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Efficacy of electroconvulsive therapy: is it in the *BDNF* gene?

"The neurobiological mechanisms of action in electroconvulsive treatment have been reported to involve, among others, the induction of BDNF ... in the hippocampus and entorhinal cortex."

KEYWORDS: BDNF ■ electroconvulsive ■ major depressive disorder ■ treatment ■ treatment-resistant depression

Since its invention in 1938, electroconvulsive treatment (ECT) of the brain has had a controversial reputation, which its original name, electroshock treatment, did nothing to extenuate. Having been a common symbol of evil in psychiatry in literature and movies in the past, it continues to be seen partly as a mythical and exceptional form of treatment in the modern era of neuroscience-based psychiatry. Despite the drama and its demonstrably superior effect compared with any other medical intervention in psychotic and treatment-resistant major depressive disorder (MDD), ECT raises negative attitudes, which are likely to persist until its rapid mechanism of action has been thoroughly elucidated. It is noteworthy that neurostimulation treatments introduced in the 1990s, such as repetitive transcranial magnetic stimulation (rTMS) or deep brain stimulation have not been subjected to such emotionally loaded ethical debate.

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"...the change in expression with both antidepressive agents and electroconvulsive stimuli in acute and long-term administration on functionally different BDNF exons resulted in a ... clear and long-term expression increase in all five exons studied with electroconvulsive stimuli."

The neurobiological mechanisms of action in ECT have been reported to involve, among others, the induction of BDNF secretion by prolonged increase of both BDNF and *trkB* or *NTRK2* mRNA expression in the hippocampus and entorhinal cortex [1]. BDNF belongs to the neurotrophin family of trophic factors [2]. The *trkB* receptor binds and shows a particular responsiveness to BDNF [3]. The functions of

mature BDNF (mBDNF) involve stimulating the development and differentiation of new neurons, neuron survival and promoting long-term potentiation. BDNF is expressed throughout the brain, and in muscle, liver and adipose tissues [4]. The neuronal plasticity generating effect of BDNF resulting in turnover of new neurons and synaptogenesis in the hippocampus, which have been intensively studied as a possible mechanism for the clinical effect of antidepressants, are related to *TrkB* receptor activation through phosphorylation [5].

In the *BDNF* gene, the nine promoter regions and 11 exons produce at least 34 different transcripts (FIGURE 1), all of which are translated into mBDNF protein [6]. Transcripts are likely to be regulated differentially by different neuronal activity regulating stimuli, and exons may have unique functions with relation to intracellular targeting and in controlling translation [7]. For example, the change in expression with both antidepressive agents and electroconvulsive stimuli (ECS) in acute and long-term administration on functionally different *BDNF* exons resulted in a biphasic genetic response to antidepressive agents in contrast to a clear and long-term expression increase in all five exons studied with ECS [8]. There is also evidence of variations in activity level in different brain regions for different *BDNF* transcripts [6].

It has been suggested that functional polymorphisms in the *BDNF* gene correlate with a number of neuroanatomical and behavioral changes, including susceptibility to depression and anxiety disorders [9]. A total of 130 SNPs have been detected in the *BDNF* gene, of which six had a moderate association with depression and eight with antidepressive response [10]. Of the depression associated SNPs one was further

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Figure 1. *BDNF* gene regulation mechanisms related to electroconvulsive therapy.

VTA: Ventral tegmental area.

associated with the efficacy of ECT in MDD [11]. Also, a meta-analysis of 14 studies revealed an association between MDD susceptibility and *BDNF* Val66Met Met-genotype in males [12], and the same allele associated with smaller hippocampal volumes in both MDD patients and controls in a MRI study [13]. Detected with RNA amplification and laser microdissection techniques in the gyrus dentate area of rat hippocampus, gene-expression changes following repeated ECS were measurable in several genes, including *BDNF*, *NPY*, *TRH* and *Gadd45β*, and in the *EAAC1/Slc1A1* genes [14].

A possible mechanism for increased BDNF serum levels detected after ECT [15] may be owing to *BDNF* gene upregulation mediated by histone H3 and H4 acetylation [16]. However, according to an animal model the downregulation of BDNF expression in the ventral tegmental area, and not the upregulation of hippocampus could be a more likely mechanism of action for ECT [17]. Likewise the BDNF hippocampal and cortical levels after repeated ECS have not directly correlated with serum level changes [18], but the serum BDNF levels may reflect the temporal changes in brain tissue levels [19]. According to several studies, serum BDNF levels have been found to be low in patients with MDD and elevated after

antidepressant treatment [20]. It is possible that the neurostimulation induced release from platelets, where BDNF is taken up in plasma, is weaker in depressed patients than in healthy controls [5]. On the other hand, the antidepressive response does not necessarily correlate with BDNF serum levels, neither in ECT or rTMS [21].

“...functional polymorphisms in the *BDNF* gene correlate with a number of neuroanatomical and behavioral changes, including susceptibility to depression and anxiety disorders.”

Recently, secretion of the precursor of mBDNF, proBDNF, was found to be increased after a single administration of ECS in rat hippocampal synaptosomes through increased secretion of the pro-BDNF processing proteases PC1 and t-PA [22]. However, although repeated ECS did indeed increase both the proBDNF and t-PA levels, no similar mechanism was detected during long-term imipramine administration [22].

The role of BDNF as a central neurotrophic factor seems essential to the efficacy of ECT. There is ample evidence of the inductive effects of both single and repeated ECT on BDNF secretion in brain, and reflective changes in

serum. These alterations have been suggested to have a temporal difference when compared with corresponding changes with antidepressive agents, which concurs with the different onset of action between these two forms of treatment. Likewise the neurotrophic effects of BDNF may at least in part explain the rapid and potent effects of ECT in MDD.

The genetic regulation of BDNF production, and especially the role of different *BDNF* transcripts on the balance of BDNF production between different parts of the brain seems an important mechanism when considering the BDNF level changes in the CNS. In this sense the specific functions of different exons and their transcripts deserve more attention in future studies. Also, the ECT-induced genetic regulation, such as transcript altering mechanisms affecting BDNF expression, need to be further investigated. Furthermore, the impact of other genes involved in BDNF functions, such as the *trkB* gene and other neurotrophins (e.g., VEGF) still remain to be clarified. On the other hand, the role of proBDNF seems interesting given the rapid onset of action with ECT. The remaining challenge is to identify the process starting from the electrical stimulus, further inducing gene

expression and protein synthesis, and finally resulting in the target response explaining the alleviation of symptoms at a satisfactory level.

“...the neurotrophic effects of BDNF may at least in part explain the rapid and potent effects of electroconvulsive treatment in major depressive disorder.”

During this age of increasing treatment options with different forms of neurostimulation in mood disorders, it would also be valuable in future to study the significance of BDNF and its genetic regulation in parallel with ECT in the nonconvulsive neurostimulation therapy forms, such as deep brain stimulation and rTMS.

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References

- Madsen TM, Treschow A, Bengzon J, Bolwig TG, Lindvall O, Tingstrom A. Increased neurogenesis in a model of electroconvulsive therapy. *Biol. Psychiatry* 47(12), 1043–1049 (2000).
- Leibrock J, Lottspeich F, Hohn A *et al.* Molecular cloning and expression of brain-derived neurotrophic factor. *Nature* 341(6238), 149–152 (1989).
- Soppet D, Escandon E, Maragos J *et al.* The neurotrophic factors brain-derived neurotrophic factor and neurotrophin-3 are ligands for the *trkB* tyrosine kinase receptor. *Cell* 65(5), 895–903 (1991).
- Noble EE, Billington CJ, Kotz CM, Wang C. The lighter side of BDNF. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 300(5), 1053–1069 (2011).
- Castren E, Rantamaki T. The role of *BDNF* and its receptors in depression and antidepressant drug action: reactivation of developmental plasticity. *Dev. Neurobiol.* 70(5), 289–297 (2010).
- Pruunsild P, Kazantseva A, Aid T, Palm K, Timmusk T. Dissecting the human *BDNF* locus: bidirectional transcription, complex splicing, and multiple promoters. *Genomics* 90(3), 397–406 (2007).
- Baj G, Tongiorgi E. *BDNF* splice variants from the second promoter cluster support cell survival of differentiated neuroblastoma upon cytotoxic stress. *J. Cell. Sci.* 122(1), 36–43 (2009).
- Khundakar AA, Zetterstrom TS. Biphasic change in *BDNF* gene expression following antidepressant drug treatment explained by differential transcript regulation. *Brain Res.* 1106(1), 12–20 (2006).
- Greenberg ME, Xu B, Lu B, Hempstead BL. New insights in the biology of BDNF synthesis and release: implications in CNS function. *J. Neurosci.* 29(41), 12764–12767 (2009).
- Licinio J, Dong C, Wong ML. Novel sequence variations in the brain-derived neurotrophic factor gene and association with major depression and antidepressant treatment response. *Arch. Gen. Psychiatry* 66(5), 488–497 (2009).
- Viikki ML, Jarventausta K, Leinonen E *et al.* *BDNF* polymorphism rs11030101 is associated with the efficacy of electroconvulsive therapy in treatment-resistant depression. *Psychiatr. Genet.* 23(3), 134–136 (2013).
- Verhagen M, van der Meij A, van Deurzen PA *et al.* Meta-analysis of the *BDNF* Val66Met polymorphism in major depressive disorder: effects of gender and ethnicity. *Mol. Psychiatry* 15(3), 260–271 (2010).
- Frodl T, Schule C, Schmitt G *et al.* Association of the brain-derived neurotrophic factor Val66Met polymorphism with reduced hippocampal volumes in major depression. *Arch. Gen. Psychiatry* 64(4), 410–416 (2007).
- Ploski JE, Newton SS, Duman RS. Electroconvulsive seizure-induced gene expression profile of the hippocampus dentate gyrus granule cell layer. *J. Neurochem.* 99(4), 1122–1132 (2006).
- Bocchio-Chiavetto L, Zanardini R, Bortolomasi M *et al.* Electroconvulsive therapy (ECT) increases serum brain derived neurotrophic factor (*BDNF*) in drug resistant depressed patients. *Eur. Neuropsychopharmacol.* 16(8), 620–624 (2006).
- Tsankova NM, Kumar A, Nestler EJ. Histone modifications at gene promoter regions in rat hippocampus after acute and chronic electroconvulsive seizures. *J. Neurosci.* 24(24), 5603–5610 (2004).
- Taliaz D, Nagaraj V, Haramati S, Chen A, Zangen A. Altered brain-derived neurotrophic factor expression in the ventral tegmental area, but not in the hippocampus,

- is essential for antidepressant-like effects of electroconvulsive therapy. *Biol. Psychiatry* 74(4), 305–312 (2012).
- 18 Kyeremanteng C, James J, Mackay J, Merali Z. A study of brain and serum brain-derived neurotrophic factor protein in wistar and wistar-kyoto rat strains after electroconvulsive stimulus. *Pharmacopsychiatry* 45(6), 244–249 (2012).
- 19 Sartorius A, Hellweg R, Litzke J *et al.* Correlations and discrepancies between serum and brain tissue levels of neurotrophins after electroconvulsive treatment in rats. *Pharmacopsychiatry* 42(6), 270–276 (2009).
- 20 Sen S, Duman R, Sanacora G. Serum brain-derived neurotrophic factor, depression, and antidepressant medications: meta-analyses and implications. *Biol. Psychiatry* 64(6), 527–532 (2008).
- 21 Gedge L, Beaudoin A, Lazowski L, du Toit R, Jokic R, Milev R. Effects of electroconvulsive therapy and repetitive transcranial magnetic stimulation on serum brain-derived neurotrophic factor levels in patients with depression. *Front. Psychiatry* 3, 12 (2012).
- 22 Segawa M, Morinobu S, Matsumoto T, Fuchikami M, Yamawaki S. Electroconvulsive seizure, but not imipramine, rapidly up-regulates pro-BDNF and t-PA, leading to mature BDNF production, in the rat hippocampus. *Int. J. Neuropsychopharmacol.* 16(2), 339–350 (2013).