance tests conducted on humans. The experimental protocol was performed according to our previous study (2).

Assessment of Motor Function

The OF test is a behavioral experiment in which locomotor activity is evaluated. Motor function was evaluated using the total distance (cm) and velocity (cm/s) (3).

Assessment of Cognitive Function

The NOR test evaluates attention or short-term memory activities. We used an experimental protocol as described previously (1). The discrimination index (DI) and the duration spent with the novel object (seconds) were evaluated.

Biochemical Analysis

Protein measurements

Homogenization of hippocampus tissues and measurements of protein concentrations were performed according to our previous research (4).

ELISA

The concentrations of Ca^{2+}, glutamate, and NMDAR1 were measured by ELISA as described previously (4).

Statistical Analysis

Data were subjected to one-way ANOVA followed by Tukey's post hoc test. Results are expressed as mean ± SEM and considered significant only when $p<0.05$.

RESULTS

Table I shows the results of the behavioral tests. Body weights that were measured on day 2 (Figure 2A) showed a nonsignificant reduction in the IR and IR+tDCS groups compared with those in the sham group. Motor behavior indices that were measured on day 2 of ischemia–reperfusion (Figure 2B) showed considerable increases in the IR and IR+tDCS groups compared with those in the sham group; however, the indices in the IR+tDCS group showed a decrease compared with those in the IR group. The motor function, analyzed using the OF test (Figures 2C, D), showed significant reductions in the IR group compared with that in the sham group ($p<0.01$). tDCS treatment significantly increased the motor function in the IR+tDCS group compared with that in the IR group ($p<0.05$) (Figures 2C, 2D). Short-term memory was analyzed using the NOR test (Figures 2E, 2F), which revealed a substantial reduction in learning in the IR group compared with that in the sham group ($p<0.01$); however, there was a substantial increase in the IR+tDCS group compared with that in the IR group ($p<0.05$). The mean ± SEM concentrations of Ca^{2+}, glutamate, and NMDAR1 are shown in Table II, revealing a substantial increase in the IR group compared with those in the sham group; however, there was a substantial increase

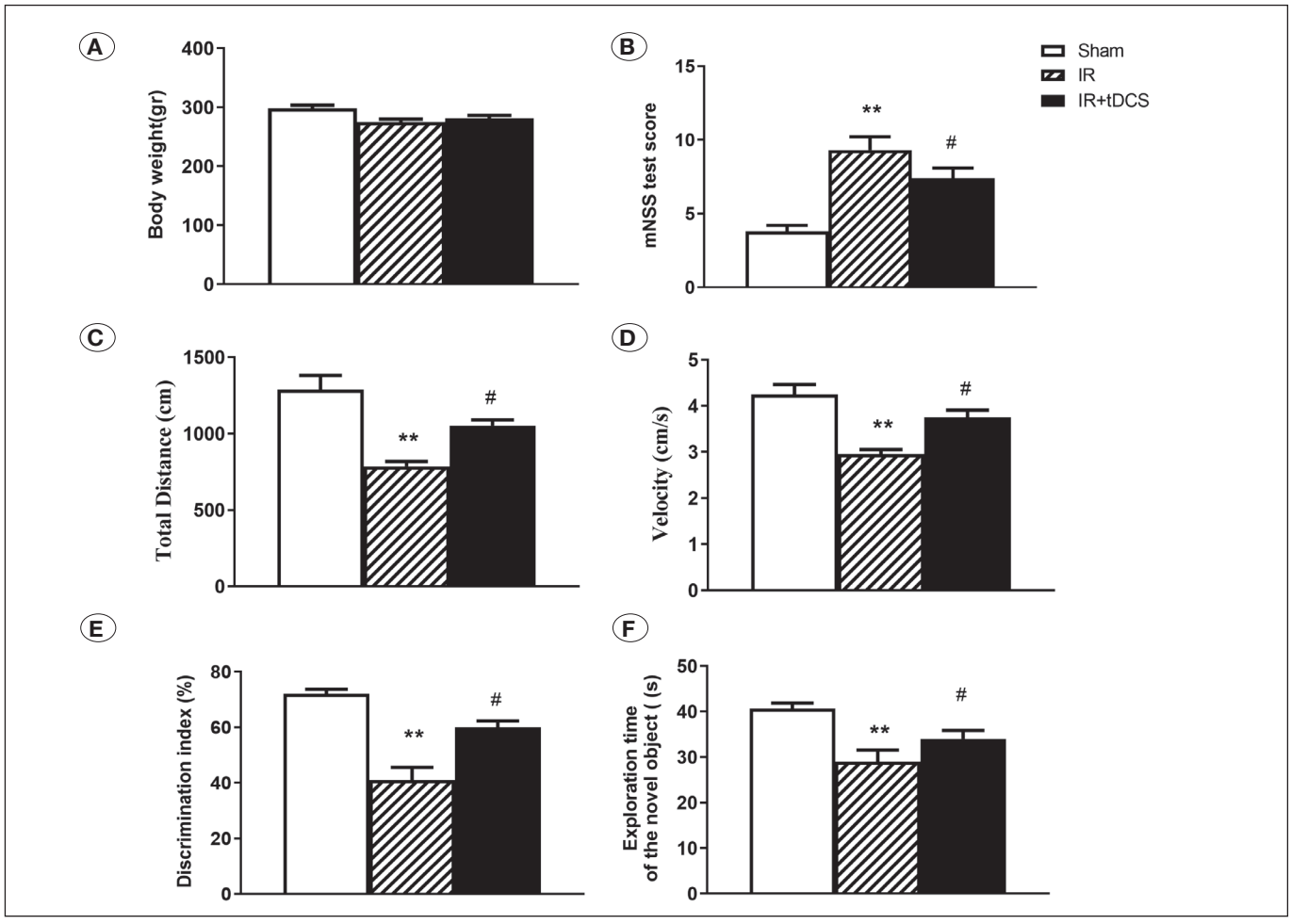

Figure 3: Behavioral results of experimental groups. **A)** 2nd-day body weights of rats, **B)** 2nd-day motor behavior indexes of the groups, **C)** Total distance (cm) in the OF test, **D)** Velocity (cm/s), **E)** Discrimination index (%), and **F)** Exploration time of the novel object (seconds) (*p<0.05, **p<0.01, vs. sham, #p<0.05, vs. IR, n=10, for each group).

Table II: ELISA Results

	Sham		IR		IR+tDCS	
	Mean	**SEM**	**Mean**	**SEM**	**Mean**	**SEM**
Ca^{2+} (µg/ml/g protein)	1.30	0.05	**1.63****	0.04	**1.45**#	0.03
Glutamate (µg/ml/g protein)	0.67	0.05	**1.07****	0.07	**0.87**#	0.02
NMDAR1 (µg/ml/g protein)	1.18	0.05	**2.07****	0.20	**1.61**#	0.12

***p<0.01 compared to sham, #p<0.05, ##p<0.01 compared to IR, one-way ANOVA test, followed by Tukey post hoc test. All data are presented as means ± SEM, n = 10for each group)*

in these concentrations in the IR+tDCS group compared with those in the IR group after tDCS treatment (Figure 3).

DISCUSSION

Cerebrovascular diseases cause bleeding of blood vessels due to changes in the blood vessels supplying the brain or in the properties of blood. Cerebrovascular diseases account for >80% of neurological disorders requiring hospital treatment, of which 87% are ischemic and 13% are hemorrhagic strokes. Improvements in diagnosis and treatment methods in developed countries have led to a decrease in the mortality rates caused by stroke. Therefore, it is important to develop treatment methods that will accelerate the recovery of patients by preventing reperfusion damage after ischemia in stroke (7,33).

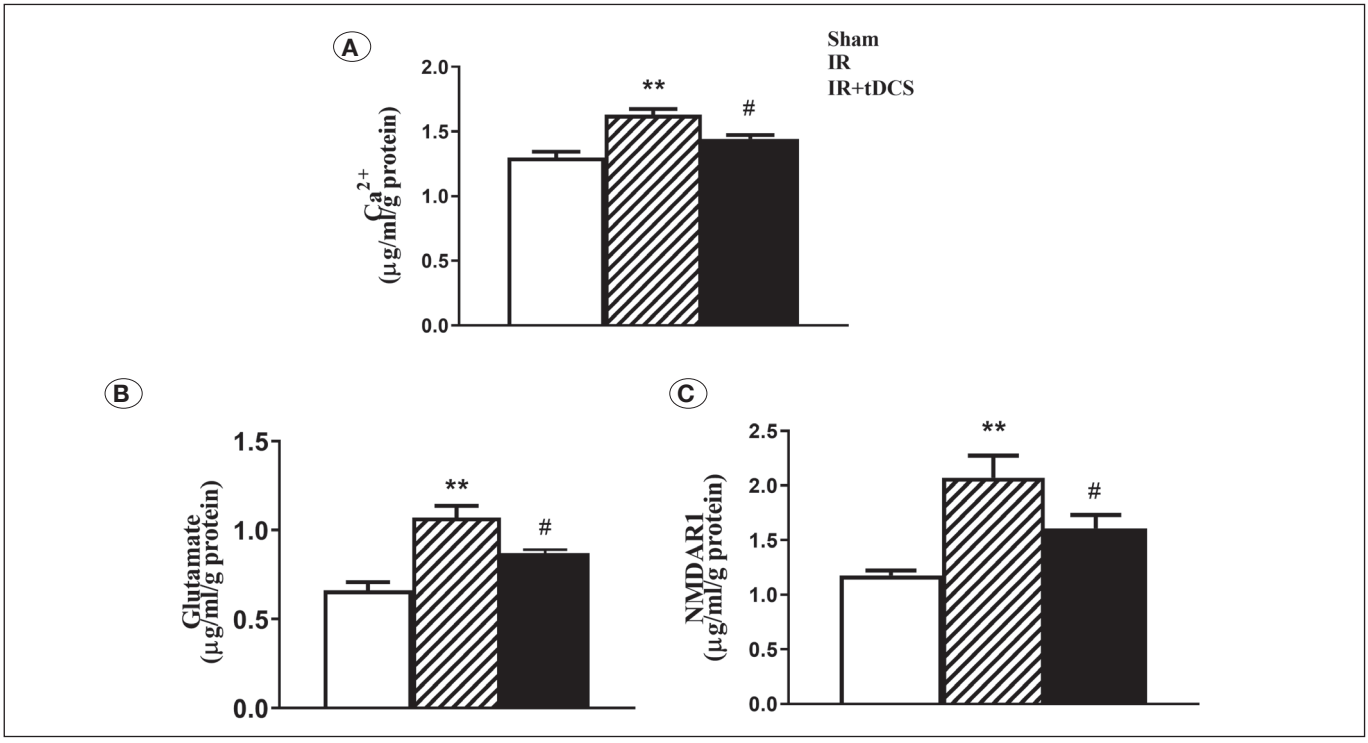

Figure 4: Results of ELISA. **A)** Ca^{2+} concentrations in the hippocampus, **B)** Glutamate concentrations in the hippocampus, and **C)** NMDAR1 concentrations in the hippocampus (**p<0.01, vs. sham, #p<0.05, vs. IR, n=10, for each group).

Studies have shown that tDCS therapy improves motor and cognitive functions in patients with Parkinson's disease (4), modulates brain activity in patients with stroke (5), and improves working memory performance in patients with Alzheimer's disease (19). Jiang et al. demonstrated that 0.1-mA anodal stimulation of rats using the MCAO model improved motor activity and increased neuronal plasticity (12). In our study also, we investigated the efficacy of tDCS treatment after MCAO and showed that tDCS reduces cell damage and improves learning and memory loss (2). We have earlier reported that tDCS treatment is especially by the regulation of AMPAR1, NMDAR1, and NMDAR2A receptors (2). In the present study, our aims were to increase the current value by decreasing the duration of treatment and to increase the efficacy of treatment more rapidly. Accordingly, we explored whether tDCS treatment exerts therapeutic efficacy in rats with focal ischemia induced by MCAO. Compared with the other groups, the IR group showed decreased body weight, hemiplegia, balance, and poster impairment. Stroke-related motor and cognitive dysfunction was observed after the stroke; however, tDCS treatment improved the motor and cognitive dysfunction.

Glutamate is the most important excitatory neurotransmitter in the mammalian brain. Glutamate stimulates Ca^{2+} channel receptors such as NMDARs and triggers ischemic neuronal damage and intracellular Ca^{2+} increase, leading to enzymatic cellular death (17,27). In animal stroke models, high concentrations of extracellular amino acids such as glutamate, aspartate, and glycine have been detected after focal cerebral ischemia (20,34). An 80-fold increase in glutamate levels occurs, especially in the ischemic area of stroke (10). Glutamate and its receptors play a vital role in the pathology of ischemia because the excessive increase in glutamate levels in the extracellular space during ischemia and the excessive activation of glutamate receptors in the postsynaptic region cause glutamate–calcium toxicity. Pascual et al. demonstrated an increase in glutamate level in neurons and astrocytes after 60 min of focal MCAO (26). Goldberg et al. also demonstrated that hypoxic injury increased the concentrations of glutamate and glutamine (6). In the present study, we found increased levels of Ca^{2+}, glutamate, and NMDAR1 in the hippocampus tissue of the IR group, which is consistent with the literature. The amount of glutamate increases in the first 4 h after stroke (11,22); however, in our study, tDCS application was applied to the IR+tDCS group 2 h after ischemia. Decreased glutamate levels reduce neuronal damage and infarct volume, thus playing a protective role for glutamate transporters in stroke (13). When we evaluated our data in the light of this information, we observed that the decrease in Ca^{2+}, glutamate, and NMDAR1 levels after tDCS treatment contributed to the neuronal damage and behavioral improvements. The binding of glutamate to ionotropic NMDA and AMPA receptors results in increased Ca^{2+} entry during ischemia (21,32). The activation of NMDA and AMPA receptors plays a critical role in Ca^{2+} toxicity leading to ischemic brain damage (2). Several studies have demonstrated that the stimulation of NMDARs causes cell death (14,30,37). Increased glutamate release or impaired glutamate reuptake in the ischemic region results in an excessive accumulation of glutamate in the extracellular space, causing excessive activation of NMDARs and cell death by excessive Ca^{2+} entry (28,31). However, when overactivat-

ed in ischemic stroke, NMDARs initiate toxic pathways that cause neuronal death (8,9,15,16,29). NMDARs are especially effective in brain damage associated with acute ischemic stroke. Another study on rats showed that NMDA gene and protein expression increased after transient MCAO (2). Zaric et al. demonstrated that 15 min of transient global cerebral ischemia caused a significant increase in the hippocampal NMDAR1 protein level (36). Our NMDAR1 findings are similar to the results reported in the literature, wherein we observed an increase in NMDAR1 levels after IR, which might be related to the excessive stimulation of NMDARs by glutamate after IR. After ischemia, tDCS treatment decreased the NMDAR1 level. tDCS regulates membrane potential by modulating AMPA and NMDA receptors (2). Na^+ and Ca^{2+} ion transients occur through these ionotropic glutamate receptors. Because Na^+ and Ca^{2+} ions play a role in processes such as cell stimulation, cell death, and apoptosis, tDCS treatment after ischemia may reduce NMDAR activation and reduce Na^+ and Ca^{2+} ion transients into the cell, which may reduce cell stimulation and prevent cell death and loss of motor and cognitive functions (2,4). We also observed that tDCS treatment decreases the increased glutamate and Ca^{2+} activation after ischemia, which can be achieved by reducing NMDAR activation.

tDCS treatment may exert a neuroprotective effect against cognitive and motor dysfunctions by reducing ischemia-induced calcium and glutamate excitotoxicity. We also concluded that tDCS treatment acts as an antagonist on NMDARs, which plays a critical role in ischemic damage.

In summary, this study demonstrated that early tDCS treatment after cerebral ischemia is effective in the treatment of motor and cognitive dysfunction by regulating glutamate and calcium excitotoxicity.

CONCLUSION

Although we investigated the therapeutic efficacy of tDCS on the glutamatergic pathway after cerebral ischemia–reperfusion, it is known that the excitatory and inhibitory balance plays a vital role in brain damage. In this context, we investigated only the excitatory pathway, i.e., the glutamatergic pathway, and did not investigate the GABAergic pathway, which is considered a limitation of our study. In future studies, we intend to explore the effectiveness of tDCS treatment on the GABAergic pathway.

Declarations

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Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

Disclosure: The authors declare no competing interests.

AUTHORSHIP CONTRIBUTION

Study conception and design: GA, DK
Data collection: GA, YME, CC
Analysis and interpretation of results: GA, DK, TG
Draft manuscript preparation: GA, DK, AY, FD, TG
Critical revision of the article: GA
All authors (GA, FD, DK, TG, AY, YME, CC) reviewed the results and approved the final version of the manuscript.

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