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Short Communication

Biological and Neurobiological Mechanisms of Transcranial Direct Current Stimulation

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Abstract

Objective: Changes in cortical excitability and neuroplasticity are important parts of the neuropathology and pathophysiology of many neuropsychiatric disorders. Noninvasive brain stimulation is a high-potential therapeutic approach to modify cortical activities. One of the most popular of these techniques is transcranial direct current stimulation (tDCS). However, the biological and neurobiological effects of tDCS should be better clarified to enable its optimal use in clinical and therapeutic practices. In this paper, we summarize the neurophysiological and physiological effects and mechanisms of action of tDCS.
Method: An update literature review was conducted on the biological responses of tDCS reported in human, in vitro and in vivo studies, with a focus on cellular cascades related to neuroplasticity, neuronal reorganization and inflammation caused by applied direct current electric fields.
Results: The regulatory mechanisms of tDCS on motor and cognitive functions can be described by membrane polarization and transmembrane potential with a main subsequent effect on neurotransmission systems, neuronal excitability, synaptic microenvironment and neuronal connectivity to neuronal reorganization and neurogenesis in association with synaptic plasticity as well as inflammatory processes. In general, the effects of tDCS may include acute- or after-effects and direct or indirect effects and can be examined at different levels including the neurochemical, the neuroelectrical and the brain oscillatory levels.
Conclusion: A deep understanding of the molecular and cellular responses to tDCS is very important and crucial. This therapeutic technique can be utilized in various clinical trials with a perspective of being routinely suggested and presented to patients with different pathological conditions influencing the central or peripheral nervous system.

Key words: *Neuromodulation; Neurobiology; Neuropsychiatry; Transcranial Direct Current Stimulation*

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Transcranial direct current stimulation (tDCS) is a low-current non-invasive therapeutic technique wide-used for stimulating the cortical areas of the brain by externally delivering a direct current electric field. Interesting clinical results achieved for different disorders along with this important point that tDCS is safe, inexpensive, portable, well-tolerated and easy to use have accelerated the admissibility of this technique and its applications in clinical settings (1). It has been utilized in various neuroscience researches to understand brain-behavior relationships and in numerous clinical trials for rehabilitation purposes and cognitive enhancement (2-5). Despite increasing evidence in support of the positive effects of tDCS as an alternative therapy for pathological conditions, there is no sufficient clarification regarding the mechanisms of action that control its effects. The primary effect of tDCS is to alter the polarity of the neuronal membrane, leading to a subthreshold change in membrane potentials at resting-state to hyperpolarization or depolarization according to the polarity of tDCS (i.e., the direction of current flow relative to axonal orientation) (6). In a bipolar montage, anodal tDCS is considered to have an excitatory effect on the underlying cortex, while cathodal tDCS is thought to cause opposite effects (7). According to the somatic theory proposed for this stimulation technique (8), the anode is the sink of direct current entering the brain, leading apical dendrites to hyperpolarization and then neural soma and axonal hillock to depolarization. On the other hand, the cathode is the source of direct current flowing out of the brain, leading to depolarize apical dendrites and then hyperpolarize neural soma. However, a high-definition montage (HD-tDCS) may be utilized to have either more focal direct current fields or a multifocal protocol in order to produce larger modulation effects (9).

The classical polarity-based effects of tDCS on neuronal excitability (that is, inhibitory cathodal stimulation versus excitatory anodal one) should not be accepted as a generic principle, because several conditions may turn excitatory effects into inhibitory, or vice versa. The local effects of an electric field on the neural structure is highly complicated, depending on the orientation of the axon's axis and its distance relative to an induced field (10, 11). The synaptic terminals of the axons are considered to be more susceptible to the polarization effects induced by tDCS than somas up to two or three times. However, radial current flow does not result in the similar alterations in synaptic efficacy at the level of the terminals of axon, based on the polarity of the stimulation (12). Indeed, the orientation of the axons can specify whether the electric fields are inhibitory or excitatory, while the orientation of the dendrites can influence the extent of tDCS effects, but not their directions (13). Furthermore, computational models demonstrated that anodal tDCS excites fibers that are perpendicular to the surface of the electrode, whereas a focal cathodal tDCS over a gyrus excites horizontal fibers that are parallel to the electrode surface (14). Eventually, even though an electric field causes coherent hyperpolarizing or depolarizing effects on neuron populations concerning electrode polarity and fiber orientation, the resulting physiological effects of tDCS depend on whether the stimulated network is dominantly excitatory or inhibitory (10). In addition, it should be noted that if the modulation mechanisms are dependent on the neuronal orientations in the electrical fields, it is difficult to establish the polarization of neuronal sub-compartments in complex brain structures, since the dendrites and axons forming synapses are not all directed in the same orientation (12).

Short-duration stimulations of a few seconds can lead to changes in excitability only during stimulation, whereas a long-duration stimulation in the order of several minutes leads to excitability changes that can continue for one to several hours (15, 16). As reported in a transcranial magnetic stimulation study, excitability changes in the primary motor cortex become steadily considerable after the stimulation period rather than during stimulation (17). Similar effects of tDCS were reported after the stimulation of somatosensory and visual cortices (18, 19). Therefore, tDCS mechanisms of action should not be only attributed to alterations in the transmembrane potential. Accumulating evidence demonstrated that tDCS changes the synaptic microenvironment. Calcium-specific synaptic plasticity in glutamate neurotransmission is considered to be responsible for prolonging cortical plastic effects of tDCS because blockade of N-methyl D-aspartate receptors (NMDARs) decreases tDCS effects (20). Furthermore, regardless of stimulation polarity, tDCS can locally diminish gamma-aminobutyric acid (GABA) neurotransmission and this may affect glutamate-related plasticity owing to the tight relation between GABA and glutamate neurotransmitters (21). Other neurotransmitters and factors are also involved. In many types of cells, membrane receptors like acetylcholine move and cumulate at one end of the electric field to induce a cell migration effect. In neurites, this mechanism can contribute to the after-effects of tDCS in the stimulated areas of the brain (22). Other factors are also involved in this neuromodulation mechanism, including alterations in the expression of brain-derived neurotrophic factor (BDNF) (23). Motor skill acquisition in human subjects expressing the BDNF Val66Met polymorphism is significantly lower than in normal subjects following a 5-day tDCS application (24). As shown by magnetic resonance spectroscopy, γ-aminobutyric acid levels in the primary motor cortex are further decreased in normal human adults after tDCS (25). Anodal tDCS delivered over the motor cortex results in blocking the reuptake of serotonin which induces long-term potentiation (LTP) and inverts cathodal long-term depression (LTD) effect into LTP (26), while D2 antagonists delay anodal and stop

cathodal tDCS-induced plasticity in healthy individuals (27), indicating the significance of serotonin and dopamine in the tDCS. In summary, the release of neurotrophic factors and neurotransmitters suggests a role for electric fields induced by tDCS in neuroplasticity, all of which are probably mediated by NMDARs.

Beyond local direct mechanisms of action, connectivity changes among different brain networks induced by tDCS have also been reported as indirect effects (28). Neuron populations are more affected by tDCS than individual neurons and induced electric fields may affect synchronization, brain oscillations and functional connectivity in different subcortical and cortical networks, including the motor and prefrontal cortices (29).

In addition, tDCS may induce non-synaptic effects contributing to its long-lasting after-effects, because it impacts the whole axons (30). These non-synaptic effects of electric fields may be attributed to the alterations in structure and function of molecules with axon, including axonal transport function cytoskeleton, or membrane structure while subjected to tDCS (23). Furthermore, it should be noted that nearly all cells, tissues and organs are affected by electric current and, thus, direct current stimulation may also produce important alterations in the non-neuronal brain structures, such as lymphocytes, glial endothelial cells (31). These non-neural mechanisms have not been consistently examined, but they may contribute to the tDCS effects in different rehabilitation applications. Direct current electric fields have shown substantial influences on the inflammation responses in the peripheral and/or central nervous system. In addition to neuroinflammatory disorders (e.g., acute disseminated encephalomyelitis), inflammation of the CNS has been involved in some psychiatric illnesses (e.g., neurodegeneration progression in Alzheimer's disease) (32). The conformation of pathological proteins such as beta-amyloid may be altered when subjected to a direct current field, possibly changing their susceptibility to degradation (33). Furthermore, electric fields induced by tDCS can augment neurite outgrowth and axonal regeneration, and therefore decelerate the progression of Alzheimer's. In general, in vitro and in vivo studies suggest that both pro- and anti-inflammatory mechanisms of tDCS are contingent upon the intensity and direction of applied electric fields (34).

Initial state of the recruited neuronal populations and synaptic afferent inputs has a key role in the polarity after-effects of tDCS (35). LTP, a neural mediator of memory and learning, presents both theoretical and practical tools to explain fundamental details of changes in cognitive functions; its induction (using tDCS) is affected by the previous level of synaptic activities. These activity-specific modulations caused by following induction of synaptic plasticity are known as metaplasticity or priming (36). Indeed, synaptic depression or fatigue is more possible to occur when postsynaptic activity is high, while synaptic potentiation is more likely to occur when postsynaptic activity is low (37). Several clinical observations have shown that tDCS priming could elicit metaplastic outcomes (38). Therefore, neuroplasticity induced by tDCS differs whether electric fields are delivered to a relaxed person or a person doing motor or cognitive tasks. This leads to different clinical protocols combining the tDCS technique with training/learning methods, rehabilitation strategies, or pharmacological procedures for priming the state of the brain to be more responsive to tDCS (39). Previous works have demonstrated that priming protocols can regulate and govern the functional connectivity between neuronal populations and networks, the association between synaptic inputs and the primary state of cortical excitability (40, 41). Therefore, metaplastic protocols can largely affect the subsequent effects and mechanisms induced by tDCS. Furthermore, it has been demonstrated that brain volume and thickness (i.e., brain morphometry) affect the outcomes of tDCS on different levels. For instance, tDCS has shown to produce larger effect on GABAergic neurotransmission when the right dorsolateral prefrontal cortex has a larger volume (42). Grey matter volume of the prefrontal cortex has also shown to link to tDCS antidepressant outcomes (43).

Neuronal activation using tDCS is also thought to reduce membrane resistance. This decrease in resistance leads to an increase in membrane conductance; this is probably important for the mechanisms of tDCS because direct current fields could induce greater alterations in membrane potential of resting neurons with lower conductance as compared to active neurons with higher conductance (44). Thus, tDCS effects are dependent on complex relations between the active area under stimulation, its regions of projection, the adjacent structures at resting-state, the pathological changes in neurotransmitter system, the individual genetic polymorphisms, and the medications taken by the patient (45, 46).

Finally, the main role of technical and clinical parameters including duration, intensity and session repetition scheduling should be considered, which elucidate the nonlinear relation between tDCS parameters and the produced physiological effects. For instance, extending the duration and increasing the intensity of stimulation can augment its acute and after effects in some conditions (47), but this should not be accepted as a generic principle. Indeed, raising the stimulation strength may lead to switching the direction of cortical excitability; doubling intensity (e.g., from 1 to 2 mA) could turn inhibition induced by cathodal tDCS of the primary motor cortex into excitation (48). Furthermore, increasing the stimulation strength results in deeper induced effects on the brain that may change the nature of the affected neuronal populations, leading to unwanted clinical and biological effects (49). In

addition, little changes in the size, form or location of the electrodes can significantly affect the distribution and transmission of the electric current and also the geometries of the applied electric fields into the brain (50, 51). As a result, the clinical outcomes produced by direct current stimultion may substantially alter depending on many neuroanatomical and technical factors. All these considerations can elucidate the inconsistent outcomes reported in tDCS experiments in different pathological conditions. Therefore, they should be carefully considered to design tDCS protocols and interpret the effects of stimulation when utilized for neuropsychiatric disorders (2, 3).

Conclusion

Intuitive neuromodulation effects can be achieved by tDCS, but many factors and variables should be controlled for optimizing these effects, including the intensity of stimulation, the duration and repetition timing of sessions, the montage (bipolar, focal, multifocal), or the feasibility of combined designs with various metaplastic or priming protocols. So far, strong and interesting clinical outcomes have been achieved by relatively plain procedures. However, designing more sophisticated protocols is critical from the technical and clinical viewpoint. Development of therapeutic tDCS protocols will be contingent upon the better comprehending of the underpinning physiological mechanisms of action based on the clinical indication and the procedures used. No general rule must be considered for an approach that lends itself notably well to an individualized therapy tailored to each patient.

Conflict of Interest

None.

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