Alpha Psychiatry

EDITORIAL COMMENT
Alpha Psychiatry 2022;23(2):57-58
DOI: 10.5152/alphapsychiatry.2022.0003

Biomolecular Research on Electroconvulsive Therapy for Mental Disorders: State of the Art and Future Directions

Electroconvulsive therapy (ECT) has been used in psychiatry since the 1930s and, with substantial changes leading to much more refined techniques, it remains an important therapeutic option for severe mental disorders such as drug-resistant mood disorders, schizophrenia, and catatonia.[1] The unique role of ECT in the management of treatment-refractory psychiatric conditions is attributable to its potential higher efficacy over standard psychopharmacological treatments.[1] Although data on efficacy and tolerability would support a broader administration, ECT is still underused in clinical practice for several reasons, including stigma, lack of knowledge of modern ECT techniques, and concerns about its safety, primarily regarding cognition.[1] Cognitive side effects – firstly memory loss – have been associated with neuronal damage, possibly related to alterations of several mechanisms including neurogenesis, glial activity, neurotransmission, neuroinflammation, and oxidative stress response.[2] In view of this, research has attempted to elucidate the precise mechanisms of action of ECT, even though the molecular changes underlying its efficacy and possible negative outcomes remain largely unclear.

The review by Atagün and Canbek,[3] which is published in this issue, analyzes the effects of ECT on markers of oxidative stress in both experimental models and humans with major mental disorders, showing mixed and contrasting evidence. Whilst highlighting the shortcomings of the existing literature and the need for more research, the authors concluded that current findings do not clearly suggest an association of ECT with long-term oxidative sequelae, with changes in oxidant-antioxidant balance that seem to be acute and transient, apparently not causing durable damage to the brain.[3]

Beyond oxidative stress, several other biomolecular mechanisms have been proposed as underlying the biological response to ECT and its implications in terms of both efficacy and adverse effects. Immune-inflammatory response, putatively involved in multiple psychiatric disorders, may represent a key mediator of the effects of ECT. Indeed, whilst being transiently amplified following a lone ECT session (likely as part of an acute stress reaction), immune-inflammatory response seems to be down-regulated at the end of a full treatment course, as shown by relevant fluctuations in the concentrations of inflammation-related biomarkers such as tumor necrosis factor alpha.[2] In this regard, it has been hypothesized that an inflammatory stimulation might reinforce neurotrophin expression, suggesting that a targeted potentiation, rather than suppression, of inflammatory mechanisms may be of therapeutic relevance.[4] ECT may induce alterations in the synthesis of neurotrophins that are indicative of neuroprotection and neuroproliferation. Neurotrophic effects of ECT have actually been claimed, putatively linking changes in neurotrophin concentrations to the therapeutic effectiveness of ECT and also suggesting them as possible markers of response to treatment.[5] On the other hand, it has been postulated that neurotrophins, such as vascular endothelial growth factor and brain-derived neurotrophic factor, might play a mediating role in several mechanisms determining hippocampal volume possibly involved in ECT-induced neurocognitive changes.[6,7] Similarly, the kynurenine pathway, which has been suggested as a possible common link between immune-inflammatory response, oxidative stress, glutamatergic neurotransmission, and neuroplasticity in schizophrenia and mood disorders,[8,9] may be involved in the response to ECT. Although neurotoxic metabolites of the pathway, such as quinolinic acid, have been associated with cognitive dysfunctions, it has been shown that a treatment with ECT might actually shift tryptophan catabolism towards compounds with

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Cite this article as: Cavaleri D, Bartoli F. Biomolecular research on electroconvulsive therapy for mental disorders: state of the art and future directions. *Alpha Psychiatry*. 2022;23(2):57-58.

neuroprotective properties such as kynurenic acid while decreasing the production of neurotoxic molecules.[10]

Nonetheless, the evidence on ECT-induced biomolecular changes remains limited, considering that most of the available studies are affected by small sample sizes and methodological heterogeneity. Available literature in this field highlights the undeniable need for further research aimed at better elucidating the neurobiological underpinnings of ECT. Progress in the knowledge of oxidative, immune-inflammatory, and neurotrophic response to ECT may not only pave the way for a deeper insight into the biomolecular mechanisms of action of ECT but also help overcoming controversies, misunderstandings, and stigmatization of this treatment.

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