CHAPTER 1

Mechanism of action of ECT

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Seventy-five years after its introduction, ECT remains the most effective treatment for severe depressive disorder (UK ECT Review Group, 2003). Nevertheless, ECT is relatively underresearched compared with other forms of treatment for mental disorders; in particular there has been a relative lack of research using newer brain imaging techniques. Possible factors for the neglect of ECT include its adverse public image, funding priorities, the interests of researchers and the practical and ethical difficulties in studying this group of severely ill patients. Here, we briefly review some of the important neurobiological effects of ECT, concentrating on those related to its use in treating affective disorders, its principal indication. For more detailed information, see the reviews by Nobler & Sackeim (2008), Pigot *et al* (2008), Kato (2009), Merkl *et al* (2009) and Scott (2011).

A frequent criticism of ECT is that its mode of action is not understood. This is scarcely surprising given that the same can be said of other biological treatments in psychiatry. For example, although we understand much about the pharmacology of antidepressant and antipsychotic drug treatments, we still do not know how these pharmacological effects bring about improvement in mood or psychosis. Similarly for ECT, we know that both the generalised seizure and the dose of electricity used are important in bringing about its therapeutic effects, and that it has multiple, varied and lasting effects on the central nervous system (Merkl *et al*, 2009; Scott, 2011). Nevertheless, how these are translated into clinical effects remains obscure.

In recent years, advances in neuroscience have led to the development of various models of psychiatric disorders, particularly mood disorders, which encompass biological, psychological, social and developmental aspects (Mayberg, 2002; Seminowicz *et al*, 2004; Ebmeier *et al*, 2006; Beck, 2008; Akil *et al*, 2010). A common feature of these models is that psychiatric disorders are the result of disruptions of neural circuits, the functional networks of neurons that mediate thought, feelings and behaviour. Key areas concerned with networks involved in mood disorders include the hippocampus and amygdala, cingulate cortex (especially sub- and pregenual

regions) and other areas of the prefrontal cortex. Underlying these networks are the structural and functional attributes of neurons and their connections. It is at this level that biological treatments are thought to exert their effects. There is good evidence that ECT has important effects on the function, and possibly structure, of neurons in these networks.

Putative mechanisms of ECT

Changes in brain structure, function and neural connectivity

Depression is associated with reduction in volume of the hippocampus (Arnone *et al*, 2012*a*) and excessive levels of circulating corticosteroids may play a causal role (Goodyer *et al*, 2010). Successful short-term antidepressant drug treatment has recently been shown to increase hippocampal grey matter in patients with depression (Arnone *et al*, 2012*b*). Although previous research has not found that ECT causes structural brain changes (UK ECT Review Group, 2003; Nobler & Sackeim, 2008), one study found that ECT caused an increase in bilateral hippocampal volume (Nordanskog *et al*, 2010). An earlier study, using magnetic resonance spectroscopy, found increased hippocampal choline concentrations, a putative measure of membrane turnover after ECT (Ende *et al*, 2000). This suggests that ECT may affect the structure of the hippocampus, a key component of neural circuitry involved in mood. The effects of ECT on the hippocampus may also underlie its effects on cognition, particularly memory (Gregory-Roberts *et al*, 2010).

As discussed above, prefrontal and medial temporal cortex have all been implicated in the genesis of depression; studies of the effect of ECT on regional cerebral blood flow (rCBF) and cerebral metabolic rate (rCMR) have however produced inconsistent results. Reviews have concluded that the most consistent finding is reduced anterior cingulate/prefrontal cortex rCBF or rCMR, possibly with some relationship with adverse cognitive effects (Nobler & Sackeim, 2008; Schmidt *et al*, 2008; Scott, 2011). However, other studies have found increased anterior cingulate and hippocampal rCMR correlating with improvement in symptoms (McCormick *et al*, 2007), as well as normalisation of reduced anterior cingulate theta wave activity (McCormick *et al*, 2009).

In summary, although there is evidence that ECT alters the function and the structure of important brain areas, especially the frontotemporal circuits involved in mood, methodological factors such as small and heterogeneous samples mean that a consistent picture has yet to emerge.

Effects on neurotransmitters

Monoamines

The monoamine theory of depression and antidepressant action goes back to the development of the first antidepressants and has been

influential in driving the development of virtually all currently available antidepressant medications. More recent theories of antidepressant action emphasise adaptive changes in receptors and post-receptor mechanisms (e.g. Blier & Abbott, 2001). Preclinical studies investigating the effects of electroconvulsive shock (ECS), the animal equivalent of ECT, have found enhanced postsynaptic serotonergic (5-hydroxytryptamine, 5-HT) receptor sensitivity, downregulation of 5-HT_2 receptors, α_2- and β-adrenoceptors and increased striatal dopamine and dopamine receptors (Lisanby & Belmaker, 2000; Dremencov *et al*, 2003; Merkl *et al*, 2009). A human positron emission tomography (PET) study reported decreased anterior cingulate dopamine-D_2 receptor binding after ECT (Saijo *et al*, 2009), while in a non-human primate PET study, ECS decreased cortical 5-HT_2 receptor binding (Strome *et al*, 2005).

In support of the importance of monoamines in the effect of ECT, functional polymorphisms of the dopamine D_2 receptor which regulate postsynaptic effects, and the *COMT* gene which metabolises noradrenaline and dopamine have been associated with differential response to ECT (Merkl *et al*, 2009). However, neither using tryptophan depletion to decrease 5-HT function nor using α-methyl-para-tyrosine to reduce dopamine and noradrenaline function has been associated with symptomatic relapse after ECT (Cassidy *et al*, 1997, 2009). This suggests that increased levels of serotonin or catecholamines are not necessary to maintain improvement immediately after a course of ECT.

Other neurotransmitters and neuromodulators

An early model of the mechanism of action of ECT linked its anticonvulsant and antidepressant properties through common effects on gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter (Kato, 2009; Merkl *et al*, 2009). One theory has proposed that GABA-ergic inhibition may be restored by ECS as a result of upregulation of immediate early gene production modulating ion channel function (Kato, 2009). There has also been considerable interest in the role of glutamate in depression and its treatment (Mitchell *et al*, 2010). Electroconvulsive shock has been shown to alter modulate glutamate receptor expression or function (Naylor *et al*, 1996; Dong *et al*, 2010; Mitchell & Baker, 2010). In humans receiving ECT, pre-treatment low glutamate plus glutamine/glutamate concentrations have been found in dorsolateral prefrontal cortex (Michael *et al*, 2003) and anterior cingulate cortex (Pfleiderer *et al*, 2003; Merkl *et al*, 2011), which either normalised after ECT (Michael *et al*, 2003; Pfleiderer *et al*, 2003) or predicted treatment response (Merkl *et al*, 2011). In addition, it has been proposed that the adverse cognitive effects of ECT are mediated through indiscriminate activation of glutamate receptors in the hippocampus at the time of the seizure (Gregory-Roberts *et al*, 2010). Electroconvulsive therapy also has effects on peptide neuromodulators; for example, as with other antidepressant treatments, ECT increases brain and cerebrospinal neuropeptide Y concentrations (Mathe *et al*, 2007).

In summary, ECT has a variety of actions on neurotransmitter systems involved in neuronal functioning and these are likely to contribute to both its therapeutic and adverse effects.

Endocrine effects

There is a long history of interest in endocrine mechanisms in depression, most notably the hypothalamic–pituitary–adrenal (HPA) axis; hypercortisolaemia in Cushing's disease has long been known to be associated with depression. Hypothalamic–pituitary–adrenal axis abnormalities, including cortisol hypersecretion and impaired central cortisol feedback, are found in severe depression (de Kloet *et al*, 2007). Electroconvulsive therapy normalises HPA axis dysfunction, including restoring dexamethasone suppression of cortisol (Merkl *et al*, 2009). It is possible that central effects of ECT on neural systems involving corticosteroid receptors in structures such as the hippocampus may be important in its action. Acutely, ECT treatment is also associated with surges in plasma catecholamines and other hormones, which are important in its cardiovascular effects (see Chapter 21), but these have not been found to be associated with efficacy.

Gene expression, neurogenesis and synaptic plasticity

In animals, ECS induces widespread changes in gene expression. These include changes in proteins associated with neurotransmitters, neuropeptides and neuroprotective factors as well as those associated with synaptic plasticity (e.g. increased production of the immediate early gene product Homer1a) and neurogenesis (e.g. increased brain derived neurotrophic factor, BDNF) (Kato, 2009). Electroconvulsive shock has been shown to increase cell proliferation in areas such as the hippocampus in common with other antidepressant treatments (Kato, 2009; Merkl *et al*, 2009). Neurogenesis and alterations in synaptic plasticity have been proposed as a common mechanism underlying antidepressant activity (Racagni & Popoli, 2008), which would influence neuronal function and connectivity between brain structures relevant to mood and cognition.

Conclusions

We now have considerable evidence for the effects of ECT on brain function, although a comprehensive picture has still to emerge. The challenge remains to integrate the findings from different approaches and from mechanisms acting at different levels into a coherent model. It seems likely that multiple neurobiological effects modulating brain circuits associated with mood contribute to ECT's action and that these also interact with, or are dependent on, individual anatomical, biochemical, physiological and psychological variables.

The hope for the future is that a better understanding of the mechanisms underlying the action of ECT will allow refinement in its application as well

as progress in the treatment of those mental (and some physical) disorders helped by ECT. This is important in order to address the two Achilles' heels of ECT: the high rates of relapse after successful treatment and the adverse cognitive effects. It should be possible to address both issues when we have a better understanding of how ECT works. The lack of research into ECT is concerning and may prove a major obstacle to progress.

Key points

- Electroconvulsive therapy does not just cause a general non-specific disruption of brain function and there is no evidence it produces brain damage.
- Electroconvulsive therapy produces diverse changes in brain functional and structural components, including cerebral blood flow and metabolism, gene expression, neurogenesis and synaptic plasticity, with resultant effects on neurotransmitter pathways and endocrine systems.
- The effects of ECT, as with other biological treatments, are likely to be acting to normalise abnormal brain function underlying the illness state.
- It is not yet clear which changes are responsible for improvement and which may cause adverse effects.

References

Akil, H., Brenner, S., Kandel, E., *et al* (2010) The future of psychiatric research: genomes and neural circuits. *Science*, **327**, 1580–1581.

Arnone, D., McIntosh, A. M., Ebmeier, K. P., *et al* (2012*a*) Magnetic resonance imaging studies in unipolar depression: systematic review and meta-regression analyses. *European Neuropsychopharmacology*, **22**, 1–16.

Arnone, D., McKie, S., Elliott, R., *et al* (2012*b*) State-dependent changes in hippocampal grey matter in depression. *Molecular Psychiatry*, 6 Nov, doi: 10.1038/mp.2012.150. (Epub ahead of print.)

Beck, A. T. (2008) The evolution of the cognitive model of depression and its neurobiological correlates. *American Journal of Psychiatry*, **165**, 969–977.

Blier, P. & Abbott, F. V. (2001) Putative mechanisms of action of antidepressant drugs in affective and anxiety disorders and pain. *Journal of Psychiatry and Neuroscience*, **26**, 37–43.

Cassidy, F., Murry, E., Weiner, R. D., *et al* (1997) Lack of relapse with tryptophan depletion following successful treatment with ECT. *American Journal of Psychiatry*, **154**, 1151–1152.

Cassidy, F., Murry, E., Weiner, R. D., *et al* (2009) Antidepressant response to electroconvulsive therapy is sustained after catecholamine depletion. *Progress in Neuropsychopharmacology and Biological Psychiatry*, **33**, 872–874.

de Kloet, E. R., Derijk, R. H. & Meijer, O. C. (2007) Therapy insight: is there an imbalanced response of mineralocorticoid and glucocorticoid receptors in depression? *Nature Reviews Endocrinology*, **3**, 168–179.

Dong, J., Min, S., Wei, K., *et al* (2010) Effects of electroconvulsive therapy and propofol on spatial memory and glutamatergic system in hippocampus of depressed rats. *Journal of ECT*, **26**, 126–130.

Dremencov, E., Gu, E., Lerer, B., *et al* (2003) Effects of chronic antidepressants and electroconvulsive shock on serotonergic neurotransmission in the rat hippocampus. *Progress in Neuropsychopharmacology and Biological Psychiatry*, **27**, 729–739.

Ebmeier, K. P., Donaghey, C. & Steele, J. D. (2006) Recent developments and controversies in depression. *Lancet*, **367**, 153–167.

Ende, G., Braus, D. F., Walter, S., *et al* (2000) The hippocampus in patients treated with electroconvulsive therapy: a proton magnetic resonance spectroscopic imaging study. *Archives of General Psychiatry*, **57**, 937–943.

Goodyer, I. M., Croudace, T., Dudbridge, F., *et al* (2010) Polymorphisms in BDNF (Val66Met) and 5-HTTLPR, morning cortisol and subsequent depression in at-risk adolescents. *British Journal of Psychiatry*, **197**, 365–371.

Gregory-Roberts, E. M., Naismith, S. L., Cullen, K. M., *et al* (2010) Electroconvulsive therapy-induced persistent retrograde amnesia: could it be minimised by ketamine or other pharmacological approaches? *Journal of Affective Disorders*, **126**, 39–45.

Kato, N. (2009) Neurophysiological mechanisms of electroconvulsive therapy for depression. *Neuroscience Research*, **64**, 3–11.

Lisanby, S. H. & Belmaker, R. H. (2000) Animal models of the mechanisms of action of repetitive transcranial magnetic stimulation (RTMS): comparisons with electroconvulsive shock (ECS). *Depression and Anxiety*, **12**, 178–187.

Mathe, A. A., Husum, V., El Khoury, A., *et al* (2007) Search for biological correlates of depression and mechanisms of action of antidepressant treatment modalities. Do neuropeptides play a role? *Physiology and Behaviour*, **92**, 226–231.

Mayberg, H. S. (2002) Modulating limbic-cortical circuits in depression: targets of antidepressant treatments. *Seminars in Clinical Neuropsychiatry*, **7**, 255–268.

McCormick, L. M., Boles Ponto, L. L., Pierson, R. K., *et al* (2007) Metabolic correlates of antidepressant and antipsychotic response in patients with psychotic depression undergoing electroconvulsive therapy. *Journal of ECT*, **23**, 265–273.

McCormick, L. M., Yamada, T., Yeh, M., *et al* (2009) Antipsychotic effect of electroconvulsive therapy is related to normalization of subgenual cingulate theta activity in psychotic depression. *Journal of Psychiatric Research*, **43**, 553–560.

Merkl, A., Heuser, I. & Bajbouj, M. (2009) Antidepressant electroconvulsive therapy: mechanism of action, recent advances and limitations. *Experimental Neurology*, **219**, 20–26.

Merkl, A., Schubert, F., Quante, A., *et al* (2011) Abnormal cingulate and prefrontal cortical neurochemistry in major depression after electroconvulsive therapy. *Biological Psychiatry*, **69**, 772–779.

Michael, N., Erfurth, A., Ohrmann, P., *et al* (2003) Metabolic changes within the left dorsolateral prefrontal cortex occurring with electroconvulsive therapy in patients with treatment resistant unipolar depression. *Psychological Medicine*, **33**, 1277–1284.

Mitchell, N. D. & Baker, G. B. (2010) An update on the role of glutamate in the pathophysiology of depression. *Acta Psychiatrica Scandinavica*, **122**, 192–210.

Naylor, P., Stewart, C. A., Wright, S. R., *et al* (1996) Repeated ECS induces GluR1 mRNA but not NMDAR1A-G mRNA in the rat hippocampus. *Brain Research: Molecular Brain Research*, **35**, 349–353,

Nobler, M. & Sackeim, H. (2008) Neurobiological correlates of the cognitive side effects of electroconvulsive therapy. *Journal of ECT*, **24**, 40–45.

Nordanskog, P., Dahlstrand, U., Larsson, M. R., *et al* (2010) Increase in hippocampal volume after electroconvulsive therapy in patients with depression: a volumetric magnetic resonance imaging study. *Journal of ECT*, **26**, 62–67.

Pfleiderer, B., Michael, N., Erfurth, A., *et al* (2003) Effective electroconvulsive therapy reverses glutamate/glutamine deficit in the left anterior cingulum of unipolar depressed patients. *Psychiatry Research*, **122**, 185–192.

Pigot, M., Andrade, C. & Loo, C. (2008) Pharmacological attenuation of electroconvulsive therapy-induced cognitive deficits: theoretical background and clinical findings. *Journal of ECT*, **24**, 57–67.

Racagni, G. & Popoli, M. (2008) Cellular and molecular mechanisms in the long-term action of antidepressants. *Dialogues in Clinical Neuroscience*, **10**, 385–400.

Saijo, T., Takano, A., Suhara, T., *et al* (2009) Electroconvulsive therapy decreases dopamine D(2) receptor binding in the anterior cingulate in patients with depression: a controlled study using positron emission tomography with radioligand [11C]FLB 457. *Journal of Clinical Psychiatry*, **71**, 793–799.

Schmidt, E. Z., Reininghaus, B., Enzinger, C., *et al* (2008) Changes in brain metabolism after ECT-positron emission tomography in the assessment of changes in glucose metabolism subsequent to electroconvulsive therapy – lessons, limitations and future applications. *Journal of Affective Disorders*, **106**, 203–208.

Scott, A. I. F. (2011) Mode of action of electroconvulsive therapy: an update. *Advances in Psychiatric Treatment*, **17**, 15–22.

Seminowicz, D. A., Mayberg, H. S. , McIntosh, A. R., *et al* (2004) Limbic-frontal circuitry in major depression: a path modelling metanalysis. *Neuroimage*, **22**, 409–418.

Strome, E. M, Clark, C. M., Zis, A. P., *et al* (2005) Electroconvulsive shock decreases binding to 5-HT2 receptors in nonhuman primates: an in vivo positron emission tomography study with [18F]setoperone. *Biological Psychiatry*, **57**, 1004–1010.

UK ECT Review Group (2003) Efficacy and safety of electro-convulsive therapy in depressive disorders: a systematic review and meta-analysis. *Lancet*, **361**, 799–808.