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The Involvement of D1 and D2 Dopamine Receptors in the Restoration Effect of Left Frontal Anodal, but not Cathodal, tDCS on Streptozocin-Induced Amnesia

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Abstract

Background: Transcranial direct current stimulation (tDCS) is a non-invasive method that improves learning and memory. In this study, the effect of tDCS on streptozotocin (STZ) induced amnesia in the presence or absence of SCH23390 (D1 dopamine receptor antagonist) and sulpiride (dopamine D2 receptor antagonist) has been investigated in male Wistar rats.

Methods: Passive avoidance memory, locomotor activity and pain perception have been assessed by step-through, open-field and hot-plate instruments, respectively. Anodal and cathodal tDCS were exerted on the left frontal cortex with an intensity of 0.2 milliamps for 20 minutes twice a day in 2 successive days.

Results: Our study showed that STZ at doses of 30 and 60 mg/ml/kg caused amnesia, while they did not alter locomotor activity and a higher dose of STZ induced analgesia 14 days after injection. SCH23390 (0.001 mg/mL/kg) and sulpiride (0.1 mg/mL/kg) did not alter memory formation by themselves and amnesia induced by STZ (30 and 60 mg/mL/kg), while SCH23390 restored the analgesia induced by STZ (60 mg/mL/kg). Moreover, left frontal anodal and cathodal tDCS restored memory impairment induced by STZ (30 and 60 mg/mL/kg). Also, SCH23390 and sulpiride could prohibit the anodic stimulating effect on memory impairment induced by a dose of 60 mg/ml/kg, but they did not hinder the effect of the cathodal stimulation on this phenomenon.

Conclusion: The study showed that D1 and D2 dopamine receptors are involved in the restoration effect of left frontal anodal- but not cathodal-tDCS in STZ-induced amnesia.

Keywords: Amnesia, SCH23390, Streptozotocin, Sulpiride, tDCS

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Introduction

Diabetes is the most common endocrine disease in the world, annually responsible for 4 million deaths which are predicted to amount to 439 million in 2030.[1] Diabetes affects the metabolism of lipids and carbohydrates leading to microvascular complications (retinopathy, nephropathy, neuropathy, and impaired wound healing) and macrovascular complications (stroke and cardiovascular complications). It also causes problems in cognition, learning, mood flexibility and memory including emotional memory.[2-4] For example, an interesting study showed emotional declarative memory impairment in type 2 diabetes.[5] It seems that the emotional arousal can improve memory processing through a possible interconnection between amygdala and dorsolateral prefrontal region (for working memory) and medial temporal lobe (declarative memory).[6] Among these, neuropathy, as one of its commonest complications, brings about disorders in the sensitivity of central nervous system to pain stimuli.[7] It is reported that approximately 50% of diabetic patients in some stages of life illustrate increased pain perception[8,9] via pro-inflammatory cytokines[10,11] inasmuch as these factors increased sensory transmission.

Hence, the risk of Alzheimer's and other dementia diseases in people with diabetes is 2 or 3 times higher than in healthy people.[12] Although the mechanism of brain damage, including the memory impairment caused by diabetes and streptozotocin (STZ) induced diabetes

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is unknown, it appears to be a multifactorial process in which changes in glucose levels, reducing insulin signaling, metabolic and vascular disorders such as acute and chronic reduced blood flow,[13] changes in the cellular calcium homeostasis[14] and defects in the induction of long-term potentiation (LTP) might be involved.[15,16] Moreover, empirical studies indicate that STZ induced diabetes results in oxidative stress in brain regions such as cortex and hippocampus[17-20] and also there is a change in neurotransmitters like dopamine and acetylcholine.[21-23] That is why in the future, cognitive problems, especially memory problems in people with diabetes will become one of the most important and challenging issues in the treatment of these people.

Dopamine as a neurotransmitter is involved in activities like learning, memory and reward process. This neurotransmitter plays its role through G-protein receptors, such as pseudo D1 receptors (including D1 and D5) and pseudo D2 receptors (including D2, D3 and D4).[24,25] The number of D1 receptors in the frontal cortex is more than the number of D2 receptors. Many behavioral studies show that D1 receptors in the frontal cortex play an important role in memory, including working memory. D2 receptors are also involved in working memory.[26-28]

Transcranial direct current stimulation (tDCS) is a noninvasive and painless method in which a weak electric current is sent directly to the brain through the electrodes attached to the scalp.[29,30] The tDCS, according to polarity changes in the excitability of neurons during or after stimulation, induces changes in brain function. The effect of tDCS applied to the brain is not limited only to the time of applying the current. They can also last up to several minutes or even hours after the current is applied. This method, compared to other similar methods, particularly the repetitive transcranial magnetic stimulation (rTMS) and other invasive methods, is safer, more economical and more bearable.[31,32] Many studies have been done on the effects of tDCS. In animal models, tDCS improved learning and recognition memory in Alzheimer's disease[29] and it has been beneficial in the regeneration of neurons in Parkinson's disease, depression and stroke.[33-35] This method also increases the activity of frontal cortex neurons and the consistency of the midbrain areas.[36] Human studies also show that tDCS facilitates neural connections and improves learning and memory.[31,37]

The effects of tDCS on the improvement of memory corruption have been reported in several experimental models including fear memory[38] and emotional memory.[39] On the other hand, empirical studies indicate that STZ induced diabetes cause emotional memory corruption; however, no study has been performed to determine the effects of tDCS on the memory defect induced by STZ. With these in mind, and with respect to the increasing prevalence of diabetes and the fact that no specific treatments have been found for controlling the cognitive impairment caused by diabetes, the present study was performed to investigate the effects of tDCS on amnesia induced by STZ in the presence or absence of D1 and D2 dopamine receptor antagonists, because these receptors are involved in this kind of memory.[40]

Materials and Methods

Animals

In this study, male Wistar rats weighing 200–220 were used which were taken from the animal room of the Institute of Cognitive Sciences (ICSS). Animals were housed at the temperature of 22 ± 2°C in 12 hours of light and 12 hours of darkness and in groups of 3 to 4 animals per cage. Animals had free access to food and water. To do each test, 7 rats from all groups were used and each animal was used only once. Animals were kept under the Guide for the Care and Use of Laboratory Animals issued by NIH (NIH publication no. 85–23, revised 1985) and the instructions for keeping lab animals made by the Institute of Cognitive Sciences. Experimental design timeline has been summarized in Figure 1.

Surgery

The rats were anesthetized by intraperitoneal injection of ketamine hydrochloride (50 mg/kg) together with xylazine (5 mg/kg) and then were put in a stereotaxic apparatus (Industrial Tower Examiner, Iran). After removing the scalp, the skull was cleaned with alcohol and the electrode (which could provide 3.5 mm^2 of effective contact surface area when filled with normal saline) was placed in the anterior (1.5 mm) and left (1.5 mm) from Bregma which is related to the left frontal cortex. This was done in such a way that the tip of the electrode would be kept at the center of the region. To fix the electrodes dental cement was used in which acrylic monomers were used. Then the mice returned to the cage and allowed to rest for 7 days to recover from the effects of anesthesia.

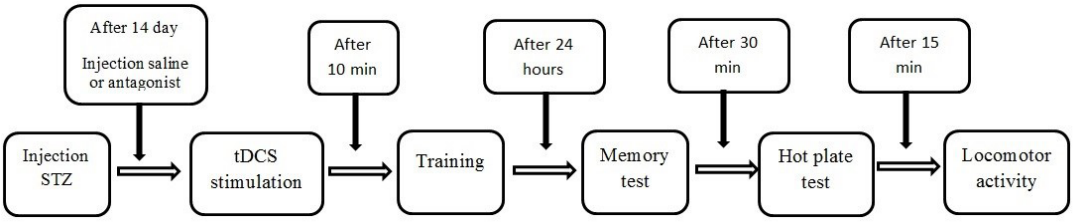

Figure 1. Experimental Design Timeline.

Stimulation

A week after surgery and recovery, a device (Nerurostim 2 Brain Stimulation Device from SinaPsycho Company, Tehran, Iran) was used to produce stimulating direct current. To stimulate the frontal cortex, an electrode was used which was fixed directly on the skull. In order to create an effective contact area the electrode was filled with saline solution (NaCl 0.9%) and another carbon electrode, as the counter electrode, with the length of 9.5 cm. was covered in wet sponge and fastened to the animal's breast like a vest which would provide safe and efficient stimulation. Moreover, it would minimize the electric current bypass. The rats received anodal and cathodal stimulation at the intensity of 0.2 mA for 20 minutes twice a day in 2 consecutive days in according previous studies.[41-44]

Memory Test

The Step-through Inhibitory Avoidance Apparatus

The device (Borj Sanat Azma, Iran) consisted of a box made up of 2 parts: a light section (30 × 20 × 20 cm) and a dark one (30 × 20 × 20 cm) which were separated by a guillotine door (7 × 9 cm). The floor of the dark side was covered by steel bars (with a thickness of 2.5 mm and at 1-cm intervals). The electric shock would pass to the animal's feet through these bars. The electric shock (50 Hz, 3 seconds, at the intensity of 1 mA) would be transmitted from the stimulator (Borj Sanat Azma, Iran) to the floor of the dark side.

Training

The animals were transferred to the test room 60 minutes before the test. Then, to get acquainted with the device, each animal was gently placed in the light side of the device and after 5 seconds the guillotine door would open and the animal with its natural tendency to dark environment would go to the dark side. Its delay time for entering the dark side was recorded. Animals with more than 100 seconds delay were excluded. When the animal completely entered the dark side, the guillotine door would close and after 10 seconds the rat would be gently removed from the device and would be returned to the cage. Thirty minutes later the test animals were transferred to the light side and after 5 seconds the guillotine door would open. As soon as the animal fully entered the dark part, the door would close and a mild shock would be applied through the bars at the floor of the dark side. After 20 seconds the rats would be removed from the dark side and the whole procedure would be repeated after 2 minutes. When the rat disdained from entering the dark side after 120 seconds, it would mark the end of training. The number of entries into the dark room was recorded.[45-47]

Retrieval Test

Twenty-four hours after training, each rat would be gently placed in the light side. After 20 seconds the door would open, and the delay for entering the dark side would be recorded. When the animal did not enter the dark side within 300 seconds, it would mark the end of the test.

Measurement of Locomotor Activity

The device for recording motor activity (Borj Sanat Azma, Iran) consisted of an unenclosed Plexiglas box with walls made of Pyrex glass and the floor made of black Pyrex. The locomotor activity of the animal was recorded within 5 minutes by 16 photo cells embedded in the floor sides of the device.

Hot Plate Test

In this test, animals were individually placed into a glass cylinder on a hot plate (Borj Sanat Azma, Iran) with the temperature adjusted to 52 ± 1°C. The latency to the first sign of paw licking or jump response to avoid the heat was taken as an index of the pain threshold; the cut-off time was 60 seconds in order to avoid damage to the paw.

Drugs

The drugs used in this study consisted of STZ at doses of 30 and 60 mg/mL/kg, SCH23390 (R (+) - 7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hy-drochloride) as dopamine D1 receptor antagonist, at a dose of 0.001 mg/mL/kg and sulpiride as dopamine D2 receptor antagonist, at a dose of 0.1 mg/mL/kg. All the drugs were provided by Sigma, St. Louis, USA. The STZ and SCH23390 were dissolved in saline 0.9% immediately before injection, while sulpiride was dissolved in one drop of acetic acid. The control groups received saline or vehicle (1 mL/kg). All drugs were injected intraperitoneally (i.p).

Diabetes Induction

Three days after the injection of STZ, in order to control blood sugar changes and to determine the time and the severity of experimental diabetes a glucometer (Elegans, Germany) was used to test blood sugar levels after a 12-hour fasting. The blood glucose levels above 250 mg/dL were considered as diabetic.[48]

Statistical Analysis

All data were reported as mean ± SD. In order to compare the time of memory corruption induced by STZ in 7th and 14th days, one-way analysis of variance (ANOVA) was used and to compare the effect of stimulation in the absence or presence of SCH23390 and sulpiride the two-way ANOVA was used. The pairwise comparison of the groups was performed using Tukey test. In this study $P < 0.05$ was considered as significant and all statistical analysis was conducted using SPSS software version 24. Moreover, the effect sizes (partial eta squared, denoted as R^2) with 95% confidence intervals (CI) reported in the result section.

Experimental Design

The Effects of STZ on Memory, Locomotor Activity and Pain Threshold

For this experiment, 5 groups of animals, including a control group and 4 intervention groups were used. The control group received normal saline (1 mL/kg) and the intervention groups received STZ at doses of 30 mg/mL/kg (2 groups) and 60 mg/mL/kg (2 groups). The relevant tests were performed 7 or 14 days after the injection. This experiment was designed to investigate the effect of STZ (30 or 60 mg/mL/kg) on memory, locomotor activity and pain threshold when injection was done 7 or 14 days before behavioral test.

The Effect of STZ on Memory, Locomotor Activity and Pain Threshold in the Presence and Absence of SCH23390 or Sulpiride

For this experiment, nine groups of animals were divided into 3 subgroups: The animals which received saline (1 mL/kg), SCH23390 (0.001 mg/mL/kg) or sulpiride (0.1 mg/mL/kg) 14 days after the injection of saline (1 mL/kg), (3 groups), STZ (30 mg/mL/kg, 3 groups) or STZ (60 mg/mL/kg, 3 groups). This experiment was designed to investigate the effect of SCH23390 and sulpiride on responses induced by STZ (30 and 60 mg/ml/kg) when injection was done 14 days before behavioral test.

The Effect of Left Frontal Anodal- or Cathodal-tDCS on Amnesia Induced by STZ

To do this experiment, nine groups of animals were divided into 3 subgroups: The animals which received saline (1 mL/kg) or STZ (30 or 60 mg/mL/kg), 14 days before sham-tDCS (control groups, 3 groups), anodal (3 groups) or cathodal (3 groups) tDCS. This experiment was designed to investigate if anodal or cathodal tDCS could alter STZ-induced amnesia.

The Effect of SCH23390 or Sulpiride on the Restoration Effect of Left Frontal Anodal tDCS on STZ-Induced Amnesia

In this experiment, 6 groups of rats were used. 14 days after the injection of saline (1 mL/kg) or STZ (30 or 60 mg/mL/kg), the animals received saline (1 mL/kg) or SCH23390 (0.001 mg/mL/kg) 15 minutes before left frontal anodal tDCS, while vehicle of sulpiride (1 mL/kg) or sulpiride (0.1 mg/mL/kg) was given 30 minutes before that. This experiment was designed to investigate if the deactivation of D1 or D2 dopamine receptor could block memory restoration effect of left frontal anodal tDCS on STZ-induced amnesia.

The Effects of SCH23390 or Sulpiride on Restoration Effect of Left Frontal Cathodal tDCS on STZ-Induced Amnesia

In this experiment, 6 groups of rats were used. Fourteen days after the injection of saline (1 mL/kg) or STZ (30 or 60 mg/mL/kg), the animals received saline (1 mL/kg) or SCH23390 (0.001 mg/mL/kg) 15 minutes before left frontal cathodal tDCS, while vehicle of sulpiride (1 mL/kg) or sulpiride (0.1 mg/mL/kg) was given 30 minutes before it. This experiment was designed to investigate if the deactivation of D1 or D2 dopamine receptor could block memory restoration effect of left frontal cathodal tDCS on STZ-induced amnesia.

Results

The Effects of STZ on Memory, Locomotor Activity and Pain Threshold

One-way ANOVA revealed that both doses of STZ (30 and 60 mg/ml/kg) had no impact on the inhibitory avoidance memory [R2 = 0.251, F(2, 18) = 3.0, $P>0.05$, mean differences 45.7 (95% CIs -47.5, 138.9) and -44.1 (95% CIs -137.4, 49.1) respectively, Figure 2, panel 2A] and pain threshold [R2 = 0.04, F(2, 18) = 0.4, $P>0.05$, mean differences -0.43 (95% CIs -2.2, 1.3) and 0.1 (95% CIs -1.6, 1.9), respectively, Figure 2, panel 2C] when injected 7 days before memory testing. Moreover, similar analysis and Tukey test for locomotor activity showed that the higher dose of STZ decreased locomotor activity [R2 = 0.51, F(2, 18) = 9.2, $P<0.01$, mean differences -8 (95% CIs -32.8, 16.7) and 31.4 (95% CIs 6.7, 56.2), respectively, Figure 2, panel 2B].

One-way ANOVA and Tukey test showed that STZ at doses of 30 and 60 mg/mL/kg decreased passive avoidance memory [R2 = 0.88, F(2, 18) = 67.8, $P<0.001$, mean differences 206.6 (95% CIs 153.3, 259.8) and 215.8 (95% CIs 160.6, 267.1), respectively, Figure 2 panels 3A], Also, similar analysis and Tukey test for pain threshold showed that the higher dose of STZ increased pain threshold [R2 = 0.46, F(2, 18) = 7.8, $P<0.001$, mean differences 1.3 (95% CIs -4.4, 6.9) and -6.8 (95% CIs -12.5, -1.2), respectively, Figure 2 panels 3C], while it did not alter locomotor activity [R2 = 0.06, F(2, 18) = 0.6, $P>0.05$; Figure 2, mean differences -7.3 (95% CIs -60.5, 45.9) and 5.6 (95% CIs -9.6, 20.8), respectively, panel 3B], when injected 14 days before behavioral testing.

The Effects of STZ on Memory, Locomotor Activity and Pain Threshold in the Presence and Absence of SCH23390 or Sulpiride

The one-way ANOVA showed that SCH23390 or sulpiride did not affect the animals' inhibitory avoidance memory [R2 = 0.01, F(2, 18) = 0.1, $P>0.05$, mean differences 7.8 (95% CIs -97.8, 113.5) and 14.6 (95% CIs -91.1, 120.3), respectively, Figure 3, panel 1A], locomotor activity [R2 = 0.18, F(2, 18) = 2.0, $P>0.05$, mean differences -17.1 (95% CIs -39.9, 5.6) and -3.7 (95% CIs -26.5, 19.1), respectively, Figure 3, panel 1B], and pain threshold [R2 = 0.03, F(2, 18) = 0.3, $P>0.05$, mean differences -1.4 (95% CIs -6.7, 3.8) and -1.1 (95% CIs -6.4, 4.1), respectively, Figure 3, panel 1C] by itself.

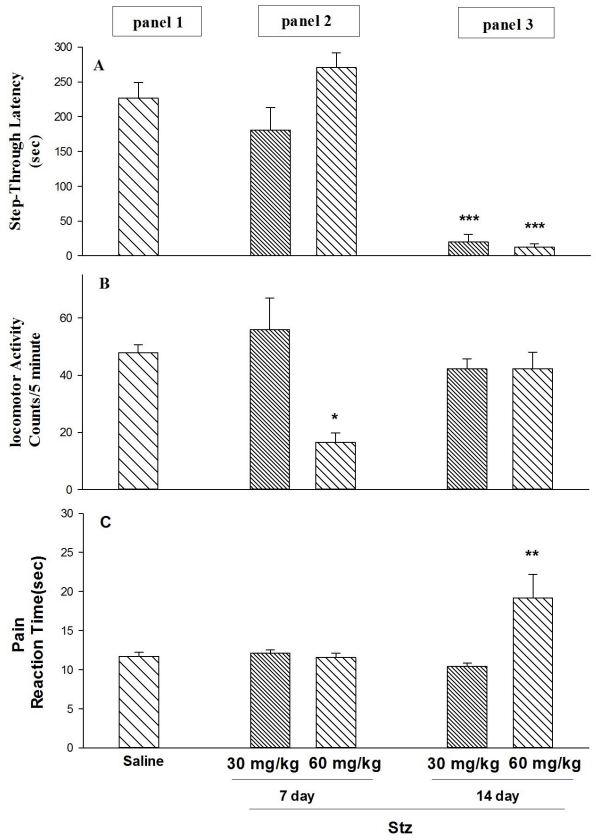

Figure 2. The Effect of STZ on Memory Formation (panels 1A, 2A and 3A), Locomotor Activity (panels 1B, 2B and 3B) and Pain Threshold (panels 1C, 2C and 3C). Five groups of animals, including a control group and 4 intervention groups were used. The control group received normal saline (1 mL/kg) and intervention groups received STZ at doses of 30 (2 groups) and 60 (2 groups) mg/ml/kg. The relevant tests were performed 7 or 14 days after the injection. Values are expressed as mean ± SD. (n = 7 in each group). *P < 0.05, **P < 0.01 and ***P < 0.001 compared to the saline control group.

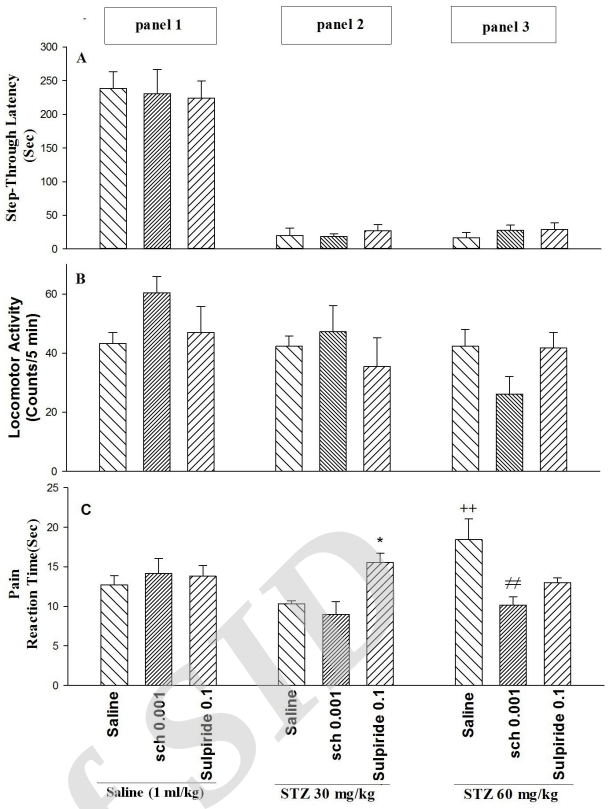

Figure 3. The Effect of STZ on Memory (panels 1A, 2A and 3A), Locomotor Activity (panels 1B, 2B and 3B) and Pain Threshold (panels 1C, 2C and 3C) in the Presence and Absence of SCH 23390 or Sulpiride. Nine groups of animals were divided into 3 subgroups. The animals received saline (1 ml/kg), SCH23390 (0.001 mg/ml/kg) or sulpiride (0.1 mg/mL/kg) 14 days after injection of saline (1 mL/kg, 3 groups), STZ (30 mg/mL/kg, 3 groups) or STZ (60 mg/mL/kg, 3 groups). Values are expressed as Mean ± SD. (n = 7 in each group). *P<0.05 compared to control group in the panel 2. ++P<0.01 compared to the control group in panel 1. **P<0.01 compared to the control group in panel 3.

Similar analysis showed that SCH23390 or sulpiride did not alter the memory corruption induced by STZ at the dose of 30 mg/mL/kg [R2 = 0.03, F(2, 18) = 0.3, P> 0.05, mean differences 1.3 (95% CIs -29.1, 31.7) and -7.3 (95% CIs -37.7, 23.1), respectively, Figure 3, panel 2A] or at the dose of 60 mg/mL/kg [R2 = 0.07, F(2, 18) = 1.4, P> 0.0.5, mean differences -11.3 (95% CIs -41.4, 18.8) and -12.0 (95% CIs -42.1, 18.1), respectively, Figure 3, panel 3A]. Moreover, the locomotor activity induced by STZ at the dose of 30 mg/mL/kg [R2 = 0.06, F(2, 18) = 3.6, P> 0.05, mean differences -5.0 (95% CIs -33.2, 23.7) and 6.8 (95% CIs -21.4, 35.1), respectively, Figure 3, Panel 2B] or at the dose of 60 mg/mL/kg [R2 = 0.22, F(2, 18) = 2.6, P> 0.05, mean differences 16.1 (95% CIs -4.4, 36.7) and 0.6 (95% CIs -19.9, 21.1), respectively, Figure 3, panel 3B] did not alter following SCH23390 or sulpiride injection, either.

Moreover, Similar analysis showed that sulpiride increased the pain threshold induced by STZ at the dose of 30 mg/mL/kg [R2 = 0.50, F(2, 18) = 9.0, P< 0.05, mean differences 1.9 (95% CIs -2.9, 5.5) and -5.9 (95% CIs -9.5, -1.1), respectively, Figure 3, panel 2C] and SCH23390 decreased the pain threshold induced by STZ at the dose of 60 mg/mL/kg [R2 = 0.41, F(2, 18) = 6.3, P< 0.01, mean differences 8.9 (95% CIs 2.2, 14.3) and 5.4 (95% CIs -0.6, 11.5), respectively, Figure 3, panel 3C].

The Effects of Left Frontal Anodal- or Cathodal-tDCS on Amnesia Induced by STZ

The two-way ANOVA and post hoc Tukey's test showed that left frontal anodal tDCS [STZ effect: R^2 = 0.7, F(2, 36) = 43.5, P< 0.001, mean differences 171.1 (95% CIs 132.1, 210.2) for STZ 30 mg/kg and 132.5 (95% CIs 93.5, 171.5) for STZ 60 mg/kg; tDCS effect: R^2 = 0.63, F(1, 36) = 60.752, P< 0.001, mean differences -122.4 (95% CIs -154.3, 90.6); STZ and tDCS interaction effect: R^2 = 0.37, F(2, 36) = 10.8, P< 0.001, mean differences 171.1 (95% CIs 124.1, 218.2) for STZ 30 mg/kg and 132.5 (95% CIs 85.5, 179.5) for STZ 60 mg/kg; Figure 4, panel 2A) or cathodal tDCS [STZ effect: R^2 = 0.59, F(2, 36) = 43.5, P< 0.001, mean differences 148.3 (95% CIs 96.6, 200.0) for STZ 30 mg/kg and 165.5 (95% CIs 113.7, 217.2) for STZ 60 mg/kg; tDCS effect: R^2 = 0.41, F(1, 36) = 60.752, P< 0.001, mean differences -103.8 (95% CIs -146.0, -61.5); STZ and tDCS interaction effect: R^2

= 0.19, F(2, 36) = 10.8, $P<0.001$, mean differences 148.3 (95% CIs 85.9, 210.6) for STZ 30 mg/kg and 165.5 (95% CIs 103.2, 227.8) for STZ 60 mg/kg] restored the amnesia induced by both doses of STZ 14 days after injection of STZ.

Furthermore, the two-way ANOVA reveled that left frontal anodal tDCS [STZ effect: R^2 = 0.1, F(2, 36) = 0.2, $P>0.05$, mean differences -2.4 (95% CIs -13.0, 8.3) for STZ 30 mg/kg and -3.2 (95% CIs -13.9, 7.4) for STZ 60 mg/kg; tDCS effect: R^2 = 0.08, F(1, 36) = 3.2, $P>0.05$, mean differences 7.7 (95% CIs -1.0, 16.4); STZ and tDCS interaction effect: R^2 = 0.02, F(2, 36) = 0.4, $P>0.05$, mean differences -2.4 (95% CIs -15.2, 10.5) for STZ 30 mg/kg and -3.2 (95% CIs -16.1, 9.6) for STZ 60 mg/kg; Figure 4, panel 2B] or cathodal tDCS [STZ effect: R^2 = 0.03, F(2, 36) = 0.5, $P>0.05$, mean differences 4.2 (95% CIs -5.2, 13.2) for STZ 30 mg/kg and 3.9 (95% CIs -4.2, 8.4) for STZ 60 mg/kg; tDCS effect: R^2 = 0.27, F(1, 36) = 13.5, $P<0.001$, mean differences 14.0 (95% CIs 6.3, 21.7); STZ and tDCS interaction effect: R^2 = 0.02, F(2, 36) = 0.3, $P>0.05$, mean differences 4.2 (95% CIs -7.2, 15.6) for STZ 30 mg/kg and 3.9 (95% CIs -3.5, 9.8) for STZ 60 mg/kg; Figure 4, panel 3B] did not alter STZ responses for locomotor activity.

Also, the two-way ANOVA reveled that left frontal anodal tDCS [STZ effect: R^2 = 0.32, F(2, 36) = 8.5, $P<0.001$, mean differences 0.0 (95% CIs -4.7, 4.6) for STZ 30 mg/kg and -8.2 (95% CIs -12.9, -3.5) for STZ 60 mg/kg; tDCS effect: R^2 = 0.14, F(1, 36) = 5.6, $P<0.05$, mean differences -4.5 (95% CIs -8.3, -0.7); STZ and tDCS interaction effect: R^2 = 0.02, F(2, 36) = 0.4, $P>0.05$, mean differences 0.0 (95% CIs -5.6, 5.6) for STZ 30 mg/kg and -8.2 (95% CIs -13.8, -2.5) for STZ 60 mg/kg; Figure 4, panel 2C] or cathodal tDCS [STZ effect: R^2 = 0.22, F(2, 36) = 5.1, $P<0.05$, mean differences 3.5 (95% CIs -0.3, 7.3) for STZ 30 mg/kg and -2.5 (95% CIs -6.3, 1.3) for STZ 60 mg/kg; tDCS effect: R^2 = 0.25, F(1, 36) = 11.9, $P<0.001$, mean differences -5.3 (95% CIs -8.4, -2.2); STZ and tDCS interaction effect: R^2 = 0.1, F(2, 36) = 2.0, $P>0.05$; mean differences 3.5 (95% CIs -1.1, 8.1) for STZ 30 mg/kg and -2.5 (95% CIs -7.1, 2.1) for STZ 60 mg/kg; Figure 4, panel 3C] did not alter STZ responses for pain threshold.

The Effects SCH23390 or Sulpiride in Restoration Effect of Left Frontal Anodal tDCS on STZ-Induced Amnesia

The 2-way ANOVA and post hoc Tukey's test revealed that the subthreshold dose of SCH23390 [STZ effect: R^2 = 0.4, F(2, 36) = 12.4, $P<0.001$, mean differences 103.3 (95% CIs 47.4, 159.3) for STZ 30 mg/kg and 129.7 (95% CIs 73.7, 185.6) for STZ 60 mg/kg; SCH23390 effect: R^2 = 0.21, F(1, 36) = 9.8, $P<0.01$, mean differences 70.5 (95% CIs 24.8, 116.2); STZ and SCH23390 interaction effect: R^2 = 0.32, F(2, 36) = 8.5, $P<0.001$, mean differences 103.3 (95% CIs 35.9, 170.8) for STZ

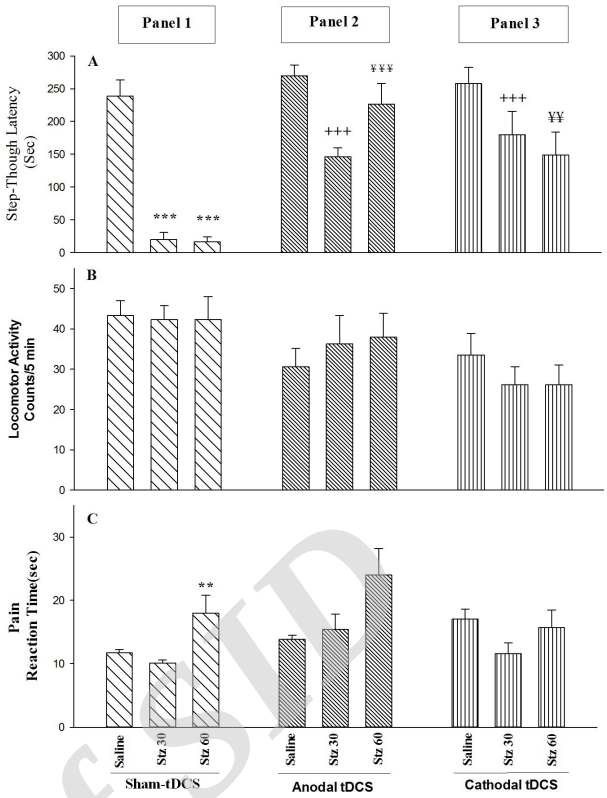

Figure 4. The Effect of STZ on Memory (panels 1A, 2A and 3A), Locomotor Activity (panels 1B, 2B and 3B) and Pain Threshold (panels 1C, 2C and 3C) in the Presence of Anodal and Cathodal tDCS in the Left Frontal Cortex. Nine groups of animals were divided into 3 subgroups. The animals received saline (1 mL/kg) or STZ (30 or 60 mg/mL/kg), 14 days before sham-tDCS (control groups, 3 groups), anodal (3 groups) or cathodal (3 groups) tDCS. Values are expressed as mean ± SD. (n = 7 in each group). $^{**}P<0.01$ and $^{***}P<0.001$ compared to the control group in panel 1. $^{+++}P<0.001$ compared to STZ at dose of 30 mg/mL/kg in panel 1. $^{¥¥}P<0.01$ and $^{¥¥¥}P<0.001$ compared to STZ at dose of 60 mg/ml/kg in panel 1.

30 mg/kg and 129.7 (95% CIs 62.3, 197.1) for STZ 60 mg/kg; Figure 5, panel 2A] or sulpiride [STZ effect: R^2 = 0.35, F(2, 36) = 9.705, $P<0.001$, mean differences 54.4 (95% CIs 7.2, 101.6) for STZ 30 mg/kg and 102.5 (95% CIs 55.3, 149.7) for STZ 60 mg/kg; sulpiride effect: R^2 = 0.2, F(1, 36) = 7.5, $P<0.01$, mean differences 52.2 (95% CIs 13.6, 90.7); STZ and sulpiride interaction effect: R^2 = 0.46, F(2, 36) = 15.3, $P<0.001$; mean differences 54.4 (95% CIs -2.5, 111.3) for STZ 30 mg/kg and 102.5 (95% CIs 45.6, 159.4) for STZ 60 mg/kg; Figure 5, panel 3A] blocked the restoration effect of left frontal anodal tDCS on STZ -induced amnesia(at the dose of 60 but not the dose of 30 mg/mL/kg).

Furthermore, similar analysis revealed that SCH23390 [STZ effect: R^2 = 0.1, F(2, 36) = 0.1, $P>0.05$, mean differences 7.2 (95% CIs -4.2, 18.6) for STZ 30 mg/kg and 11.3 (95% CIs -0.1, 22.8) for STZ 60 mg/kg; SCH23390 effect: R^2 = 0.01, F(1, 36)=2.0, $P>0.05$, mean differences 3.1 (95% CIs -6.2, 12.5); STZ and SCH23390 interaction effect: R^2 = 0.24, F(2, 36) = 1.1, $P>0.05$; mean differences 7.2 (95% CIs -6.6, 21.0) for STZ 30 mg/kg and 11.3 (95% CIs -2.4, 25.1) for STZ

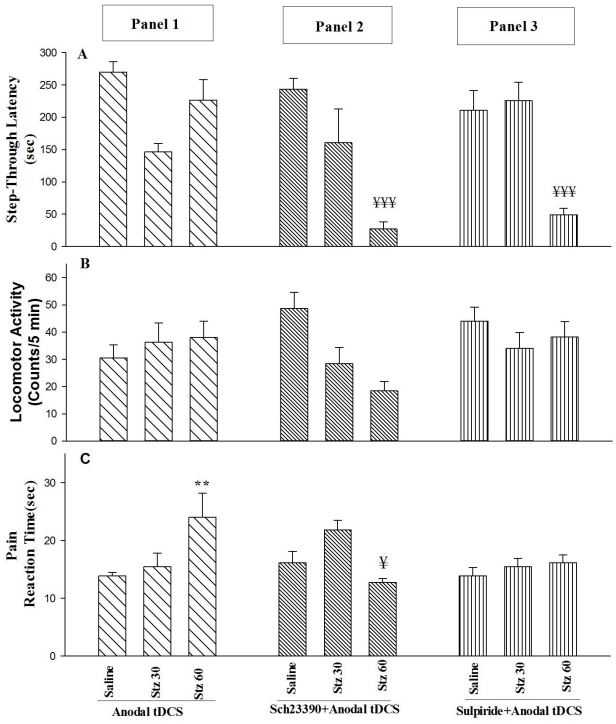

Figure 5. The Effect SCH23390 or Sulpiride in Restoration Effect of Left Frontal Anodal tDCS on STZ-Induced Amnesia. Six groups of rats were used. 14 days after injection of saline (1 mL/kg) or STZ (30 or 60 mg/mL/kg), the animals received saline (1 mL/kg) or SCH23390 (0.001 mg/mL/kg) 15 minutes before left frontal anodal tDCS, while vehicle of sulpiride (1 mL/kg) or sulpiride (0.1 mg/mL/kg) was given 30 minutes before that. Values are expressed as aean ± SD. (n = 7 in each group). **<0.01 compared to control group in panel 1. ¥<0.05, ¥¥<0.01 and ¥¥¥<0.001 compared to STZ at the dose of 60 mg/ml/kg in panel 1.

60 mg/kg, Figure 5, 2B] and sulpiride [STZ effect: R^2 = 0.008, F(2, 36) = 0.1, P > 0.05, mean differences 2.1 (95% CIs -9.5, 13.8) for STZ 30 mg/kg and -0.7 (95% CIs -12.4, 10.8) for STZ 60 mg/kg; sulpiride effect: R^2 = 0.02, F(1, 36) = 0.6, P > 0.05, mean differences -3.7 (95% CIs -13.3, 5.7); STZ and sulpiride interaction effect: R^2 = 0.06, F(2, 36) = 1.0, P > 0.05, mean differences 2.1 (95% CIs -11.9, 16.2) for STZ 30 mg/kg and -0.7 (95% CIs -14.8, 13.2) for STZ 60 mg/kg, Figure 5, panel 3B] did not alter responses induced by left frontal anodal tDCS on STZ for locomotor activity.

Also, similar analysis revealed that SCH23390 decreased the responses induced by left frontal anodal tDCS on STZ for pain threshold [STZ effect: R^2 = 0.08, F(2, 36) = 1.6, P > 0.05, mean differences -3.6 (95% CIs -8.2, 0.9) for STZ 30 mg/kg and -3.3 (95% CIs -7.9, 1.2) for STZ 60 mg/kg ; SCH23390 effect: R^2 = 0.006, F(1, 36) = 0.2, P > 0.05, mean differences 0.8 (95% CIs -2.9, 4.6); STZ and SCH23390 interaction effect: R^2 = 0.3, F(2, 36) = 8.4, P < 0.001; mean differences -3.6 (95% CIs -9.1, 1.9) for STZ 30 mg/kg and -3.3 (95% CIs -8.9, 2.9) for STZ 60 mg/kg, Figure 5, 2C] and sulpiride [STZ effect: R^2 = 0.19, F(2, 36) = 4.2, P < 0.05, mean differences -1.6 (95% CIs -6.1, 2.9) for STZ 30 mg/kg and -6.2 (95% CIs -10.7, -1.7) for STZ 60 mg/kg; sulpiride effect: R^2 = 0.05, F(1, 36) = 2.1, P > 0.05, mean differences -2.6 (95% CIs -1.1, 6.3); STZ and sulpiride interaction effect: R^2 = 0.1, F(2, 36) = 2.1, P > 0.05; mean differences -1.6 (95% CIs -6.9, 3.8) for STZ 30 mg/kg and -6.2 (95% CIs -11.6, -0.7) for STZ 60 mg/kg; Figure 5, panel 3C] did not alter responses induced by left frontal anodal tDCS on STZ for pain threshold.

The Effect of SCH23390 or Sulpiride in Restoration Effect of Left Frontal Cathodal tDCS on STZ-Induced Amnesia

The 2-way ANOVA and post hoc Tukey test showed that the subthreshold dose of SCH23390 [STZ effect: R^2 = 0.06, F(2, 36) = 1.2, P > 0.05, mean differences 41.2 (95% CIs -29.9, 112.3) for STZ 30 mg/kg and 51.0 (95% CIs -20.1, 122.1) for STZ 60 mg/kg; SCH23390 effect: R^2 = 0.04, F(1, 36) = 1.6, P > 0.05, mean differences -33.3 (95% CIs -91.4, 24.7); STZ and SCH23390 interaction effect: R^2 = 0.07, F(2, 36) = 1.4, P > 0.05; mean differences 41.2 (95% CIs -44.5, 126.9) for STZ 30 mg/kg and 51.0 (95% CIs -34.7, 136.7) for STZ 60 mg/kg; Figure 6, panel 2A] or sulpiride [STZ effect: R^2 = 0.03, F(2, 36) = 1.2, P > 0.05; mean differences 34.7 (95% CIs -29.1, 98.6) for STZ 30 mg/kg and 46.3 (95% CIs -17.6, 110.2) for STZ 60 mg/kg; sulpiride effect: R^2 = 0.1, F(1, 36) = 1.3, P > 0.05, mean differences -29.2 (95% CIs -81.4, 22.9); STZ and sulpiride interaction effect: R^2 = 0.1, F(2, 36) = 2.1, P > 0.05; mean differences 34.7 (95% CIs -42.3, 111.7) for STZ 30 mg/kg and 46.3 (95% CIs -30.7, 123.3) for STZ 60 mg/kg; Figure 6, panels 3A] did not block the restoration effect of left frontal cathodal tDCS on STZ-induced amnesia.

Furthermore, similar analysis revealed that SCH23390 [STZ effect: R^2 = 0.08, F(2, 36) = 1.6, P > 0.05, mean differences 6.5 (95% CIs -10.1, 23.1) for STZ 30 mg/kg and 14.4 (95% CIs -2.2, 31.1) for STZ 60 mg/kg; SCH23390 effect: R^2 = 0.05, F(1, 36) = 1.8, P > 0.05, mean differences -8.9 (95% CIs -22.5, 4.6); STZ and SCH23390 interaction effect: R^2 = 0.03, F(2, 36) = 0.6, P > 0.05; mean differences 6.5 (95% CIs -13.5, 26.55) for STZ 30 mg/kg and 14.4 (95% CIs -5.6, 34.5) for STZ 60 mg/kg; Figure 6, panel 3B] and sulpiride [STZ effect: R^2 = 0.06, F(2, 36) = 1.1, P > 0.05, mean differences 7.0 (95% CIs -5.0, 19.0) for STZ 30 mg/kg and 8.0 (95% CIs -3.9, 20.1) for STZ 60 mg/kg; Sulpiride effect: R^2 = 0.05, F(1, 36) = 2.0, P > 0.05, mean differences -6.8 (95% CIs -16.7, 2.9); STZ and Sulpiride interaction effect: R^2 = 0.001, F(2, 36) = 0.1, P > 0.05; mean differences 7.0 (95% CIs -7.5, 21.5) for STZ 30 mg/kg and 8.0 (95% CIs -6.4, 22.5) for STZ 60 mg/kg; Figure 6, panel 3B] did not alter responses induced by left frontal cathodal tDCS on STZ for locomotor activity.

Furthermore, similar analysis revealed that SCH23390 [STZ effect: R^2 = 0.002, F(2, 36) = 3.4, P < 0.05; mean differences 4.4 (95% CIs -0.5, 9.4) for STZ 30 mg/kg and

-1.8 (95% CIs -6.7, 3.2) for STZ 60 mg/kg; SCH23390 effect: R^2 = 0.2, F(1, 36) = 0.1, P> 0.05, mean differences 0.6 (95% CIs -3.5, 4.6); STZ and SCH23390 interaction effect: R^2 = 0.04, F(2, 36) = 0.8, P> 0.05; mean differences 4.4 (95% CIs -1.5, 10.4) for STZ 30 mg/kg and -1.8 (95% CIs -1.7, 2.4) for STZ 60 mg/kg; Figure 6, panel 2C] and sulpiride [STZ effect: R^2 = 0.04, F(2, 36) = 0.7, P> 0.05, mean differences 1.3 (95% CIs -3.7, 6.3) for STZ 30 mg/kg and -1.7 (95% CIs -6.7, 3.3) for STZ 60 mg/kg; Sulpiride effect: R^2 = 0.001, F(1, 36) = 0.1, P> 0.05, mean differences -0.3 (95% CIs -4.4, 3.7); STZ and Sulpiride interaction effect: R^2 = 0.08, F(2, 36) = 1.5, P> 0.05, mean differences 1.3 (95% CIs -4.7, 7.3) for STZ 30 mg/kg and -1.7 (95% CIs -7.7, 4.3) for STZ 60 mg/kg; Figure 6, panel 3C] did not alter responses induced by left frontal cathodal tDCS on STZ for pain threshold.

Discussion

Our study showed that STZ has induced impaired memory 14 days after the drug injection and not after 7 days. However, STZ, at a dose of 60 mg/kg, reduced locomotor activity 7 days after drug injection and increased the pain threshold 14 days after the injection. Seventy-two hours after the injection, the animals that received STZ at a dose of 60 mg/kg, were diabetized and showed symptoms like hyperglycemia, bulimia, polydipsia and polyuria. Meanwhile, the animals receiving STZ at a dose of 30 mg/kg showed no symptoms of diabetes.

The results of the present study are consistent with those of many studies which showed that STZ has significantly decreased memory. Diabetes and STZ cause memory corruption and cognitive disorders in different ways. Studies have shown that diabetes caused by STZ, possibly through increased oxidative stress and production of reactive oxygen species, may induce apoptosis, disorder in neurogenesis and consequently decreased neuronal proliferation and dendritic spine in the frontal cortex and hippocampus.[17-20]

STZ, as a diabetes inducer and insulin receptor antagonist, causes impaired glucose metabolism which is the most important fuel for the neurons.[49] On the other hand, STZ by reducing insulin decreases the amount of neurotransmitters such as dopamine and acetylcholine which are related to learning and memory,[21-23] while, by changing calcium influx and causing defects in the expression of N-methyl-D-aspartate (NMDA) receptors, it induces a defect in the induction of LTP which has an important role in the creation and establishment of learning and memory.[14-16] In addition, STZ by inducing metabolic disorders and acute and chronic cardiovascular complications, it causes decreased blood flow to the brain.[13]

Several reports indicated that STZ-induced diabetic disorder increased pain threshold level in rats[50] or mice[51] using hot plate or tail-flick apparatus, respectively.

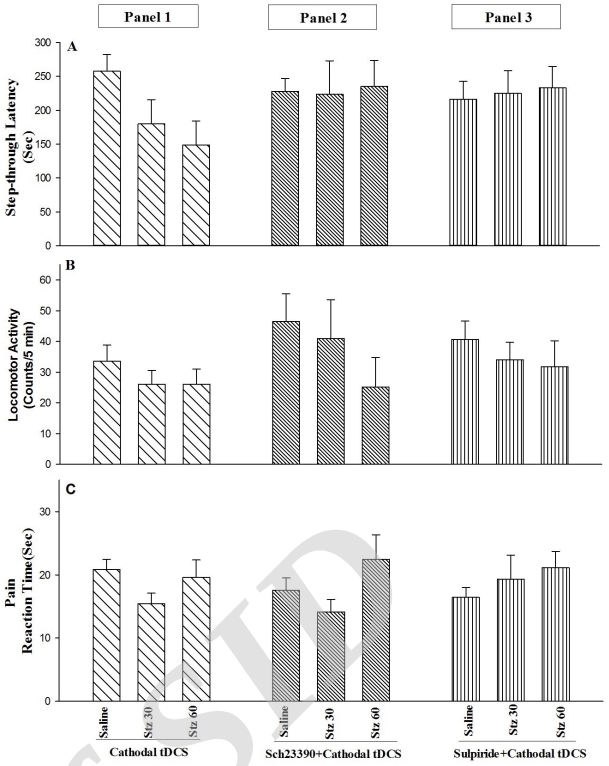

Figure 6. The Effect of Cathodal tDCS in the Left Frontal Cortex on the Memory Corruption Induced by STZ in the Presence of Sulpiride and SCH23390. Six groups of rats were used. 14 days after injection of saline (1 mL/kg) or STZ (30 or 60 mg/mL/kg), the animals received saline (1 mL/kg) or SCH23390 (0.001 mg/ml/kg) 15 minutes before left frontal cathodal tDCS, while vehicle of sulpiride (1 mL/kg) or sulpiride (0.1 mg/mL/kg) was given 30 minutes before it. Values are expressed as mean ± SD (n = 7 in each group).

In contrast, some studies showed that experimental diabetes mellitus decreased the morphine-induced antinociceptive effect in rats and mice.[52-54] It seems that the increased glucose levels in the blood contributed to the decrease of pain thresholds[55] as well as the analgesic tolerance to morphine[56,57] and the resistance to morphine dependence.[58] Thus, it is possible that the diabetic animals would be expected to be tolerant to the analgesic effects of exogenous opiates.

It was shown that left frontal cathodal and anodal tDCS in the left frontal cortex with the intensity of 0.2 milliamps each day for 20 minutes in 2 consecutive days did not alter memory formation by itself, while it could restore memory impairment induced by STZ. Several studies have shown that tDCS by changing membrane potential causes changes in neuronal activity and thereby affecting memory and learning.[59,60] tDCS induces LTP that is involved in learning and memory establishment.[60,61] LTP needs to activate NMDA receptors and brain-derived neurotrophic factor (BDNF). tDCS in vivo increases BDNF receptor phosphorylation and increases its synthesis[62] which can help to form dendritic and neuronal sprouts.[29] The tDCS also activates NMDA receptors whose effect is dependent on intracellular calcium, and tDCS with an increased level of intracellular calcium enhances the effects of these

receptors.[60,63,64] The study showed that dextromethorphan as an NMDA receptor antagonist prevented the effects of both cathodal and anodal tDCS showing the involvement of NMDA receptor in neuroplasticity induction.[61] STZ changes the calcium influx and NMDA expression and induces apoptosis which accordingly can be considered as a possible explanation of the way it affects memory.

There are studies showing that both anodal and cathodal tDCS lead to increased cerebral blood flow (CBF) during the stimulation phase.[65,66] Binkofski and colleagues showed that the short-term stimulation of neuronal activity increased glucose uptake in the brain, which was probably in response to the increased energy of the stimulation.[67] So, given that STZ and diabetes reduce blood flow and brain glucose,[13] tDCS with increased CBF and increased glucose uptake facilitates the metabolic activity of neurons and reduces their apoptosis.[66] Although some studies have suggested that cathode has inhibitory effects on locomotor function and learning by inhibiting stimulation and decreasing neuronal activity in the cortex,[68,69] some studies have shown that cathodal stimulation facilitates synaptic plasticity, working memory and learning skill and the reduction of neuronal damage in the hippocampus, possibly via some metabolic changes including an increase in BDNF which specifically induces long-term changes in cortical plasticity.[62,70,71] The contradictory results in the studies done on tDCS is probably due to the different methods of stimulation, intensity, duration, location and size of the electrodes which are all important variables in deciding the effects of tDCS[71] in such a way that in the rat stroke model the repetition of the stimulation, instead of a single stimulation, has improved motor function and the extraction of inflammatory and regenerative processes.[33] The effect of tDCS on brain may expand to other regions and the stimulation of brain regions may lead to massive changes in the brain in such a way that the cortex and subcortical regions near the stimulated region may be also affected by tDCS.[36,72]

Some studies have reported the analgesic effects of tDCS,[73] however, in our study, tDCS stimulation had no significant effect on the pain threshold induced by STZ. Our study shows that the deactivation of D1 and D2 dopamine receptor by SCH23390 and sulpiride can respectively alter the restoration effect of left frontal anodal but not cathodal tDCS on STZ-induced amnesia. Also, other studies have shown that tDCS functions through neurotransmitters and in human and animal studies tDCS improved Parkinson's symptoms.[34,74,75] On the other hand, different areas of the cerebral cortex, including sensory, motor, and the associated areas send descending routes to subcortical regions such as the basal ganglia.[76,77] These descending routes facilitate the release of dopamine in the subcortical regions. Given the fact that the stimulation is performed in the cortex and dopamine has a role in facilitating movement and cognition as well as in learning by inducing neuroplasticity, it is accepted that tDCS, especially anodal tDCS, directly or indirectly, increases extracellular levels of dopamine in the cortex and subcortex in particular by facilitating the neural stimulation in the cortex.[29,78]

Authors' Contribution

AR contributed to the acquisition of animal data. MN and MRZ were responsible for the study concept, design, assisted with data analysis and interpretation of findings. MN and AR contributed to manuscript drafting and provided critical revision of the manuscript for important intellectual content. All authors critically reviewed the content and approved the final version for publication.

Conflict of Interest Disclosures

The authors have no conflicts of interest.

Ethical Statement

This study was approved by ethics committee of Tehran Medical Sciences, Islamic Azad University, Tehran, Iran.

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