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Transcranial Direct Current Stimulation in Epilepsy

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ABSTRACT

Background: Transcranial direct current stimulation (tDCS) is an emerging non-invasive neuromodulation therapy in epilepsy with conflicting results in terms of efficacy and safety.
Objective: Review the literature about the efficacy and safety of tDCS in epilepsy in humans and animals.
Methods: We searched studies in PubMed, MedLine, Scopus, Web of Science and Google Scholar (January 1969 to October 2013) using the keywords 'transcranial direct current stimulation' or 'tDCS' or 'brain polarization' or 'galvanic stimulation' and 'epilepsy' in animals and humans. Original articles that reported tDCS safety and efficacy in epileptic animals or humans were included. Four review authors independently selected the studies, extracted data and assessed the methodological quality of the studies using the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions, PRISMA guidelines and Jadad Scale. A meta-analysis was not possible due to methodological, clinical and statistical heterogeneity of included studies.
Results: We analyzed 9 articles with different methodologies (3 animals/6 humans) with a total of 174 stimulated individuals; 109 animals and 65 humans. *In vivo* and *in vitro* animal studies showed that direct current stimulation can successfully induce suppression of epileptiform activity without neurological injury and 4/6 (67%) clinical studies showed an effective decrease in epileptic seizures and 5/6 (83%) reduction of inter-ictal epileptiform activity. All patients tolerated tDCS well.
Conclusions: tDCS trials have demonstrated preliminary safety and efficacy in animals and patients with epilepsy. Further larger studies are needed to define the best stimulation protocols and long-term follow-up.

Introduction

Transcranial direct current stimulation (tDCS), a non-invasive method that modulates cortical excitability, has reemerged as a technique of active investigation. Systematic research on tDCS dates back to the 1960s, but despite some reports the technique has not gained general clinical acceptance [1]. Initial therapeutic applications of tDCS focused on neuro-behavioral disorders. Many of these studies have been merely exploratory and the positive results have yet to be reproduced. Pathologies on which studies have been conducted include; Parkinson's disease [2], cerebrovascular events [3], central pain [4,5], fibromyalgia [6], major depression [7], Alzheimer's Disease [8] and, most recently, epilepsy [9–13].

Epilepsy treatment options based on neurostimulation such as chronic intermittent vagal nerve stimulation (VNS), cortical brain stimulation, deep brain stimulation and transcranial magnetic stimulation (TMS) have gained international attention in recent years [14–17]. The underlying principle of these techniques relies on the idea that extrinsic stimulation can reduce hyperexcitability or interfere with the discharges of epileptogenic networks [15]. VNS alone or in combination with antiepileptic drugs (AEDs) offers the possibility of improving quality of life by controlling seizures, minimizing the systemic load of AEDs and improving mood [18]. Despite the hopes and expectations that were raised by VNS, its efficacy has been limited and comparable to the introduction of a new AED [15,16]. VNS is also not exempt from complications and

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adverse cardiovascular, phonatory, respiratory and, gastrointestinal reactions during its implantation and subsequent use [14,17]. Deep brain and cortical stimulation techniques have gained some acceptance, including US FDA approval for two devices (Responsive Neurostimulation System (RNS), Neuropace, Mountain View CA and Deep Brain Stimulation (DBS), Medtronic, CA). However, optimal stimulation parameters as well as selection of best possible targets are not yet clearly defined. Furthermore, these devices require surgical implantation [19,20].

tDCS is applied through two electrodes (anode and cathode) over the skull to induce widespread changes of cortical excitability through a weak constant electric current. Cortical excitability may increase following anodal stimulation, while it generally decreases after cathodal stimulation [1,21]. Based on this principle, hyperpolarization using cathodal tDCS has been proposed as therapy to suppress epileptiform discharges and clinical seizures in basic and clinical studies.

Compared to VNS, DBS and RNS; tDCS and repetitive transcranial magnetic stimulation (rTMS) are non-invasive techniques [15,22]. However, tDCS has several advantages over rTMS in that it is more economical and it can be safely used with compact equipment [7]. The present review focuses on analyzing the information on the efficacy and safety of tDCS in epilepsy in humans and animals.

Material and methods

Our systematic review was conducted according to the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions [23], and the present report follows PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [24].

Literature search

We searched for articles in PubMed, MedLine, Scopus, Web of Science and Google Scholar from January 1969 to October 2013 using the keywords 'transcranial direct current stimulation' or 'tDCS' or 'brain polarization' or 'galvanic stimulation' and 'epilepsy' in animals and humans. We also looked for articles in the reference lists of retrieved articles and tDCS review articles and contacted experts in the field.

Selection criteria

The following criteria were adopted: (1) articles written in English (although there were no manuscripts in other languages), (2) original articles and (3) case reports. We therefore excluded the following articles: (1) review articles; (2) articles reporting duplicate data or data extracted from original articles; (3) articles addressing only the effects of other brain stimulation techniques such as alternating electrical current stimulation or rTMS.

Data extraction

For each study, two authors extracted data independently (D.S and A.O.G.) and two other authors (L.M.Q. and F.F.) checked data extraction. Any discrepancies were resolved by consensus with the corresponding author (D.S.) consulted if necessary. We elaborated a structured checklist in order to extract the following variables: (1) Demographic and clinical characteristics, such as total sample, animals or humans, sex (male/female), type of epilepsy, model of epilepsy, and age (years). (2) Study design characteristics, such as frequency of stimulation sessions and control group. (3) Treatment characteristics, which included anode and cathode positioning, dose of electric current (mA), size of electrodes (cm^2), type of electrodes, duration of session (min), current density (A/cm^2), which was calculated using the formula:

$$J = I/a$$

where J = current density (A/m^2), a = contact surface area (m^2) and I = electric current (A), and electric charge (C) (calculated using the formula described in Brunoni AR et al., 2011 [25]):

$$Q = I/t$$

where Q = electric charge, I = electric current, and t = time (s).

(4) Adverse effects (AEs), in which we considered either an 'all-or-none' reporting (e.g. 'all patients tolerated treatment well'; 'all subjects reported a tingling sensation'; 'no side-effects were reported', etc.) or a detailed description of adverse events – in such cases, we collected data on reporting of itching, burning, tingling, discomfort, and headache. These adverse events were chosen because comprehensive reviews and a consensus article regarded them as common events related to the stimulation [26,27]. (5) In order to better understand we defined efficacy as the reduction of inter-ictal epileptiform activity or percentage reduction of clinical seizures.

Quality assessment

According to the methodology of Jadad [28] we addressed the following issues that influence data quality: (1) selective outcome reporting [29] – we identified whether and to what extent AEs and outcomes were reported; which method (passive monitoring vs. active surveillance) was used for assessing AEs or efficacy; and whether studies reporting AEs and efficacy discussed them or not; (2) year of publication [23] and (3) presence of control group.

Since our aim is to identify safety and efficacy related to tDCS, we took a broad approach and did not discard studies based on risk bias; instead, we undertook separate analyses according to study quality.

Quantitative analysis

All analyses were performed using Excel and due to the small number of studies, we showed the results using descriptive statistics. A meta-analysis was not possible due to methodological, clinical, and statistical heterogeneity of included studies.

Results

We retrieved 166 articles. However, after excluding studies according to our selection criteria, 9 articles with different type of design (3 animals/6 humans) were selected with 109 animals and 65 humans with epilepsy; 8 articles presented more than one experiment and no articles presented duplicated studies (Fig. 1). In total 5/65 (8%) epileptic patients – 4 tDCS and 1 sham group – reported mild AEs. All clinical studies presented a high risk of bias.

Basic research on tDCS in epilepsy

Table 1 summarizes the results of animal studies using tDCS. *In vivo* studies showed favorable results applying tDCS to treat induced epileptic seizures in rats. The first study, by Liebetanz et al. (2006), evaluated the antiepileptic potential of tDCS in a modified cortical ramp-stimulation seizure model in rats. To determine the threshold for localized seizure activity (TLS) in this model, a single train (50 Hz; 2 ms; 2 μA) of bipolar rectangular pulses with steadily increasing current intensity was applied through a unilateral epicranial electrode to the cortex. When the first signs of convulsive behavior were registered, stimulation was interrupted and the point defined as the TLS. In four sessions, one group ($n = 7$) received tDCS

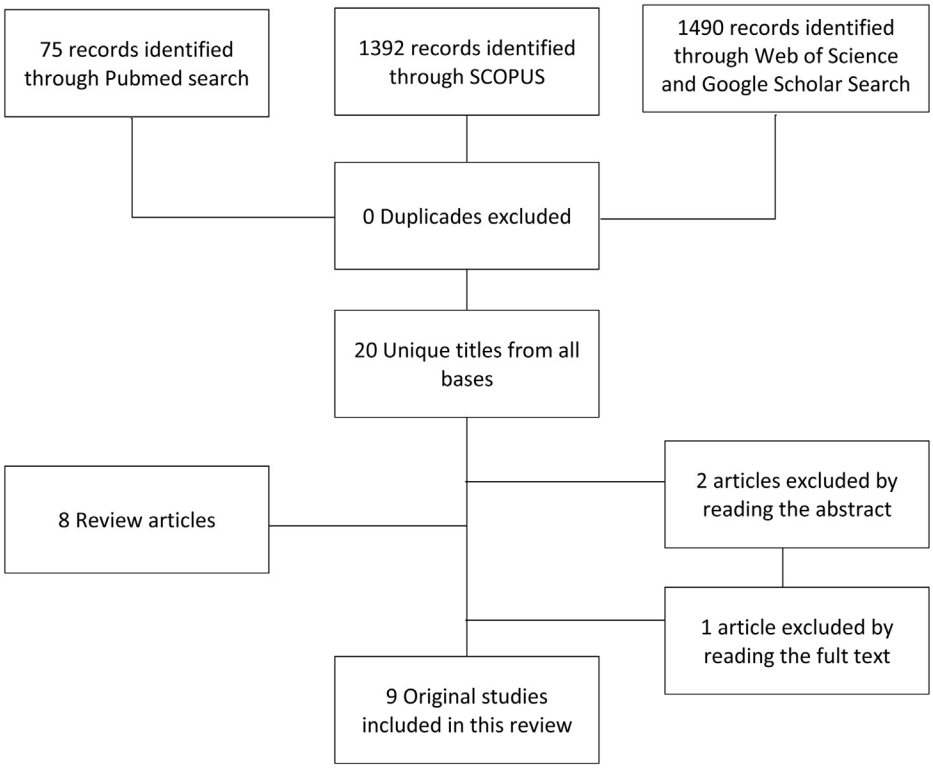

Figure 1. Flowchart of the selection of the studies for this review.

at a current intensity of 100 μA, in the sequence: cathodal tDCS for 30 and 60 min, anodal tDCS for 60 min, and again 60 min of cathodal tDCS. In a further group ($n = 8$), the current intensity was increased to 200 μA. In the four sessions, these animals received cathodal tDCS for 15 and for 30 min, anodal tDCS for 30 min, and again cathodal tDCS for 30 min. The main finding of this study was that cathodal stimulation could increase the threshold of focalized convulsive activity lasting for $\leq$2 h. It also showed that the anticonvulsive effect is polarity specific since anodal stimulation had no effect on the threshold. It also showed that the effects of tDCS on TLS were related to current intensity and stimulation duration. In addition, this study conducted a morphological and immunohistochemical analysis studying the expression of the microglial ED1 marker in four rat brains that received 30 min of anodal and cathodal tDCS at 200 μA. No deleterious effects were reported which suggests that this procedure did not cause any tissue damage [30].

Another study investigated the effects of tDCS on seizures and spatial memory as well as neuroprotective effects after status epilepticus (SE) induced by pilocarpine in rats. Cathodal tDCS was applied at 200 μA during 30 min for 2 weeks. Results showed 21% seizure reduction, rescue of cognitive impairment and slightly reduced hippocampal cell loss and sprouting. These results suggest that tDCS has a possible neuroprotective and antiepileptic effect after pilocarpine induced SE, and is associated with improvement in cognitive performance [31].

Zobeiri et al. (2013) used an *in vivo* genetic model of absence epilepsy to show that bilateral cathodal tDCS, has short lasting antiepileptic effects on the number of spike and slow-waves discharges proportional to the intensity of the stimulus [32].

Clinical research on tDCS in epilepsy

Currently, tDCS has been applied in 65 patients with the main objective of diminishing seizures and/or electroencephalographic epileptiform activity and evaluate the safety of the procedure [9–13]. Table 2 summarizes the human studies of the safety and efficacy of tDCS.

Fregni et al. (2006) conducted the first exploratory randomized sham controlled study of the effects of tDCS in 19 patients with refractory epilepsy and malformations of cortical development (MCD) randomly assigned to either active or sham treatment groups. The patients under active treatment ($n = 10$; 1 session; 1 mA, 20 min) placing the cathode over the epileptogenic zone (as identified by baseline EEG) and the anode over an area without epileptiform activity. In patients receiving sham treatment ($n = 9$), the electrodes were placed in the same position; however, the stimulator was turned off after 5s to generate only the itching sensation produced by tDCS. The number of EEG epileptiform discharges and number of seizures were recorded at baseline, immediately after and 15 and 30 days. Results showed a significant reduction of epileptiform discharges (64.3%) in the active treatment group as well as a trend towards seizure reduction. The most important finding of this study was that cathodal tDCS does not induce or increase seizures and that it is well tolerated by patients with refractory epilepsy [9].

In another double blinded sham-controlled crossover study that included 5 pediatric (6–11 year old) patients with continuous spikes and waves syndrome during slow sleep (CSWS), tDCS was used to diminish epileptiform activity. Electroencephalographic monitoring was continued for two days and cathodal tDCS applied as sham treatment on the first day and active treatment on the second day. Cathodal tDCS was applied over the epileptogenic focus during 20 min at 2 mA; while sham treatment followed the same protocol except the stimulator was shut off after 5 s. In this study, stimulation was oriented in the same direction as the epileptiform discharge as determined by a 3D voltage map of the focal epileptiform discharge. Use of a cathodal electrode (25 cm^2) smaller than the reference electrode (100 cm^2) increased focality of treatment.

Table 1
Summary the safety and efficacy of animals studies using tDCs in epilepsy models.

Author (year)	Type and design of article	Animal	No. of total sample	Age (months)	Sex (% males)	I = current; dosage (A)/ J = current density (A/m^2) Q = electrical charge (C)	Montage	Model of epilepsy/ type of epilepsy	Type and size of electrodes	Frequency and duration of session	Adverse effects	Outcome
Liebetanz et al. (2006) [29]	Original Experimental	Rats	65	2	100	$I_{max} = 100$ μA $I_{min} = 200$ μA $J_{max} = 57.142$ A/m^2 $J_{min} = 28.571$ A/m^2 $Q_{max,\ 15\ min} = 222$ nC $Q_{max,\ 30\ min} = 111$ nC $Q_{max,\ 60\ min} = 56$ nC $Q_{min,\ 15\ min} = 111$ nC $Q_{min,\ 30\ min} = 56$ nC $Q_{min,\ 60\ min} = 28$ nC	2 mm left and 2 mm anterior to the bregma	*In vivo* ramp model	3.5 mm^2 ($a = 3.5 \times 10^{-6}$ m^2)	4 sessions (50 Hz, 2 ms pulse train) separated by one week 1. Cathodal tDCS for 30 and for 60 min, anodal tDCS for 60 min, and again 60 min of cathodal tDCS. 2. Cathodal tDCS for 15 and for 30 min, anodal tDCS for 30 min, and again cathodal tDCS for 30 min.	None	After tDCS, the threshold for localized seizure activity was determined repeatedly for 120 min at intervals of 15 min. The anticonvulsive effect induced by cathodal tDCS depends on stimulation duration and current strength and may be associated with the induction of alterations of cortical excitability that outlast the actual stimulation.
Kamida et al. (2011) [31]	Original Experimental	Rats	18	0.7	100	$I = 200$ μA $J = 57.142$ A/m^2 $Q = 111$ nC	1.5 mm to the right and 2 mm anterior to the bregma	*In vivo* pilocarpine-induced status epilepticus	2.1-mm inner diameter and 3.5 mm^3 ($a = 3.5 \times 10^{-6}$ m^2)	2 weeks; 30 min	?	Neuroprotective effects on the immature rat hippocampus, including reduced sprouting and subsequent improvements in cognitive performance. The convulsions were reduced 21% in the postnatal day 55.

Zobeiri et al. (2013) [32]	Original Experimental	Rats	26	6	100	$I_{I,II} = 100$ μA $I_{III} = 150$ μA $J_{I,II} = 28.571$ A/m^2 $J_{III} = 42.857$ A/m^2 $Q_{I,II} = 28$ nC $Q_{III} = 42$ nC	The active EEG electrode was placed on the motor cortex of the right hemisphere with two wires as ground and reference on top of the cerebellum	*In vivo* genetic model of absence epilepsy	Tripolar EEG recording electrode and inner diameter of 2.1 mm and a contact area of 3.5 mm^2 ($a = 3.5 \times 10^{-6}$ m^2)	I. 10 rats received 4 series of 15 min cathodal and anodal stimulation of 100 μA with an interval of 1 h and 45 min in counter balanced order. II. 8 rats received 4 sessions of 15 min of cathodal stimulation of 100 μA III. 8 rats, similar protocol to II, except 150 μA	None	I. Neither anodal nor cathodal stimulation had significant long-lasting aftereffects on the number or on the mean duration of SWDs in the 1-h 45-min post-stimulation intervals. II and III. The number of SWDs was reduced on the stimulation day compared to baseline and increase (II) or decrease (III) in the mean duration of SWDs from baseline in 1-h 45 min post-stimulation. There were no significant differences for the number and mean duration of SWDs between the baseline day and post-stimulation day Bilateral cathodal tDCS, has short lasting antiepileptic effects on the numbers of SWDs and longer lasting (1-h 45-min) intensity-dependent effects on the mean duration of the spike and slow-waves discharges.

SWDs: spike and slow-wave discharges.

Table 2
Summary the human studies of the safety and efficacy using tDCS in epileptic patients.

Author (year)	Type and design of article	No. of total sample	Age (year [mean ± SD or range])	Sex (% females)	I = current; dosage (A)/J = current density (A/m^2)/ Q = electrical charge (C)	Montage	Model of epilepsy/type of epilepsy	Type and size of electrodes	Frequency and duration of session	Adverse effects	JADDAD	Outcome
Fregni et al. (2006) [9]	Experimental randomized sham controlled non blinded	19	24.16 ± 7.9	42	I = 1 mA J = 0.285 A/m^2 Q = 833 nC	Cathodal stimulation over the epileptogenic focus according to EEG baseline	Focal refractory epilepsy due to cortical dysplasia	Sponge electrode 35 cm^2 ($a = 3.5 \times 10^{-3}$ m^2)	Single session; 20 min	Itching (3 active and 1 sham groups)	3	A significant reduction in the number of epileptiform discharges was found (mean 64.3%), however, not clinical reduction of seizure was seen in 30 days of follow-up.
San Juan et al. (2011) [10]	Case report, experimental non controlled neither blinded	2	23	0	I_{min} = 1 mA I_{max} = 2 mA J_{min} = 203.018 A/m^2 J_{max} = 406.091 A/m^2 Q_{min} = 69 nC Q_{max} = 139 nC	C3, F2	Rasmussen's encephalitis	Subdermal needle 12 mm in length and 0.4 mm in diameter ($a = 4.925 \times 10^{-6}$ m^2)* *calculating only surface area	60 min in four sessions (on days 0, 7, 30, and 60)	None	1	One patient was seizure free and other patient with 50% of seizure frequency reduction within 6 month of follow-up.
Varga et al. (2011) [11]	Experimental double blinded sham-controlled crossover	5	6–11 8.5 ± 2.5	40	I = 1 mA J = 0.4 A/m^2 Q = 833 nC	Determined by visualizing a 3D voltage-map of the focal epileptiform discharge	Continuous spikes and waves syndrome during slow sleep	Sponge electrode 25 cm^2 ($a = 2.5 \times 10^{-3}$ m^2)	20 min	None	2	Cathodal tDCS did not reduce the spike-index in any of the patients after 2 days of stimulation session in the evening; sham in the first night and tDCs in the second night.
Yook et al. (2011) [12]	Case report Experimental	1	11	100	I = 2 mA J = 0.8 A/m^2 $Q_{20\ min}$ = 1.667 μC $Q_{5\ days}$ = 8.333 μC $Q_{2\ weeks}$ = 16.667 μC	Midpoint between P4 and T4	Bilateral perisylvian syndrome	Sponge electrode 25 cm^2 ($a = 2.5 \times 10^{-3}$ m^2)	5 days a week, during 2 weeks. Repeating procedure after 2 months; 20 min	None	0	During the first two months after treatment; the patient had only six seizures, with an evident clinical improvement, after the second intervention the patient had just one seizure attack over two months.

Faria Paula et al. (2012) [33]	Cross-over controlled trial	2	11 and 7	0	I = 1 mA/J = 0.285 A/m^2 Q = 556 nC	Based in 10-10 International system positions in a cap (mostly C5-C6)	Drug-refractory Continuous Spike-Wave Discharges During Slow Sleep	Sponge electrode 35 cm^2 ($a = 3.5 \times 10^{-3}$ m^2)	Once weekly, to three afternoon sessions of 30 min each.	None	1	Cathodal tDCS is safe and well-tolerated in patients with refractory epilepsy. They found a large reduction in inter-ictal epileptiform EEG discharges in C5 (mean 32.1%) during and after the tDCS (10 min).
Auvichayapat et al. (2013) [13]	Experimental randomized controlled with sham unblinded	36	6–15	28	I = 1 mA J = 0.285 A/m^2 Q = 833 nC	Based in the international 10-20 EEG system (mostly C3-F3)	Focal refractory epilepsy with different etiologies	Sponge electrode 35 cm^2 ($a = 2.5 \times 10^{-3}$ m^2)	Single session; 20 min	One patient (2.7%) developed a transient (<2 h) erythematous rash with no pruritus or pain under the reference electrode	2	Cathodal tDCS can suppress epileptiform discharges in 57.6% for 48 h, but the effect of a single session on EEG abnormalities was not sustained for 4 weeks. A statistical reduction in the frequency of seizures was found (4.8%) in the post-hoc analysis.

The study failed to find decrease of epileptiform activity induced by tDCS, but it did show the safety of the procedure in this pediatric population. Furthermore, it should be noted that – after treatment- the spike pattern was detected over a more focalized area in three patients, which might suggest that the main effect of tDCS is suppressing propagation of epileptiform activity [11].

Recently, Auvichayapat et al. (2013) treated 36 children (6–15 years old) with partial epilepsy with a single session of tDCS (20 min, 1 mA) and showed that cathodal tDCS can suppress epileptiform discharges for 48 h, with a small (clinically negligible but statistically significant) decrease in seizure frequency [13]. Faria et al. (2012) applied tDCS (30 min; 1 mA) in 2 pediatric patients with drug-refractory continuous spike-wave discharges during slow sleep and found similar results in safety and reduction of the inter-ictal epileptiform EEG discharges [33].

Yook et al. (2011) published a case of successful application of two sessions of tDCS (2 mA for 20 min 5 days a week, during 2 weeks, interval 2months) in an 11-year-old female with focal cortical dysplasia and pharmacoresistant epilepsy with mean seizure frequency of 8 seizures per months. At the end of intervention the patient had just one seizure over two months. Therapy had no notable side-effects [12]. Later, San Juan et al. (2011) reported two adult patients with Rasmussen encephalitis who were successfully treated with tDCS (1–2 mA for 60 min in 4 sessions [days 0, 7, 30 and 60]) applied to the affected hemisphere. The patients did not experience any AEs, which attest to the safety of the procedure [10].

Discussion

Several *in vitro* and *in vivo* animal studies have shown that direct current (DC) and tDCS can successfully induce suppression of epileptiform activity in electroencephalographic recordings [30–32,34–36].

In 1996, Gluckman et al. used a rat model of epilepsy induced by high potassium concentration to study the effect of DC electrical fields on synchronous activity in CA1 and CA3 from transverse and longitudinal type hippocampal slices. The low voltage ($\leq$5–10 V) current suppressed epileptiform activity in 31/33 samples. In this study it was observed that suppression of epileptiform activity occurred independent of region studied and type of slice, but was highly dependent on field orientation with respect to the apical dendritic–somatic axis [35].

In vitro studies have shown that the antiepileptic effect induced by DC is mediated by hyperpolarization and orientation of the electrical field. These effects were demonstrated in a study by Ghai et al. (2000) in a low calcium epilepsy model in which epileptic activity was completely suppressed, and in a study by Lian et al. (2001) that compared the effects of DC and alternate current (AC) on epileptiform activity suppression [34,36].

Basic principles of the tDCS in epilepsy

tDCS has been proposed as an alternative safe, feasible, and low cost method to non-invasively modify cortical excitability. Its effects on cortical excitability seem to be similar to the effects induced by rTMS [37,38]. In the case of epilepsy, it has been attempted to reduce the number of seizures and epileptiform patterns by cathodal stimulation and its apparent hyperpolarization effect [9–12].

Current tDCS protocols involve placement of two scalp electrodes, one serving as an anode and the other as a cathode, and the use of DC of 1–2 mA between electrodes. Current flux from the anode to the cathode is distributed over the scalp and the cerebral cortex, resulting in an increase or decrease of neural excitability depending on the direction and intensity of the current [39]. Anodal tDCS generally has an excitatory effect on the cerebral cortex due to neuronal depolarization, while the contrary holds true under the cathode via a hyperpolarization process [14]. The effects of a single stimulation session persist for 1–48 h [13,40].

Mechanisms of action of tDCS

The complete mechanism of action of tDCS is unknown, but appears to involve a combination of hyperpolarization and depolarization of axons as well as alterations of synaptic functions. Pharmacological studies provide certain clues to the mechanism of action. Sodium and calcium channel blockers eliminate both the immediate and long-term effects of anodal stimulation, while blocking of NMDA receptors (glutamate) prevents the long-term effects of tDCS, regardless of directionality [41,42].

Effects produced by tDCS depend upon some characteristics distinctive to the induction of synaptic neuroplastic processes: the duration of the effect depends upon stimulation intensity, it is of intracortical origin and dependent on NMDA receptor activity [22]. Increasing reference electrode size and reducing stimulation electrode size increases focality of treatment [43].

Studies have explored the effects of cathodal tDCS on spontaneous neural activity and evoked motor responses of the central and peripheral nervous system and concluded that the resulting effects of tDCS involve a non-synaptic mechanism of action based on changes of neural membrane functions [44–46]. These authors suggested a number of mechanisms including localized changes in ion concentrations, alterations of transmembrane proteins, and electrolytic changes related to hydrogen induced by exposure to a constant electrical current [44–46]. During stimulation, cathodal tDCS reduces intracortical facilitation [47,48], however, the mechanism underlying cathodal tDCS-induced intracortical changes has not been fully elucidated. Some studies [30,36,41,49] suggest that DC stimulation produces postsynaptic hyperpolarization, leading to a reduction of presynaptic input and to an NMDA receptor-mediated depression of synaptic strength. Also, cathodal tDCS induces migration of transmembrane proteins and alters the local tissue acid-balance, leading to NMDA system dysfunction [44]. Long-lasting effects of tDCS are thought to reflect alterations in NMDA receptor efficacy [41,42] and could contribute to neuroprotective effects on the immature hippocampus, improvement in cognitive performance and antiepileptic effects [31].

In partial epilepsy, seizures are associated with pathologically increased excitability or synchronization as well as deficient inhibitory control within the epileptic focus [50–52]. At the cellular level, the generation of burst discharges depends on the stability of the membrane potential, which is determined by ion homeostasis. The altered homeostasis of intracellular calcium is thought to play a central role in both epileptogenesis and seizure propagation [53–56]. Cathodal tDCS induces a decrease in cortical excitability, which is thought to result from a shift of membrane potentials and a subsequent alteration of synaptic efficacy [30,41], antiepileptic effects are particularly expected from cathodal tDCS. The synaptic consolidation of these plastic changes may be mediated by decreased intracellular calcium influx [41]. Magnitude and duration of the cathodal tDCS induced after-effect threshold for localized seizure activity is related to current intensity and stimulation duration. At a current intensity of 100 μA, relevant after-effects are obtained only when tDCS is applied for 60 min. When current intensity is increased to 200 μA, similar threshold elevations are induced by stimulation duration of only 30 min. The tDCS-induced anticonvulsant effects are reversible, and the repetition of effective tDCS applications leads to a reproducible threshold increase of localized seizure activity [30].

Pharmacological studies using cathodal tDCS have shown that the excitability reduction was not affected by carbamazepine or flunarizine. Dextromethorphan induced NMDA receptor inhibition completely prevented the post-stimulation excitability enhancement and abolished the excitability diminution caused by cathodal tDCS. This finding suggests that anodal tDCS requires the depolarization of membrane potential since CBZ stabilizes the voltage dependent membrane potential [41,42]. Also, the interactions between the serotonergic system and tDCS were studied using citalopram. Citalopram enhanced and prolonged the facilitation by anodal tDCS, while the cathodal tDCS-induced inhibition was abolished and actually become facilitation. The mechanism of these effects is not well understood [1], but, even if more studies are needed, they may indicate that the effects of tDCS are blocked in patients with epilepsy or comorbid mood disorders being treated with citalopram [56].

Involvement of the GABAergic inhibitory system was also tested. The application of a $GABA_A$ agonist (lorazepam) caused no effect on cathodal TDC-elicited excitatory diminutions at the motor cortex. Lorazepam also caused an abolition of intracortical tDCS induction of neuroplastic excitability. The origin of these effects is not clear [55]. Stagg et al. (2009), used magnetic resonance spectroscopy to provide evidence that excitatory (anodal) tDCS causes locally reduced GABA, while inhibitory (cathodal) stimulation causes reduced glutamatergic neuronal activity with a highly correlated reduction in GABA [57]. These authors interpret the reduction in glutamate following cathodal stimulation as a consequence of a decreased rate of glutamate synthesis from glutamine with reduced excitatory neuronal transmission. The initially counterintuitive decrease in GABA seen after cathodal stimulation can be explained by the biochemical relations between glutamine and GABA. A correlated reduction in concentrations is consistent with functional regulation of glutamic acid decarboxylase 67 by the concentration of its substrate glutamate [57]. The lack of effect of $GABA_A$ receptor agonists on the neurophysiological changes of cathodal stimulation seen in previous studies [55] raises a theoretical concern that cathodal tDCS could reduce the antiepileptic effects of GABAergic drugs.

In summary, the complete mechanism of action of tDCS is unknown, but appears to involve a combination of hyperpolarization and depolarization of neural axons and interactions controlled by synaptic activity. Epilepsy, conceived as a "network" pathology with the intrinsic characteristic of hypersynchronous activity, represents the model for abnormal hyperexcitatory plastic changes within cortical circuitry. tDCS is a potential modulatory tool for neuroplasticity and could disrupt or promote electrochemical alterations that may have an impact in these hyperexcitable networks.

Efficacy and safety of tDCS in epilepsy animal models

Cathodal tDCS in animal models of epilepsy has shown an increase of the threshold for localized seizure activity [30] and decrease of sprouting in the immature hippocampus (31). In some experiments, the convulsions were reduced up to 21% [31] others showed a reduction of the number and decrease in the mean duration of the spike and slow-wave discharges in the 1-h 45-min post-stimulation [32]. In addition, animal studies have not shown any injury [30,31].

Efficacy and safety of tDCS in epileptic patients

tDCS clinical studies are promising with 4 out of 6 (67%) studies having shown an effective decrease in epileptic seizures and 5/6 (83%) a reduction of epileptiform activity. However, some results are not conclusive or negative for several reasons: The number of patients in each study has been relatively small and heterogenous. Furthermore, therapy has been applied with different parameters [9–13]. The main achievement so far has been the demonstration that tDCS is seemingly safe in humans (adult and pediatric patients) [9–12]. Further studies are needed to define the best stimulation protocols and understand the long-term effects of tDCS.

Use of tDCS in experimental protocols has resulted in only minor AEs, including mild headache and itching at the site of electrode placement [3,4]. tDCS does not cause heating effects under the electrodes and does not elevate levels of neuron specific enolase [30,31]. There is no evidences of induced brain edema, alterations in brain tissue or blood brain barrier (BBB) as detected by magnetic resonance imaging (MRI) [58], or late adverse cognitive effects [4].

In conclusion, tDCS is a re-emerging technique for neuromodulation of cortical activity. tDCS trials have demonstrated preliminary safety and efficacy in animals and patients with epilepsy. Further larger studies are needed to define the best stimulation protocols, the mechanism of action and long-term effects.

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