Neurosci. Bull. June, 2017, 33(3):339–347
DOI 10.1007/s12264-016-0094-x

www.neurosci.cn
www.springer.com/12264

REVIEW

Potential Mechanisms Underlying the Therapeutic Effects of Electroconvulsive Therapy

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Received: 5 August 2016 / Accepted: 23 November 2016 / Published online: 28 December 2016

Abstract In spite of the extensive application of electroconvulsive therapy (ECT), how it works remains unclear. So far, researchers have made great efforts in figuring out the mechanisms underlying the effect of ECT treatment *via* determining the levels of neurotransmitters and cytokines and using genetic and epigenetic tools, as well as structural and functional neuroimaging. To help address this question and provide implications for future research, relevant clinical trials and animal experiments are reviewed.

Keywords Electroconvulsive therapy · Neurotransmitters · Neurotrophins · Inflammatory factors · Epigenetics · Neuroimaging

Introduction

Electroconvulsive therapy (ECT) was first used to treat mental disorders in 1938 as a substitute for the chemical induction of seizures [1]. It involves deliberately inducing seizures for therapeutic purposes by administering an electrical stimulus to a patient's brain *via* electrodes applied to the scalp. Although modified ECT (using anesthesia and muscle relaxants) significantly alleviates the discomfort during the procedure and prevents severe adverse side-effects such as fractures, unmodified ECT is still preferred in Asia, Africa, and Latin America [1]. Today, brief-pulse wave ECT rather than sine-wave ECT with a constant voltage and energy is recommended [2]. Bilateral placement is the most common electrode placement [1]. Almost 80 years have passed since its first use, and ECT is still widely administered worldwide [1]. It is largely considered to be a treatment for affective disorders in most western countries, while in many eastern countries such as India, Thailand, and Japan, as well as in parts of Africa, ECT is mainly applied as a first-line treatment for schizophrenia [1]. For depression, ECT is probably more effective than pharmacotherapy [3]. For schizophrenia, ECT combined with antipsychotics is a treatment option when the patient does not respond to pharmacotherapy alone or rapid improvement is desired [4]. ECT is also used for other severe conditions such as refractory status epilepticus [5] and malignant catatonia [6]. Despite the extensive use of ECT, the mechanisms of how its broad and notable therapeutic effectiveness is generated remain poorly understood.

Discredited Theories of ECT

Although ECT has proven to be an effective and safe intervention [3, 4], its image in the media and in the public domain remains negative [7, 8]. McCall *et al.* have listed some misconceptions concerning the mechanism underlying the treatment effects of ECT, such as brain damage and the placebo effect [9]. Anderson *et al.* performed a post-mortem brain examination on an 84-year-old man after 422 ECT sessions and found no identifiable structural changes

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in his brain [10], which further confirmed the results of previous research [11, 12]. It is notable that in Anderson's study, the time interval between the last ECT treatment and the postmortem examination was less than a month, which is much shorter than in the previous reports (one year and 12 years). This provided evidence that ECT has no impact on the structure of the brain even immediately after the end of substantive ECT treatments. Besides pathological changes, researchers have also explored the relationship between ECT and brain damage by analyzing relevant biomarkers. In previous trials, no elevations were found for neuron-specific enolase or protein S-100 (S100b), which are highly-specific and widely-used biomarkers of nervous tissue damage [13–16]. There were also studies identifying small and transient increases in S100b after ECT, which showed no association with cognitive impairment [17, 18]; rather, such alterations of S100b may indicate neural growth and synaptogenesis [19]. To date, both *in vivo* and *ex vivo* evidence indicates that the therapeutic effects of ECT are not generated by damaging the central nervous system, although there is great concern about this issue [20, 21].

Although ECT is known to be significantly more effective than a sham procedure [3], discussion about whether the placebo effect plays an important role in ECT continues. Reviewers have criticized such trials in that there are particular methodological and ethical limitations with regard to the adequacy of placebo controls as a consequence of insufficient allocation concealment [22]. Since sham ECT is ineffective and it would be ethically wrong to mimic the common side-effects of real ECT, participants may be able to guess their allocation. As a consequence, we are not able to rule out the possibility that the placebo effect does contribute to its therapeutic effects. In fact, emerging evidence favors ECT over active controls like antidepressants and repetitive transcranial magnetic stimulation [23, 24], further demonstrating that ECT may be the most effective treatment for major depression. Placebo effects cannot be the mainstay of such a powerful weapon against various severe mental disorders. However, discussion concerning the role of the placebo effect in ECT is likely to continue until the mechanism is fully understood.

ECT and Neurotransmitters

ECT is mainly used to treat depression and schizophrenia [1]. The main treatments of both disorders are pharmacotherapies involving the modulation of serotonin (5-HT) in the case of antidepressants and an antagonistic effect on dopamine D2 receptors in the case of antipsychotics [25, 26]. Thus, many researchers have investigated the mechanism underlying the effects of ECT by identifying its impact on the 5-HT and the dopamine systems in the brain.

Most studies have shown no significant changes in 5-hydroxyindoleacetic acid, a major metabolite of 5-HT, in cerebrospinal fluid (CSF) with ECT [27–31]. Using a positron emission tomography (PET), Lakshmi *et al*. found a widespread reduction in 5-HT2A receptor binding in all of the cortical regions of patients with major depressive disorder (MDD) [32]. These results are consistent with the findings from studies on antidepressant agents [33–35] and in non-human primates [36]. Moreover, the reductions in the right medial prefrontal cortex, right lingual gyrus, and parahippocampal gyrus showed a trend to be correlated with improvement in depressive symptoms. In addition, variation in the 5-HT2A receptor gene is a potential predictor of the response to ECT [37] and antidepressants [38, 39]. Lanzenberger *et al*. found a widespread reduction in 5-HT1A receptor binding in cortical areas and the hippocampus-amygdala region [40], while Saijo *et al*. reported no significant changes in the brains of MDD patients [41]. On the basis of the limited data from these three trials, one might hypothesize that ECT and antidepressant agents share a common mechanism, the down-regulation of 5-HT receptors, in the treatment of depressive disorders. However, these findings in human participants are inconsistent with most of the preclinical experiments, which indicate that electroconvulsive shocks (ECS) up-regulate 5-HT receptors in the central nervous system [42].

Similarly, ECT did not produce any significant changes in CSF homovanillic acid, a major metabolite of dopamine, in most studies [27–31]. Using PET with [^{11}C]FLB 457, Saijo *et al.* found that dopamine D2 receptor binding decreases in the anterior cingulate among patients with depression following ECT [43]. Nevertheless, Tiger *et al.* reported a 98% increase in dopamine D2 receptor binding with [^{11}C]raclopride in half of the patients, while there was virtually no change in the other half [44]. This sharp discrepancy might partially be attributed to the impact of dopamine receptor polymorphism on the ECT response [45–47]. The results of preclinical studies are relatively consistent, and most indicate that ECT activates the dopamine system at various levels, including hormone release, neurotransmission, and receptor binding [42].

ECT and Neurotrophins

Brain-derived neurotrophic factor (BDNF) plays an important role in mediating the differentiation and survival of neurons, as well as in synaptic plasticity [48]. It is the most extensively-studied neurotrophin in psychiatry, and numerous meta-analytic reviews have suggested that BDNF decreases in various mental disorders and increases after pharmacological treatments [49–56].

Polyakova *et al.* have performed a comprehensive meta-analysis concerning the impact of ECS/ECT on BDNF

levels in experimental animals and in patients with MDD or bipolar disorder [57]. They reported an increase in the BDNF protein and its mRNA in the brains of rodents, with the greatest change in the dentate gyrus, as well as an increase in blood BDNF levels in patients irrespective of their response to ECT. The increase in BDNF after ECT/ECS is correlated with the number of intervention sessions. It seems that ECT does raise the BDNF levels in the brain but the increase has nothing to do with its therapeutic effects. However, subgroup analysis revealed more information. Although there were no significant differences between responders and non-responders, the BDNF increase (pre- *versus* post-treatment) was significant only in responders (pre- and post-treatment). And an increase in blood BDNF levels was found in the plasma of participants, but there was no change in the serum of either rats or humans. More recent evidence has confirmed the potential of BDNF as a predictor of the response to ECT [58–61]. Nevertheless, it is notable that most of the results are markedly heterogeneous, and this cannot be settled by subgroup analysis, thus, the findings of this study are not conclusive. In addition to the direct assessment of BDNF, researchers have also explored the role of BDNF in the effects of ECT by investigating the influence of BDNF gene polymorphisms on its efficacy [47, 62–64]. Yet only the polymorphism rs11030101 has been associated with the therapeutic effects of ECT [63].

Although not as thoroughly evaluated as BDNF, an association between vascular endothelial growth factor (VEGF) and the efficacy of ECT has also been evaluated. VEGF, a key growth factor for blood vessels, has various effects on neurons [65] and is increased in the blood of MDD patients [66]. Minelli *et al.* conducted a series of trials, and consistently found that a serum VEGF increase is associated with a reduction of depressive symptoms [67–69]. These results further confirm the conclusions drawn from preclinical research that VEGF plays an important role in the mechanism of ECT [70–73].

ECT and the Immune System

Meta-analytic reviews have revealed significant changes in inflammatory cytokines in various mental diseases [74–80] as well as their potential as predictors of disease development and treatment response in depression and psychosis [81–84]. Increases in C-reactive protein, interleukin-6, and tumor necrosis factor alpha (TNF-α) in the blood of patients with depression or psychosis are consistently reported by these studies.

Despite the great efforts to identify cytokine changes following ECT since the beginning of the twenty-first century [85–92], only a few studies have shown that ECT works by normalizing the inflammatory factor levels in the same way as pharmacotherapy [93, 94]. In fact, many studies have suggested that ECT raises the concentration of these cytokines which were already elevated before treatment. But some relatively promising results have been reported, such as a reduction in TNF-α, a consistently raised inflammatory cytokine in depressed patients [86]. In addition, significantly low serum interleukin-5 (IL-5) and tumor necrosis factor beta (TNF-β) have been reported, both correlated with the severity of depressive symptoms [89]. These results are consistent with previous findings of up-regulated IL-5 and TNF-β in MDD patients [95–98]. In addition, an increase in indoleamine 2,3 dioxygenase (IDO) has been found in MDD and its level drops following ECT [91], providing evidence for the IDO activation theory of mood disorders [99]. In another study, lower serum levels of TGF-β in schizophrenic patients have been reported, and they increase following ECT, showing a negative correlation with a reduction of psychotic symptoms [92]. Nevertheless, these results contradict previous evidence that TGF-β increases in schizophrenic patients and is normalized after antipsychotic treatments [81].

ECT and Epigenetics

Epigenetics commonly refers to a stably heritable phenotype as a consequence of chromosome modification without changing DNA sequences [100]. It may be involved in the development of various mental diseases and thus indicate new directions for treatment [101–104]. It is a novel approach to investigating the mechanism of ECT, but most research remains preclinical and methodologically limited. The main findings from these very preliminary studies include an increase in histone H4 acetylation, alterations of DNA methylation patterns, and changes in miRNA levels [105]. We found two reports concerning the epigenetic effects of ECT on human subjects. In MDD patients, Kleimann *et al.* found a lower methylation rate in the BDNF promoter in ECT responders than in non-responders, and a negative correlation between the methylation rate and serum BDNF levels [106]. In addition, changes in the blood concentrations of several miRNAs following ECT in MDD patients have been reported by Kolshus *et al.* [107]. In short, a limited number of studies preliminarily reveal the potential of investigating the mechanism of ECT *via* epigenetic means.

ECT and Structural Neuroplasticity

In addition to the molecular-level changes noted above, ECT may also be able to reverse the structural abnormalities found in patients with mental diseases. Examples of these abnormalities are the multiple structural and microstructural changes in both the cortical and subcortical areas among MDD patients [108–113], and hippocampal

Table 1 Summary of relatively consistent findings

Levels	Relatively consistent findings	Symptomatic correlations	Genetic correlations
Neurotransmitters	Cortical 5-HT2A receptor binding↓ [32, 36]	± [32]	+ [37]
Neurotrophins	Blood BDNF↑ [57–61]	+ [58–61]	+ [63, 106]
	Blood VEGF↑ [67–72]	+ [67, 69]	−
Inflammatory factors	Blood TNF-α↓ [86]	−	−
	Blood TNF-β↓ [89]	+ [89]	−
	Blood IL-5↓ [89]	+ [89]	−
Structural changes in brain	Hippocampus↑ [115–121]	+ [115, 120]	−
	Amygdala↑ [115, 117, 119, 120]	+ [115, 120]	−
Functional changes in brain	Frontal glucose uptake↓ [141–145]	+ [142]	−
	Resting state network↑ [118, 146–150]	+ [118, 146–150]	−

↑ Increase; ↓ decrease; + statistically significant; ± showing a trend; − neither significant nor showing a trend.

size is a potential predictor of response to medication [114].

Recently, Joshi *et al*. found that ECT normalizes the decreased volumes of the hippocampus and the amygdala, and the changes are correlated with clinical improvement [115]. Several other studies showed that ECT enlarges the hippocampus and the amygdala [116–119], with correlations between volume increases and symptomatological improvement [120]. One study suggested that such increases reverse within six months and are not likely to be induced by edema [121]. These results are consistent with previous findings that the hippocampus and the amygdala are involved in the dysfunction of emotion regulation among depressive patients [122]. Although evidence of an association between hippocampal volume changes and autobiographical memory function has been found [123], a reasonable explanation of the discrepancy in hippocampal volume increases and autobiographical memory dysfunction following ECT has yet to be provided [124].

As for microstructural changes, fractional anisotropy (FA), which is a measure of white matter coherence, is the most used image biomarker in research on depression. Decreased FA is a stable finding in depression despite the fact that the reported regions are relatively inconsistent with different analytical methods [109, 111, 113]. In addition, there is evidence associating non-remitters with lower FA [125]. However, the results of recent studies concerning the impact of ECT on brain FA values vary substantially. Two studies have revealed increased FA [126, 127], one revealed no changes [128], and one revealed a decreased FA [119].

ECT and Neural Functional Changes

Using various techniques such as single positron emission computer tomography, near-infrared spectroscopy, and PET, investigators have examined the impact of ECT on regional cerebral blood flow, but found mixed results [129–140]. Interestingly, one study showed significant normalization of frontal hypoperfusion in MDD patients with an excellent response to ECT but not in those with a minimal or moderate response [133]. In addition, a higher degree of perfusion was found in ECT treatments producing generalized seizures than in those which did not induce such seizures [139]. Changes in glucose metabolism are stably reported following ECT. Most relevant studies report decreased uptake in some frontal regions after ECT [141–145], and a correlation between such decreases and the reduction of depressive symptoms has also been reported [142]. In contrast, most resting-state network analysis has revealed increased connectivity correlated with clinical improvement, but the reported regions are inconsistent [118, 146–150]. Notably, van Waarde *et al.* claimed promising accuracy of two networks in predicting the ECT response, one centered in the dorsomedial prefrontal cortex with a sensitivity of 84% and specificity of 85%, and the other centered in the anterior cingulate cortex with a sensitivity of 80% and a specificity of 75% [150]. In addition, normalization of default mode network coherence was found in ECT responders but not in non-responders [151].

Summary

Despite decades of tremendous effort, a comprehensive understanding of how ECT works is still a distant goal. With regard to molecular changes, consistent positive results towards normalization correlated with symptom improvement are rare. For neuroimaging changes, inconsistencies in altered regions are the main limitation. The small number of samples, the diversity of methods used in

both data collection and data analysis, and the heterogeneity within a certain mental disorders may all contribute to the inconsistency of current findings. Large trials and meta-analytic reviews are necessary to tackle these shortcomings.

Fortunately, there are still some promising findings despite the fact that they cannot fully explain the mechanism of ECT. Relatively consistent findings are listed in Table 1. Among the molecular biomarkers, neurotrophins seem more likely to be able to solve the mystery of the therapeutic effects of ECT and have become a hotspot in this field. Increases in blood BDNF and VEGF are consistently found after ECT, and many studies have revealed a positive correlation between the improvement of symptoms and these two neurotrophins. For similar reasons, we also recognize the volume increases of the hippocampus and amygdala to be the most promising structural imaging biomarkers, and increased connectivity of the resting state network to be the most promising functional imaging biomarker.

Besides exploring new biomarkers, what we already have must be fully utilized. For example, whether volume and functional changes of brain structures are mediated by neurotrophins must be further investigated. In addition, models using these biomarkers either separately or in an integrated manner should be built to see whether they can accurately predict clinical responses. The work discussed above may not only provide a better understanding of the mechanism of action of ECT, but also eventually facilitate clinical decision-making.

Acknowledgements This review was supported by the grants of Shanghai Hospital Development Center, China (SHDC12014111), the Science and Technology Commission of Shanghai Municipality, China (14411961400 and 13dz2260500), and the Shanghai Health System Leadership in Health Research Program, China (XBR2011005).

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