

# Theories on Mechanism of Action of Electroconvulsive Therapy

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## Abstract

*Electroconvulsive therapy (ECT) is a useful yet controversial mode of treatment. Despite being in use for over 70 years, its mechanism of action (MOA) is still not clearly understood. Various theories on MOA of ECT have been proposed over the years. These have included looking at psychological, neurophysiological, neurochemical, neuroendocrine, and neuropeptides mechanisms. An attempt is made here to review the existing literature on the MOA of ECT in a historical perspective. Various theories are discussed in context of the available pre-clinical and clinical research evidence with highlighting of the methodological issues and looking at the relevance of each theory. In summary, there is no single theory that satisfactorily explains the MOA of ECT in various psychiatric illnesses. The need for properly designed, ethically sound pre-clinical and clinical studies is highlighted (German J Psychiatry 2005; 8: 70-84).*

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## Introduction

Since the inception of therapeutic convulsions induced chemically by Meduna in 1934 and electrically by Cerletti and Bini in 1938, electroconvulsive therapy (ECT) has established its usefulness as a rapidly acting treatment for schizophrenia and bipolar disorders among others. Yet its use has remained controversial. On the one hand it is rejected because it is widely perceived as intrinsically invasive and coercive. On the other hand there is a lack of understanding of its mechanism of action (MOA).

Despite early recognition of generalised seizure activity as the essential therapeutic component, the exact MOA has remained elusive. An indirect testimony to our ignorance on this subject is the numerous theories proposed by various researchers; way back in 1948 one researcher counted up to

50 theories (Gordon, 1948). The theories on MOA of ECT that have been proposed over the years have spanned a wide variety of mechanisms: psychological, neurophysiological, neurochemical, neuroendocrine, and neuropeptides.

The utility of a theory for the mechanism of action of any treatment intervention cannot be overstated. A hypothetical understanding that generates researchable questions can be used towards refining a treatment as well as contributing to knowledge of the conditions for which efficacy exists. Hence this review was planned to try to discuss the current understanding of each of these theories.

*Data search methodology:* The data search strategies for this review included electronic databases as well as hand-search of relevant publications or cross-references. The electronic search included PUBMED and other search engines (e.g. PsychINFO etc.). Cross-searches of electronic and hand-search key references often yielded other relevant material. The search terms used, in various combinations, were: con-

vulsive, electroconvulsive, treatment, mechanism of action, psychology, physiology, neurochemistry, neurotransmitters.

*Data review methodology:* The research/data inclusion for this review was dictated by the following principles. Some of the ECT literature has a historical/heuristic value and may not be making any direct contribution to our understanding of the MOA of ECT. Most research from the earlier eras - pre-/immediate post world war II - was flawed by today's standards of research methodology, yet it gave enough insights on which the modern research is based. Even in the modern times the research methods are constantly refining and evolving so that using a fixed methodological standard would leave one with a very tiny fraction of the total data base as eligible for inclusion in a methodologically sound review. Hence, we were deliberately over-inclusive and liberal in our approach and did not stick to any standardised methodology for data inclusion. Rather we tried to include as much research as possible to cover as many aspects of the research on the MOA of ECT. Wherever applicable the strengths and the limitations of the research being cited were discussed alongside the description of the research.

## Psychological Theories

These were the earliest theories to explain the MOA of ECT emerging in the context of the then dominant psychological explanation of the mental illness and its treatment. These psychological theories can be divided into psychoanalytic and non-psychoanalytic.

### *Psychoanalytic Theories*

The three common psychoanalytic theories are Fear, Regression and Punishment theories. The *fear theory* postulated that the fear of ECT was the effective agent. The *regression theory* postulated that ECT induced regression to infantile behaviour was therapeutic. The *punishment theory* regarded ECT as a punishment in which the patients handed themselves over to a strict but forgiving and just parent figure, who meted out punishment and allowed atonement. These theories lost ground with the introduction of muscle relaxant and anaesthetic 'modified' ECT and the demonstration of superior efficacy of 'real' vs 'sham' ECT (Miller, 1967).

### *Non-Psychoanalytic Theories*

The non-psychoanalytic psychological theories of MOA of ECT assumed that as a treatment inducing a fairly permanent behaviour change ECT must be correlated with changes in the central nervous system (CNS); these included the theories of brain damage and amnesia.

### *The Brain Damage Theory*

The brain damage theory was based on the findings that responses on Rorschach's test were similar in subjects after ECT or diffuse brain damage (Summerskill et al., 1952). But the 'damage' did not explain the behavioural change and the neuropathologic animal studies, e.g. cell counts in highest-risk regions, failed to find evidence of brain damage with seizures induced under conditions similar to the standard

clinical practice (Weiner, 1984; Dam & Dam, 1986; Meldrum, 1986). The neuronal loss in primates occurred only after 1.5-5.0 hours of continuous seizure activity, and was delayed further with adequate muscle paralysis and oxygenation (Ingvars, 1986). The reported association between ECT and lateral ventricular enlargement or cortical atrophy (Menken et al., 1979; Dolan et al., 1985; Kolbeinsson et al., 1986; Kendell & Pratt, 1983) was found to be based on retrospective studies with selection bias. Also, the pre- and post- ECT evaluation of the patients demonstrated no brain structure changes in 2-3 days (Coffey et al., 1989), or by MRI in 1 week (Pande et al., 1990). A review of brain-structure research using various radio-imaging techniques (animal electroconvulsive stimulation (ECS) and human autopsy studies/case reports) concluded that the evidence for structural brain damage due to ECT was grossly inadequate (Devanand et al., 1995).

### *The Amnesic Theory*

The theories implicating ECT induced amnesia for its beneficial effects, found that the amnesia was usually greatest for the immediate pre-treatment experiences. Thus the psychotic experiences, being recent, were more likely to be affected than the more normal experiences from the distant past (Stainbrook, 1946). Technical advancements like unilateral ECT and pulsed stimuli (which reduce amnesia but not the therapeutic effect) and the lack of correlation between the degree of amnesia and therapeutic efficacy further refuted the amnesia theory (Lawson et al., 1990).

The advancements in neurophysiology in particular were shifting the balance in favour of the physiological experiments and theories to explain the MOA of ECT.

## Neurophysiological theories

ECT induces many physiological changes. Various theories that explain the MOA of ECT on the basis of these changes are: Anticonvulsant, Antidelirium and Neurogenesis theories.

Anticonvulsant theory is based on the following evidence from the ECT/Seizure disorders: over the ECT-course seizure threshold increases and seizure duration decreases, inhibitory processes manifest in ictal and immediate postictal period, cerebral blood flow (CBF) and glucose metabolism rate show a topographically distributed reduction, slow-wave (delta) activity in EEG increases and persists, intractable seizure disorder and status epilepticus patients show anticonvulsant effect, and the increased transmission of inhibitory neurotransmitters and neuropeptides (Sackeim et al., 1983; Sackeim, 1994; Sackeim, 1999; Post et al., 1986; Post, 1990).

*Seizure Threshold:* Over a course of ECTs seizure threshold increases markedly (Kalinowsky & Kennedy 1943; Green, 1960; Sackeim et al., 1986, 1987b, 1991, 1993), averaging 40-100% (Sackeim et al., 1987b, 1993; Coffey et al., 1995b; Shapira et al., 1996); the magnitude being associated with clinical response (Sackeim et al., 1987a & 1993), a faster response in depression (Yatham et al., 1989; Roemer et al.,

1990) and mania (Mukherjee, 1989). Studies failing to show a positive correlation between threshold increase and clinical outcome have been criticised for methodological flaws (Coffey et al., 1995a; Shapira et al., 1996).

The post-ECT increase in seizure threshold has been attributed to GABA and opioid transmission alteration (Issac et al., 1986; Green & Nutt 1987; Kragh et al., 1994). Subconvulsive ECS did not alter the threshold for GABA-antagonist pentylenetetrazol induced seizures and the ECS raised the threshold for GABAergic transmission antagonistic bicuculline, pentylenetetrazol and isopropylbicyclopentylphosphate (Green et al., 1982). The conclusion is that ECT enhances GABAergic transmission that contributes to the threshold increase or that the antagonism of GABAergic transmission is a key mechanism for ECT induced seizures.

In animals the ECS increases the concentration of endogenous opioids and the density of specific opioid receptor subtypes (Holaday et al., 1986; Tortella & Long 1988; Tortella et al., 1989) and repeated ECT and long term morphine exposure show cross sensitisation. Intraventricular transfer of CSF from ECS treated cats to naïve cats led to increase in threshold for flurothyl-induced seizure in recipient cats (Issac & Swanger, 1983) and naloxone pretreatment of the recipient animals blocked this effect (Tortella & Long, 1985). The implication is that ECS release endogenous anticonvulsant substance/s with opioid like properties.

Despite conflicting reports regarding the magnitude of the ECT induced seizure threshold increase and short term outcome, the evidence favouring the anticonvulsant property of ECT remains.

*Seizure Duration:* Decrease in seizure duration over the ECT course (Sackeim et al., 1986 & 1987c; Shapira et al., 1996), seizure duration being largely independent of efficacy (Sackeim et al., 1987c, 1991, 1993; Nobler et al., 1993; Abrams, 1997; Kales et al., 1997; Folkerts, 1996) and increase in seizure threshold (Sackeim et al., 1986) are well known facts. The neurobiological substrates implicated in dissociation between seizure threshold and duration include caffeine (McCall et al., 1993; Fochtmann, 1994). Benzodiazepines (Krueger et al., 1993) prolong and decrease ECT induced seizures respectively but have no impact on seizure threshold; compared to barely suprathreshold, markedly suprathreshold dosage shortens the seizure duration (Sackeim et al., 1991). Thus the anticonvulsant process involved in the progressive reduction in seizure duration is distinct from that involved in the threshold increase and, the reduction in seizure duration may not be associated with therapeutic response.

*Expression of Seizure and Inhibitory Processes:* The inhibitory process that results in seizure termination begins during the ictus. The classic spike and wave pattern dominates the clonic phase. Excitatory input opens channels on apical dendrites for  $Ca^{++}$  entry. When this transient depolarisation is highly synchronised, the summated change in membrane events in a neuronal population produces a negative spike in the EEG. This is followed by prolonged hyperpolarization (slow wave), caused by  $K^+$  currents and forward feed and backward inhibition induced  $Cl^-$  current at the soma, which in turn produce a slow negative wave in the EEG (Engel,

1989). As the seizure progresses, spike activity is often lost and the amplitude and duration of slow waves increases. Seizures characterised by robust slow delta activity are particularly likely to be followed by bi-electric suppression. In the light of the anticonvulsant hypothesis Sackeim (1999) postulated that therapeutic effects are obtained more likely by seizures with earlier onset, higher amplitude and lower frequency of slow wave activity, and are followed by postictal suppression.

Various studies have found that RUL ECT close to seizure threshold results in delayed onset of slow-wave activity, reduced slow-wave amplitude, and reduced possibility of postictal suppression, and hence it is ineffective (Nobler et al., 1993; Krystal et al., 1993 and 1995; McCall et al., 1996). This assumption is strongly supported by the demonstration of association of postictal bioelectric suppression and superior therapeutic effects (Nobler et al., 1993; Krystal et al., 1996; Suppes et al., 1996). There is also evidence that higher amplitude slow wave delta activity is associated with superior therapeutic effects (Nobler et al., 1993; Folkerts, 1996; Krystal et al., 1996). These markers of the inhibitory processes that terminate seizure are linked to efficacy, providing additional support to anticonvulsant theory.

*Cerebral Blood Flow (CBF) and Cerebral Metabolic Rate (CMR):* Except for one study with opposite results (Bonne et al., 1996), the research reports that with ECS as well as ECT (in both depressed and manic patients, and independent of electrode placement or stimulus intensity conditions) the CBF and CMR are reduced globally but more in anterior frontal regions and in immediate postictal period; this reduction continues for weeks to months and is associated with superior clinical outcome (Engel et al., 1982, Rosenberg et al., 1988; Volkow et al., 1988; Guze et al., 1991; Duncan et al., 1993; Sestoff et al., 1993; Nobler et al., 1994). The changes in seizure threshold and global CBF are shown to be significantly associated (Nobler et al., 1994), indicating a co-variation between the two anticonvulsant effects and providing additional support to anticonvulsant theory. That such changes are not due to anaesthesia has been well established (Silfverskiold et al., 1986).

*Increased Slow-Wave EEG Activity:* A marked increase in slow wave activity in inter-ictal period may last for weeks to months after completion of an ECT-course (Weiner et al., 1986; Sackeim et al., 1996). These slow waves reflect the firing of GABAergic interneurons inhibiting pyramidal cells, or the summation of long-duration after-hyperpolarizations due to  $K^+$  currents in deep cortical pyramidal cells, or both (Schwindt et al., 1989). EEG slowing and clinical outcome with ECT show both a positive (Abrams et al., 1987) and no association (Abrams et al., 1992; Johnson et al., 1960). Sackeim et al. (1996) and Krystal et al. (1997) reported that the form of ECT with weakest antidepressant effects [low dose right unilateral (RUL) ECT weaker than high dose RUL ECT] was also the weakest in increasing slow wave activity during and after the ECT course, independent of electrode placement and stimulus intensity, and that greater delta activity in a brain area principally involving anterior and prefrontal regions was linked to a positive clinical outcome. These findings suggest that diminished functional activity in spe-

cific brain region/s may be a key neurophysiological change that subserves the therapeutic response.

*EEG Coherence:* In comparison to normal control subjects depressed patients were found to have the anterior inter-hemispheric EEG coherence that was lower and was associated with a better therapeutic response, suggesting the possibility that pathophysiologic disruption of the coupling between the frontal lobes may be involved in the lack of response to ECT which could be secondary to subcortical white matter disease (Roemer et al., 1991). While Coffey et al. (1989) confirmed this in radiological study of their patients receiving ECT, Leuchter et al. (1997) reported the presence of subcortical white matter lesions on MRI was associated with significant decrease in EEG coherence. Leuchter et al. (1997) also suggested the association between such changes and diminished antidepressant response to ECT and medication. These findings point to the anticonvulsant and antidepressant effects of ECT as correlational, may be involving diminished functional activity in a specific brain region.

*Antidelirium/Sleep Theory:* This is based on the findings that ECT leads to EEG changes (delta activity - increased amplitude and reduced frequency), similar to those seen in normal sleep and correlated with clinical improvement. Charlton (1999) hypothesised that all functional psychoses i.e. schizophrenia, depression and mania are early stages of delirium and by the time they are considered for ECT the patients often have had several months of altered sleep amounting to chronic sleep deprivation which is the common underlying cause of psychic and physical arousal or withdrawal. The generalised seizure in ECT works by its effect on arousal, probably by inducing physiologically natural and deep restorative sleep. Charlton (1999) argued that ECT is specifically effective only in patients with advanced disorder manifest by features of delirium (retardation, hallucinations, and delusions). However his theory is challenged by the fact that all functional psychoses are to be diagnosed in the absence of clouded consciousness or disorientation, and that the correlation between EEG slowing and therapeutic response is not consistent (Weiner et al., 1986; Malaspina et al., 1994) and some studies have shown sleep deprivation to be an effective antidepressant (Wu & Bunney, 1990).

*Increased Neurogenesis:* The hippocampal formation is the site for continuous neurogenesis during adult life in animals and humans (Eriksson et al., 1998; Gloud et al., 1998). ECT exerts a strong influence on diencephalic limbic structures, the biochemistry of which is disturbed in major depression. In animals extended seizures increase hippocampal neurogenesis (in association with neuronal damage) which shows maximal proliferation at 3-5 days after a single ECS, and is associated with central seizure rather than the motor activity (Benzon et al., 1997; Parent et al., 1998; Madsen et al., 2000).

It was assumed that clinical depression may be a result of stress that leads to degeneration and decreased proliferation; the ECT may reverse this imbalance by stimulating neuronal proliferation. Human studies have found decreased hippocampal volume after recurrent major depression (Shah et al., 1998; Sheline et al., 1999). Increased glucocorticoids have

been reported with hippocampal atrophy and damage in animals and in patients with depression (Young et al., 1991).

*Neurochemical Theories:* The catecholamine and indoleamine hypotheses of depression (Schildkraut, 1965; Coppen et al., 1963) have failed to generate a universally acceptable biochemical theory of depression or antidepressant effect. They postulate a deficiency of serotonin, norepinephrine (NE) or dopamine transmission in key brain regions. This may involve a neurotransmitter, a receptor complex or a failure in signal transduction distal to the receptor complex. There is evidence of serotonin transmission reduction in acute depression which persists after recovery. The CSF MHPG and plasma catecholamine excess has been reported suggesting noradrenergic overactivity, which however may reflect peripheral sympathetic and not necessarily the CNS activity. Neuroendocrine challenge studies of NE receptor function have been inconclusive. Studies of lymphocyte  $\beta$ -adenergic function indicate blunted signal transduction. The CSF and neuroendocrine studies also shows evidence of impaired dopaminergic transmission in depressed patients.

The recent research on ECT emphasises the effects on the regulation and function of the central neurotransmitters. The research, mostly animal ECS trials, has not explained how ECT actually works in patients. Most studies on ECT assume the centrality of neurochemical release without any evidence for quantitative correlation between the neurochemical and clinical change. Results from various animal studies are discrepant and the few consistently replicable results in animals have not generalised to humans.

*Serotonin:* Stimulation of presynaptic 5HT<sub>1a</sub> somatodendritic and 5HT<sub>1d</sub> terminal autoreceptors and blockade of 5HT<sub>2a</sub>, 5HT<sub>2c</sub> and 5HT<sub>3</sub> postsynaptic receptors, both lead to production of depressive symptoms. Also, stimulation of  $\alpha_2$  and  $\alpha_1$  'heteroreceptors' on serotonin neurons, reduces and enhances serotonin release respectively (Stahl, 2000). Long term ECS and 5HT<sub>1a</sub> agonist 8 OH-DPAT do not induce any change in basal firing of dorsal raphe neurons, cortex and hippocampus (Blier & Bouchard 1992; Gur et al., 1997). However, long-term ECS reduces 8 OH-DPAT induced hypothermia in both mice and rat (Goodwin et al., 1985, 1987; Stockmeier et al., 1992; Blier & Bouchard 1992) and lead to upregulation of 5 HT<sub>1a</sub> autoreceptors in dentate gyrus (Hayakawa et al., 1994) indicating that the effect of ECS on presynaptic 5 HT<sub>1a</sub> autoreceptors is inconclusive. Compared to control subjects, medication free depressed patients show a significantly blunted response to 5 HT<sub>1a</sub> receptors agonist ipsapirone. Treatment with ECT leads to an insignificant increase in the degree of ipsapirone induced hypothermia (Gur et al., 1997). Other studies reporting similar findings in depressed patients indicated that the response was further reduced after the treatment with amitriptyline (Lesch et al., 1990) and fluoxetine (Lerer et al., 1997). ECT led to decreased urinary 5HIAA (Linnoila et al., 1984a); but both unchanged (Linnoila et al., 1984b) or increased (Hoffman et al., 1996 ) plasma 5HIAA and unchanged CSF 5HIAA (Nordin et al., 1971, Abram et al., 1976, Hoffman et al., 1985; Rodorfer et al., 1991). Thus, ECS and ECT do not cause significant increase in 5HT levels but studies with antidepressants indicate that increased serotonin release is associated with therapeutic response. With long term ECS

some studies reported an increase in 5HT<sub>1a</sub> receptor sensitivity in hippocampus (deMontigny, 1984; Chaput et al., 1991; Mongeau et al., 1994), increased receptor binding in cortex (Nowak & Dulinski, 1991) and hippocampus (Hayakawa et al., 1993), while other studies have reported no change in 5HT<sub>1a</sub> postreceptor binding in the hippocampus and a decrease in cortex (Pandey et al., 1991; Stockmeier et al., 1992). Studies with ECT have shown contradictory prolactin response (Shapira et al., 1992; Mann, 1998); no relation between response to ECT and pre-treatment responsiveness of serotonergic system (Mann, 1998) and no effect of tryptophan depletion (Cassidy et al., 1998). Findings with antidepressants have shown decrease in postsynaptic 5HT<sub>1a</sub> receptor activity (Sleight et al., 1988). Thus findings of ECS and antidepressant drugs are contradictory, whereas findings from depressed patient are in line with those from antidepressant drugs.

ECS has been shown to upregulate and increase 5HT<sub>2a</sub> receptors (Kellar et al., 1985; Vetulani et al., 1981, Green et al., 1983, Burnet et al., 1995) localised in superficial layers of frontal cortex, septum and CA1 region of hippocampus in male rats only (Biegon & Israeli 1987); increase 5HT<sub>2a</sub> mRNA levels (Butler et al., 1993; Burnet et al., 1995); and enhance behavioural and functional responsiveness to a variety of serotonergic agents (Grahaeme Smith et al., 1978; Pandey et al., 1979; Vetulani et al., 1981; Lerer & Belmaker, 1982). Findings show increase in 5HT<sub>2a</sub> receptor number in cortex in suicide victims (Stanley & Mann 1983; Mann et al., 1986; Arango et al 1990; Arora & Meltzer 1989b, Yates et al., 1990) and on platelets of depressed patients including those with attempted suicide (Biegon & Israeli, 1986; Beigon et al, 1990b; Arora & Meltzer 1989a, Pandey et al., 1990, 1995; Hrdina et al., 1997). Antidepressant treatment causes decrease in 5HT<sub>2a</sub> receptor number to the level in patients who show clinical improvement (Biegon et al., 1990a), no significant change in prolactin response (Mann, 1998), and enhanced prolactin response to fenfluramine after antidepressant treatment (Shapira et al., 1989, 1992) and tryptophan (Cowen et al., 1986; Price et al., 1989). Also, tryptophan depletion causes reversal of response to SSRI (Cassidy et al., 1998) and treatment response to antidepressant is dependent on pre-treatment responsiveness of serotonergic system (Mann, 1998). However, ECT studies show increased 5HT<sub>2a</sub> platelet receptors (Stain Malmgren et al., 1998) and increased platelet transporter sites (Maj et al., 1988; Langer et al., 1986). Thus, findings from ECS and ECT are on similar lines, but are contradictory to those from the antidepressant drugs.

*Norepinephrine (NE):* The findings on effects of ECT on NE brain function can be discussed under the headings of pre-synaptic, beta receptor and alpha receptors. ECS studies have shown increase in synthesis and utilisation of NE in rodent brain (Kety et al., 1967; Modigh, 1976), enhanced activity of tyrosine hydroxylase (Musacchio et al., 1969; Kapur et al., 1993), increased affinity constant and V<sub>max</sub> of NE uptake (Minchin et al., 1983), decreased uptake and increased release (Ebstein et al., 1983) and unchanged release (Minchin et al., 1983) of NE from synaptosomal preparation – thus, most studies indicate an increase in synaptic NE levels. The effect of antidepressant drugs on tyrosine hydroxylase has been inconclusive. Studies of ECT have re-

ported no change (Slade & Checkley, 1980) or a decreased GH response to clonidine (Ballidin et al., 1992; Lerer & Sitarum 1983), the latter being similar to that seen in depressed patients and indicating no increase in norepinephrine levels and not supporting the evidence provided by the ECS studies.

In ECS studies  $\beta$ -receptors have shown decrease in receptor number in cerebral cortex (Pandey et al., 1979; Bergstrom & Keller 1979) and hippocampus (Stanford & Nutt 1982; Kellar & Bergstrom 1983; Biegon & Israeli 1986); decreased responsiveness to NE of the  $\beta$ -receptor linked cAMP system (Vetulani et al., 1976); and attenuation of stress induced rise in c-fos and NGF-1A mRNA in rat prefrontal cortex (Morinbu et al., 1995). This evidence has been countered to show that there is no significant change in  $\beta$ -receptor number following ECS in the presence of 5HT (Paul et al., 1991). Such studies have been faulted for using non-specific ligands which bind to both 5HT and  $\beta$ -receptors. Animal studies with antidepressants have shown decreased number of  $\beta$ -receptor and uncoupling of receptors from their second messenger system in response to antidepressant drugs (Vetulani & Sulser, 1975). Human studies with ECT have shown varying results i.e. no significant change in number of lymphocyte  $\beta$ -receptor in depressed patients after ECT (Cooper et al., 1985) and increased responsiveness of  $\beta$ -receptors on lymphocyte (Mann et al., 1990).

The postmortem studies show increase in number of  $\beta$ -receptor in postmortem brain tissues of suicide victims (Crow et al., 1984; Mann et al., 1986; DePaermentier et al., 1990) and human studies show down-regulation of  $\beta$ -receptor in response to antidepressant treatment.

Decreased responsiveness of somatodendritic  $\alpha_2$  receptors to the inhibitory effects of I.V. clonidine (Tepper et al., 1982), decrease in number of  $\alpha_2$  adrenoceptor number (Pilk & Vetulani, 1982) and desensitisation of  $\alpha_2$  receptors (Thomas et al., 1992) have been shown after repeated ECS. Human finding show decreased number of  $\alpha_2$  platelet receptor after long term ECT (Smith et al., 1983). Postmortem brain studies of suicide victims and studies of platelet  $\alpha_2$  adrenoceptor number in depressed patients show that  $\alpha_2$  receptor are upregulated and increased in depression (Halaris & Piletz, 1990), a finding probably reversed by treatment with antidepressants (Siever et al., 1992).

There is an increase in  $\alpha_1$  receptor number in the cortex and hippocampus after ECS. (Vetulani et al., 1983) and similar effect has been seen with various antidepressant drugs (Vetulani & Antkiewicz-Michaluk, 1985). Antidepressant and human studies have shown decrease in  $\alpha_1$  receptor number in prefrontal cortex in suicide victims, providing an indirect evidence that opposite action of treatment may have antidepressant action (Halaris & Piletz, 1990; Siever et al., 1992).

From the above discussion it can be concluded that there are similar effects on  $\alpha_1$  and  $\alpha_2$  receptors seen with ECS, ECT, and antidepressant drugs while the effect on synaptic availability of NE and on  $\beta$  receptors is inconclusive.

*Dopamine (DA):* ECS leads to increased synthesis and turnover of DA (Yoshida et al., 1997) and increase in DA medi-

ated behaviour (Berrios & Canagasabay, 1990). In depressed patients some studies have found decrease in CSF HVA levels (Post et al., 1973), ECT studies have shown no significant/lasting change in urinary HVA (Linnoila et al., 1983), plasma HVA (Linnoila et al., 1984b; Devanand et al., 1989) or CSF HVA (Cooper & King, 1982); increase in CSF HVA (Rudofers et al., 1991); increased (Costain et al., 1982) or no significant change in GH response (Balldin et al., 1980; Slade & Checkely 1980; Christie et al., 1982); increased (Balldin et al., 1980) or no significant change in prolactin response (Christie et al., 1982); and increased DA mediated behaviour i.e. eye blink rate (Berrios & Conagasabay, 1990).

ECS studies have found no change in brain DA and synthesis of DA (Evans et al., 1976; Modigh, 1976); increase in DA synthesis with single ECS (Engel et al., 1968); subsensitive presynaptic receptor (Serra et al., 1981); no change in presynaptic autoreceptor (MacNeil & Gower, 1982, Welch et al., 1982); and increased basal dopamine and increased HVA suggesting increased synthesis and turnover (Yoshida et al., 1997). Also, post synaptic findings have shown enhanced dopamine mediated behaviour after ECS (Grahame Smith et al., 1978; Modigh et al., 1984); which is dependent on intact noradrenergic but not serotonergic innervation (Green & Deakin 1980a, 1980b); increase in the level of dopamine in striatum after an electrically induced seizure, but not with chemically induced seizure (McGarvey et al., 1993); unaltered D<sub>1</sub> receptor binding (Cheetham et al., 1995); transient increase in mRNA of D<sub>1</sub> and D<sub>2</sub> receptors in nucleus accumbens (Smith et al., 1995); and increase in mRNA of tryptophan hydroxylase and neuropeptide Y in the locus ceruleus but no change in substantia nigra (Kapur et al., 1993). It can be concluded that ECT and ECS findings are inconclusive, but there is some evidence of increased dopamine in the synapse.

Finally studies of ECT induced biogenic amine changes support the hypothesis that antidepressant drugs operate via different mechanisms. This may explain why ECT is effective in some patients refractory to pharmacotherapy.

**GABA:** Paul et al. (1993 & 1994) showed long lasting reduction of glutamatergic activity after chronic treatment with all classes of antidepressant and ECS, but not with non-antidepressant drugs and postulated that antidepressants work on glutamatergic neurons through activation of GABA interneurons. Petty et al. (1992) showed decrease in GABA serum levels in patients with major depression, indirectly suggesting low levels in brain. Other studies have implicated hyperactivation of NMDA receptor as the final common pathway (Stone, 1993; Skolnick et al., 1992). Devanand et al. (1995) found higher mean GABA levels in ECT responders compared to non-responders. Other evidences in favour of the increased GABAergic theory are: increase in glutamic acid decarboxylase, the GABA synthetic enzyme after repeated ECS, enhanced GABAergic function after repeated ECS (Nutt et al., 1981), augmentation of GABA receptor after ECS (Gray & Green, 1987), and increased TRH levels in ECS treated animals. TRH is implicated to inhibit glutamatergic transmission and may inhibit epileptogenic excitation and mediate the antidepressant effect of generalised seizures (Knoblauch & Kobek 1994).

**Glutamate:** The increase in brain derived neurotrophic factor (BDNF) expression is possibly mediated via activation of glutamate receptor subtypes (Metsis et al., 1993; Naylor et al., 1996). Glutamate receptor expression is also reported to be increased by long term ECS, and this could contribute to the long lasting or enhanced induction of BDNF (Naylor et al., 1996).

## Intracellular Mechanisms

The failure of monoamine neurotransmitter system to explain the delayed action of ECS and antidepressant drugs led to studies of signal transduction pathways and analysis of target genes in their action. This generated a novel hypothesis that the pathophysiology and treatment of depression may result from alteration in the expression and function of neurotrophic factors. As the most abundant and most studied neurotrophic factor in brain BDNF influences development, survival and synaptic function of mature neurons (Lindsay et al., 1994; Thoenen, 1995). Action of BDNF is mediated through Tyrosine Kinase-B (Blenis, 1993) and regulates other protein and MPA kinase pathway.

Both short term and long term studies have shown ECS to regulate expression of BDNF (Lindfors et al., 1995; Nibuya et al., 1995a), most prominently in the dentate gyrus granular cell layer of the hippocampus (Nibuya et al., 1995a). Similar findings reported with long term antidepressant drugs, indicate this as a common action of antidepressant treatment (Nibuya et al., 1995b & 1996). This increase in BDNF expression was possibly mediated via activation of glutamate receptor subtypes which could be blocked by NMDA and AMPA receptor antagonists and the expression of BDNF was negatively regulated by activation of GABAergic receptors (Metsis et al., 1993). Other studies have demonstrated that BDNF expression is regulated by specific serotonin and norepinephrine receptors (Zafra et al., 1992, Vaidya et al., 1997), suggesting a possible role for these neurotransmitter systems in ECS induction of BDNF. Taken together, the results indicate that BDNF expression is dependent on the activity of the neurotransmitters and regulated by the major stimulatory and inhibitory neurotransmitter system.

## Neuroendocrine Evidence

Abrams & Taylor (1976) and Fink & Nemeroff (1989) proposed that ECT works by correcting a dysregulation of neuropeptides through diencephalic stimulation. They quoted evidence as: enhanced production and release of several neuropeptides some of which have demonstrated transient antidepressant effects (e.g. TRH); vegetative and neuroendocrine dysregulation - characteristics of depression and mediated by centrocephalic structures - are improved by ECT; and increased Blood Brain Barrier permeability as seen with ECT - increases distribution of neuropeptides through at the

CNS. But later studies have shown most of the observed changes could be accounted for by the non-specific effect of stress or the seizure and are not the therapeutic effect of ECT. These studies have reported increase in levels of prolactin, corticotropin, cortisol, oxytocin, vasopressin, beta endorphin and, less consistently, the growth hormone. The current consensus seems to be that increase in prolactin release is not correlated with that of plasma HVA, suggesting the rise to be independent of dopamine metabolism; ECT induced prolactin release and clinical improvement are not correlated (Deakin et al., 1983; Scott et al 1986; Whalley et al., 1982) - the prolactin release is greater with bilateral than unilateral ECT and with high dose than the low dose stimulation, but there is direct evidence that ECT induced prolactin surge and clinical improvement in depression is correlated (Lisanby et al., 1998).

## Melatonin

There is no consensus on the effect of major depression on melatonin. Rubin (1992) reported higher day time melatonin levels in depressed patients compared to controls, others have found reduced nocturnal peak levels of melatonin (Beck-Friis et al, 1985; Claustrat, 1984), while Thompson et al (1988) found no significant difference between depressed patients and control group. ECS studies have shown post ECS blunting of  $\beta 1$  receptors and decreased pineal gland activity (Monteleone et al, 1993 & 1995). Krahn et al. (2000) showed pre-ECT higher than expected day night ratios of melatonin and post-ECT decrease in melatonin levels in depressed patients. Thus findings from depressed patients are inconclusive. Decreased melatonin level being associated with clinical response to ECT does not mean that it reflects the mechanism of action.

## Neuropeptides

It is hypothesised that major treatment modalities in psychiatry i.e. ECT, antipsychotics, antidepressants and lithium exert their effects at least in part by modulating CNS neuropeptides. Due to co-localisation, there is co-release of neuropeptides and monoamines (e.g. Neuropeptide Y (NPY) with noradrenaline and dopamine, neurotensin and somatostatin with dopamine).

Studies have shown decreased NPY in rat brain in animal models of depression and no effect or decreased NPY after treatment with antidepressants (Widdowson et al, 1992) and decreased somatostatin in rat brain (Kakigi et al., 1992). Alteration in the levels of various neuropeptides in depressed patients and in response to treatment have been reported but the findings are inconclusive. ECS studies are not in consonance with the animal model of depression and antidepressants and single ECS have been shown to have no effect on any neuropeptide. However, repeated ECS effects various neuropeptides i.e. NPY increases in hippocampus and frontal and occipital cortex (Wahlestedt et. al., 1990; Mathe, 1999), somatostatin increases in frontal cortex (Orzi

et al., 1990; Mathe, 1999), and the largest increase in neuropeptide and neurokinin is in hippocampus (Mathe, 1999). Repeated ECS does not affect neurotensin, VIP or galanin concentration when compared with sham ECS treated rats. Other ECS studies have shown increased neuropeptide-Y mRNA and somatostatin expression in selected brain structure after repeated ECS (Zachrisson et al., 1995; Mikkelsen et al., 1994; Passarelli & Orzi, 1993). Human ECT studies are in line with ECS studies showing significant post ECT increase in levels of somatostatin, endothelin and NPY (Mathe et al., 1999). Thus, there is some evidence of alteration in the levels of various neuropeptides in depressed patients and in response to treatment.

## Methodological Issues

Most of the research on the mechanism of action of ECT has one or more of the following limitations: small sample size; inappropriate statistical analysis; frequent citing of the results as 'trends', 'tendencies', and 'near significant', which in turn are cited as 'facts' by other investigators; lack of untreated or sham-treated control groups; the peripheral measurements used for central neurotransmitters have lot of confounding factors (e.g. diagnostic heterogeneity, concurrent drug administration, effects of peripheral neurotransmitter production and metabolism, uncontrolled motor activity etc.) and spinal fluid studies not accounting for active transport of metabolites into the CSF and the effect of motor activity and body position at the time of tap). The ethical dilemma posed by the sham or no treatment limits ECT research in humans.

## Future directions

The evidence linking the anticonvulsant and antidepressant effects is correlational. The objective of identifying the MOA or the therapeutic component of ECT demands the evolution of the experimental models of the ECT to continue unhindered. The refinements in the methodology must involve both the technique and the technology. One area of focus could be the electric energy and its application in terms of the nature/type of the current and its application in terms of the duration and location and nature of the electrodes. The other area of focus could be the physiological parameters like electro-, neuro-, and bio- chemical markers which may be discerned as central or peripheral, direct or indirect, immediate or delayed, short or long lasting and therapeutic or non-therapeutic in the context of the MOA of ECT. Experiments are needed that would augment or block the anticonvulsant properties of ECT and to determine effects on efficacy. The host of findings reported with ECS and ECT need to be replicated demonstrating the differentiation between those effects that are primary and those which are secondary and, discerning which of these changes are truly therapeutic. In terms of the effect we need to answer the question as to what is treated by the ECT – psychosis or depression or a common element to the two conditions; and

what explains the effectiveness of the ECT in delirium. Also, the undesirable or side effects of the ECT need to be experimentally documented and their amelioration through appropriate approaches established. Lastly, as yet there is no simple answer to the an ethical dilemma of using control groups in the form of sham ECT or no treatment.

## Conclusion

Although well established as safe and effective, some basic questions about ECT remain unanswered. What is the necessary and/or sufficient therapeutic component - the generalised seizure or the postictal slow-wave state? What is the effective seizure - only a generalised/grandmal or a circumscribed one limited to one set of neurons/region? If the latter is true, seizures with specific localisation (e.g., the limbic structures or ventral striatum or frontal cortex) might be sufficiently therapeutic, while seizures in other locations (e.g. motor, parietal or occipital cortex) might constitute unwanted action/side effects. Which of the myriad post-ECT biochemical alterations in the CNS and periphery, individually or in combination, reflect the therapeutic effect. And lastly, why and how does ECT alleviate signs and symptoms of both schizophrenia and major depression; surprisingly this issue appears to have drawn only a limited scientific attention and there is a paucity of published studies focusing on biochemical/molecular effects of ECT in psychosis.

## References

- Abrams R, Taylor MA, Volavka J. ECT-induced EEG asymmetry and therapeutic response in melancholia: relation to treatment electrode placement. *Am J Psychiatry*, 1987; 144: 327-329.
- Abrams R, Taylor MA. Diencephalic stimulation and the effects of ECT in endogenous depression. *Br J Psychiatry*. 1976; 129: 482-5.
- Abrams R, Volavka J, Schrift M. Brief pulse ECT in melancholia: EEG and clinical effects. *J Nerv Ment Dis*, 1992; 180: 55-57.
- Abrams R. *Electroconvulsive Therapy*, New York: Oxford University, 1997.
- Arango V, Ernberger P, Marzuk PM, Chen J-S, Tierney H, Stanley M, Reis D.J, Mann J.J. Autoradiographic demonstration of increased 5-HT-2 and B-adrenergic receptor binding sites in the brain of suicide victims. *Arch Gen Psychiatry*, 1990; 47:1038-1047.
- Arora RC & Meltzer HY. Increased serotonin receptor binding as measured by H-LSD in the blood platelets of depressed patients. *Life Sci*, 1989a; 44: 725-734.
- Arora RC & Meltzer HY. Serotonergic measures in the brains of suicide victims : 5-HT-2 binding sites in the frontal cortex of suicide victims and control subjects. *Am J Psychiatry*, 1989b; 146: 730-736.
- Bajc M, Medved V, Basic M, Topuzovie N, Babic D, Ivancevic D. Acute effect on electroconvulsive therapy on brain perfusion assessed by hexamethylpropyleneamineoxime and single photon emission computed tomography. *Acta Psychiatr Scand*, 1989; 80:421-426.
- Balldin J, Berggren U, Lindstedt G, Modigh K. Neuroendocrine evidence for decreased function of alpha-2 adrenergic receptor after electroconvulsive therapy. *Psychiatr Res*, 1992; 41:257-65.
- Balldin J, Bolle P, Eden S, Eriksson E, Modigh K. Effects of electroconvulsive treatment on growth hormone secretion induced by monoamine receptor agonists in reserpine-pretreated rats. *Psychoneuroendocrinology*, 1980; 5: 329-337.
- Beck-Friis J, Ljunggren J-G, Thoren M, Von Rosen D, Kjellman BF, Wetterberg L. Melatonin cortisol and ACTH in patients with major depressive disorder and healthy humans with special reference to the outcome of dexamethasone suppression tests. *Psychoneuroendocrinology*, 1985; 10:173-86.
- Bengzon J, Kokaia Z, Elmer E, Nanobashvili A, Kokaia M, Lindvall O. Apoptosis and proliferation of dentate gyrus neurons after single and intermittent limbic seizures. *Proc Natl Acad Scin USA* , 1997; 94: 10432-10437.
- Bergstrom DA & Kellar KJ. Effect of electroconvulsive shock on monoaminergic receptor binding sites in rat brain. *Nature*, 1979; 278: 464-466.
- Berrios GE & Canagasabay AFB. Depression eye blink rate, psychomotor retardation, and electroconvulsive therapy-enhanced dopamine receptor sensitivity. *Convulsive Ther* , 1990; 6: 224-30.
- Biegon A & Israeli M. Localization of the effects of electroconvulsive shock on B-adrenoceptors in the rat brain. *Eur J Pharmacol* , 1986; 123:329-334.
- Biegon A & Israeli M. Quantitative autoradiographic analysis of the effects of electroconvulsive shock on serotonin-2 receptors in male and female rats. *J Neurochem*, 1987; 48:1386-1391.
- Biegon A, Essar N, Israeli M, Elizur A, Bruch S, Bar-Nathan AA. Serotonin 5 HT-2 receptor binding on blood platelets as a state dependent marker in major affective disorder. *Psychopharmacology*, 1990a; 102: 73-75.
- Biegon A, Grinspoon A, Blumenfelt B, Bleich A, Apter A, Mester R. Increased serotonin 5 HT-2 receptor binding on blood platelets of suicidal men. *Psychopharmacology*, 1990b; 100: 165-167.
- Blenis J. Signal transduction via the MAP kinases: proceed at your risk. *Proc Natl Acad Sci USA*, 1993 ; 90:5889-5892.
- Blier P & Bouchard C. Effect of repeated electroconvulsive shocks on serotonergic neurons. *Eur J Pharmacol*, 1992 ; 211:365-373
- Bonne O, Krausz Y, Shapira B, Bocher M, Karger H, Gorfine M, Chistin R, Lerer B. Increased cerebral blood flow in depressed patients responding to electroconvulsive therapy. *J Nucl Med*, 1996; 37: 1075-1080.
- Burnet PWJ, Mead A, Eastwood SL, Lacey K, Harrison PJ, Sharp T. Repeated ECS differentially affects brain 5-HT IA 2A receptor expression. *Neuroreport*, 1995; 6: 901-904.

- Butler MO, Morinobu S, Duman RS. Chronic electroconvulsive seizures increase the expression of serotonin-2-receptor mRNA in rat frontal cortex. *J Neurochem*, 1993; 61: 1270-1276.
- Cassidy F, Murry E, Carroll BJ. Tryptophan depletion in recently manic patients treated with lithium. *Biol Psychiatry*, 1998; 43: 230-232.
- Chaput Y, de Montigny C, Blier P. Presynaptic and postsynaptic modifications of the serotonin system by long-term administration of antidepressant treatments: an in vivo electrophysiological study in the rat. *Neuropsychopharmacology*, 1991; 5: 219-220.
- Charlton BG. The antidelirium theory of electroconvulsive therapy action. *Medical Hypothesis*, 1999; 52: 609-611.
- Cheetham SC, Kettle CJ, Martin KF, Heal DJ. D1 receptor binding in rat striatum: modification by various D1 and D2 antagonists, but not by sibutramine hydrochloride, antidepressants or treatments which enhance central dopaminergic function. *J. Neural Transm*, 1995; 102: 35-46.
- Christie JE, Whalley LJ, Bronwn NS, Dick H. Effect of ECT on the neuroendocrine response to apomorphine in severely depressed patients. *Br J Psychiatry*, 1982; 140: 268-273.
- Claustrat B, Chazot G, Brun J, Jordan D, Sassolas G. A chronobiological study of melatonin and cortisol secretion in depressed subject: plasma melatonin, a biochemical marker in major depressive. *Biol Psychiatry*, 1984; 19: 1215-1228.
- Coffey CE, Lucke J, Weiner RD, Krystal AD, Aque M. Seizure threshold in electro-convulsive therapy: I. Initial seizure threshold. *Biol Psychiatry*, 1995a; 37:713-720.
- Coffey CE, Figiel GS, Djang WT, Cress M, Saunders WB, Weiner RD. Subcortical White matter hyperintensity on magnetic resonance imaging: clinical and neuro-anatomical correlates in depressed elderly. *J Neuro-psychiatry*, 1989; 1: 135-144.
- Coffey CE, Lucke J, Weiner RD, Krystal AD, Aque M. Seizure threshold in electroconvulsive therapy: II. The anticonvulsant effect of ECT. *Biol Psychiatry*, 1995b; 37:777-788.
- Cooper SJ & King DJ. ECT and dopaminergic transmission. *Lancet*, 1982; 2: 710
- Cooper SJ, Kelley JG, King DJ. Adrenergic receptors in depression. Effects of electroconvulsive therapy. *Br J Psychiatry*, 1985; 147: 23-29.
- Coppen A, Shaw DM, Farrell JP. Potentiation of the antidepressive effect of a monoamine-oxidase inhibitor by tryptophan. *Lancet*, 1963; 1:90-91.
- Costain DW, Gelder MG, Cowen PJ, Grahame-Smith DG. Electroconvulsive therapy and the brain: evidence for increased dopamine-mediated responses. *Lancet*, 1982; 2: 400-404.
- Cowen PJ, Geaney DP, Schachter M, Green AR, Elliott JM. Desipramine treatment in normal subjects; effects on neuroendocrine responses to tryptophan and on platelet serotonin 5-HT related receptors. *Arch Gen Psychiatry*, 1986; 43:61-67.
- Crow T, Cross A, Cooper S, Deakin J, Terrier I, Johnson J, Joseph M, Owen F, Poulter M, Lofthouse R, Corsellis J, Chambers D, Blessed G, Perry E, Perry R, and Tomlinson B. Neurotransmitter receptors and monoamine metabolites in the brains of patients with Alzheimer-type dementia and depression, and suicide. *Neuropsychopharmacology*, 1984; 23: 1561-1569.
- Dam AM & Dam M. Quantitative neuropathology in electrically induced generalised convulsions. *Convulsive Ther*, 1986; 462: 194-206.
- de Montigny C. Electroconvulsive shock treatments enhance responsiveness of forebrain neurons to serotonin. *J Pharmacol Exp Ther*, 1984; 238: 230-234.
- Deakin JWF, Ferrier IN, Crow TJ, Johnstone EC, Lawler P. Effects of ECT on pituitary hormone release: relationship to seizure, clinical variables, and outcome. *British Journal of Psychiatry*, 1983; 46: 331-335.
- DePaermentier F, Chetham SC, Crompton MR, Katona CL, Horton RW. Brain beta-adrenoceptor binding sites in antidepressant-free depressed suicide victims. *Brain Res*, 1990; 525: 71-77.
- Devanand DP, Bwers MB Jr, Hoffman FJ Jr, Sackeim HA. Acute and subacute effects of ECT on plasma HVA, MHPG, and prolactin. *Biol Psychiatry*, 1989; 26: 408-412.
- Devanand DP, Shapira B, Petty F, Kramer G, Fitzsimons L, Lerer B, Sackeim HA. Effects of electroconvulsive therapy on plasma GABA. *Convulsive Ther*, 1995; 11: 3-13.
- Dolan RJ, Calloway SP, Mann AH. cerebral ventricular size in depressed subjects. *Psychol Med*, 1985; 15:873-878.
- Duncan R, Patterson J, Roberts R, Hadley D.M, Bone I. Ictal/postictal SPECT in the pre-surgical localisation of complex partial seizures. *J Neurol Neurosurg Psychiatry*, 1993; 56:141-148.
- Ebstein RP, Lerer B, Shlaufman M, Belmaker RH. The effect of repeated electroshock treatment and chronic lithium feeding on the release of norepinephrine from rat cortical vesicular preparation. *Cell. Mol. Neurobiol*, 1983; 3:191-201.
- Engel J, Hanson LCF, Roos BE., Strombergsson LE. Effect of electroconvulsive shock on dopamine metabolism in rat brain. *Psychopharmacologia*, 1968; 13:140-144.
- Engel JJ, Kuhl DE, Phelps ME. Patterns of human local cerebral glucose metabolism during epileptic seizures. *Science*, 1982; 218: 64-66.
- Engel JJ. Seizures and epilepsy. Philadelphia, FA Davis. 1989.
- Eriksson PS, Perfilova E, Bjork-Eriksson T. Neurogenesis in the adult human hippocampus. *Nat Med*, 1998; 4: 1313-1317.
- Evans JPM, Grahame-Smith DG, Green AR, Tordof AFC. Electroconvulsive shock increases the behavioural responses of rats of brain 5-hydroxytryptophan stimulation and central nervous system stimulant drugs. *Br J Pharmacol*, 1976; 56: 193-199.
- Fink M & Nemeroff CB. A Neuroendocrine View of ECT. *Convuls Ther*. 1989; 5(3):296-304.
- Fochtmann LJ. Animal studies of electroconvulsive therapy: foundations for future research. *Psychopharmacol Bull*, 1994; 30:321-444.
- Folkerts H. The ictal electroencephalogram as a marker for the efficacy of electroconvulsive therapy. *Eur Arch Psychiatry Clin Neurosci*, 1996; 246:155-64.

- Gloud E, Beylin A, Tanapat P. Learning enhances adult neurogenesis in the hippocampal formation. *Nat. Neurosci*, 1998; 2: 260-265.
- Goodwin GM, de Souza RJ, Green AR. Attenuation by electroconvulsive shock and antidepressant drugs of the 5-HT<sub>1A</sub> receptor-mediated hypothermia and serotonin syndrome produced by 8-OH-DPAT in the rat. *Psychopharmacology*, 1987; 91:500-505.
- Goodwin GM, de Souza J, Green AR. Presynaptic serotonin receptor-mediated response in mice attenuated by antidepressant drugs and electroconvulsive shock. *Nature*, 1985; 317: 531-533.
- Gordon H.L. Fifty shock therapy theories. *Milit Surg*, 1948;103: 397-401.
- Grahame-Smith DG, Green AR, Costain DW. Mechanism of the antidepressant action of electroconvulsive therapy. *Lancet*, 1978; 1: 245-256.
- Gray JA, Green AR. Increased GABA receptor function in mouse frontal cortex after repeated administration of antidepressant drugs or electroconvulsive shocks. *Br J Pharmacol*, 1987; 92:357-62.
- Green A, Nutt D, Cowen P. Increased seizure threshold following convulsion. In: Sandler M. ed. *Psychopharmacology of anticonvulsants*. Oxford: Oxford University Press, 1982, pp16-26.
- Green A, Nutt D. Psychopharmacology of repeated seizures: possible relevance to the mechanisms of action of electroconvulsive therapy. In: L Iversen, S Iversen, S Snyder, eds. *Handbook of Psychopharmacology*, Vol.19, New York, Plenum Press, 1987, pp 375-419.
- Green AR & Deakin JWF. Deletion of brain noradrenaline prevents electroconvulsive shock induced enhancement of 5-hydroxytryptamine and dopamine mediated behaviour. *Nature*, 1980a; 285:232-233.
- Green AR, Costain DW, Deakin JWF. Enhanced of 5-hydroxytryptamine and dopamine mediated behavioural responses following convulsions. III. The effect of monoamine and agonist and synthesis inhibition on the ability of electroshock to enhance responses. *Neuropharmacology*, 1980b; 19: 907-914.
- Green AR, Johnson P, Nimgaonkar VL. Increased 5-HT<sub>2</sub> receptor number in brain as probable explanation for the enhanced 5-hydroxytryptamine-mediated behaviour following repeated electroconvulsive shock administration to rats. *Br J Pharmacol*, 1983; 80: 173-177.
- Green MA. Relation between threshold and duration of seizures and electrographic change during convulsive therapy. *J Nerv Ment Dis*, 1960,131: 117-20.
- Gur E, Lerer B, Newman ME. Chronic electroconvulsive shock and 5-HT autoreceptor activity in rat brain: an in vivo microdialysis study. *J Neural Transm*, 1997; 104:795-804.
- Guze BH, Baxter LRJ, Schwartz JM, Szuba MP, Liston EH. Electroconvulsive therapy and brain glucose metabolism. *Convulsive Ther*, 1991; 7:15-19.
- Halaris A & Piletz J. Platelet adrenoceptor binding as a marker in neuropsychiatric disorders. Abstracts 17th CINP Congress 28. 1990.
- Hayakawa H, Shimizu M, Nishida A, Motohashi N, Yamawaka S. Increase in serotonin 1A receptor in the dentate gyrus as revealed by autoradiographic analysis following repeated electroconvulsive shock but not imipramine treatment. *Neuropsychobiology*, 1994;30: 53-56.
- Hayakawa H, Yokota N, Shimizu M, Nishida A, Yamawaka S. Repeated treatment with electroconvulsive shock increases number of serotonin 1A receptors in the rat hippocampus. *Biogenic Amines*, 1993; 9:295-306.
- Hoffman G, Linkowski P, Kerkhofs M, Desmedt D, Mendlewicz J. Effects of ECT on sleep and CSF biogenic amines in affective illness. *Psychiatr Res*, 1985, 16: 199-206.
- Hoffmann G, Linkowski P, Kerkhofs M, Desmedt D, Schmid R, Wieselmann G. 5-Hydroxy-indolacetic acid serum levels in depressive patients and ECT. *J Psychiatr Res*, 1996;30: 209-215.
- Holiday JW, Tortella FC, Meyerhoff JL, Belenky GL, Hitzemann RJ. Electroconvulsive shock activates endogenous opioid systems: behavioural and biochemical correlates. *Ann N Y Acad Sci*, 1986; 462:249-255.
- Hrdina PD, Bakish D, Ravindran A, Chudzick J, Cavazzoni P, Lappierre YD. Platelet serotonergic indices in major depression: up-regulation of 5-HT<sub>2A</sub> receptors unchanged by antidepressant treatment. *Psychiatr Res*, 1997; 66:73-85.
- Ingvars M. Cerebral flow and metabolic rate during seizures: relationship to epileptic brain damage. *Ann N Y Acad Sci*, 1986; 462:207-223.
- Issac L, & Swanger J. Alteration of electroconvulsive threshold by cerebrospinal fluid from cats tolerant to electroconvulsive shock. *Life Sci*, 1983;33:230-234.
- Issac L, Schoenbeck R, Bacher J, Skolnick P, Paul SM. Electroconvulsive shock increases endogenous monoamine oxidase inhibitor activity in brain and cerebrospinal fluid. *Neurosci Lett*, 1986; 66:252-262.
- Johnson LC, Ulett GA, Sines JO, Stern JA. Cortical activity and cognitive functioning. *Electroencephalogr Clin Neurophysiol*, 1960;12:861-874.
- Kakigi T & Maeda K. Effect of serotonergic agents on regional concentrations of somatostatin- and neuropeptide Y-like immunoreactivities in rat brain. *Brain Res*. 1992 ;599(1):45-50.
- Kales H, Raz J, Tandon R, Maixner D, DeQuwrd J, Miller A, Becks L. Relationship of seizure duration to antidepressant efficacy in electroconvulsive therapy. *Psychol Med*, 1997; 27: 1373-80.
- Kalinowsky L.B, Kennedy F. Observation in electroshock therapy applied to problems in epilepsy. *J Nerv Ment Dis*, 1943; 98:56-67.
- Kapur S, Austin MC, Underwood MD, Arango V, Mann JJ. Electroconvulsive shock increases tyrosine hydroxylase and neuropeptide-Y gene expression in the locus coeruleus. *Mol Brain Res*, 1993, 18: 121-126.
- Kellar KJ, Stockmeier CA, Gomez JM. Regulation of serotonin neurotransmission by antidepressant drugs and electroconvulsive shock: the fall and rise of serotonin receptors. *Acta Pharmacol*, 1985; (Suppl 56): 138-145.
- Keller KJ, Bergstrom DA. Electroconvulsive shock: effects on biochemical correlates of neurotransmitter receptors in rat brain. *Neuropharmacology*, 1983; 22:401-406.

- Kendell B, & Pratt RTC. Brain damage and ECT. *Br J Psychiatry*, 1983; 143:99-100.
- Kety SS, Javoy F, Thierry AM, Julou L, Glowinski J. A sustained effect of electro-convulsive shock on the turnover of norepinephrine in the central nervous system of rat. *Proc. Nat. Acad. Sc. USA*, 1967; 58: 1249-1254
- Knoblich SM. & Kubek MJ. Changes in thyrotropin-releasing hormone levels in hippocampal subregions induced by a model of human temporal lobe epilepsy: effect of partial and complete kindling. *Neuroscience*, 1994;76: 97-104.
- Kolbeinson H, Arnaldsson OS, Petrusson H, Shulason S. Computed tomographic scans in ECT a patients. *Acta Psychiatr Scand*, 1986; 73:28-32.
- Kragh J, Tonder N, Finsen BR, Zimmer J, Bolwig TG. Repeated electroconvulsive shock cause transient changes in rat hippocampal somatostatin and neuropeptide Y immunoreactivity and mRNA in situ hybridisation signals. *Exp Brain Res*, 1994; 98: 305-313.
- Krahn LE, Gleber E, Rummans TA, Pileggi T S, Lucas DL, Li H. The effect of electroconvulsive therapy on melatonin. *J ECT*, 2000; 16: 391-398.
- Krueger RB, Fama JM, Devanand DP, Prudic J, Sackeim HA. Does ECT permanently alter seizure threshold? *Biol Psychiatry*, 1993, 33:272-276.
- Krystal AD, Coffey CE, Weiner RD, Rapp PE, Albino A, Greenside HS, DeMasi M, Cellucci C. EEG correlates of the response to ECT. *Biol Psychiatry*, 1997; 41: 568.
- Krystal AD, Weiner RD, Coffey CE. The ictal EEG as a marker of adequate stimulus intensity with unilateral ECT. *J Neuropsychiatry Clin Neurosci*, 1995;7:295-303.
- Krystal AD, Weiner RD, McCall WV, Shelp FE, Arias R, Smith P. The effect of ECT stimulus dose and electrode placement on the ictal electroencephalogram: an intra-individual crossover study. *Biol Psychiatry*, 1993; 34:759-767.
- Krystal AD, Greenside HS, Weiner RD, Gassert D. A comparison of EEG signal dynamics in waking, after anesthesia induction and during electroconvulsive therapy seizures. *Electroencephalogr Clin Neurophysiol*. 1996 Aug;99(2):129-40.
- Langer SZ, Sechter D, Loo H, Raisman R, Zarifian E. Electroconvulsive shock therapy and maximum binding of platelet titrated imipramine binding in depression. *Arch Gen Psychiatry*, 1986; 43: 949-952.
- Lawson JS, Inglis J, Delva NJ, et al. Electrode placement in ECT: cognitive effects. *Psychol Med*, 1990; 20: 335-344.
- Lerer B, Gelfin Y, Gorfine M, Gelfin Y, Gorfine M. Temperature and hormone responses of normal subjects to ipsapirone challenge: effect of fluoxetine treatment. *Psychoneuroendocrinology*, 1997; 22: S166.
- Lerer B. & Belmaker RH. Receptors and the mechanism of action of ECT. *Biol Psychiatry*, 1982; 17:497-511.
- Lerer B. & Sitaram N. Clinical strategies for evaluating ECT mechanisms: Pharmacological, biochemical, and psychophysiological approaches. *Prog. Neuropsychopharmacol. Biol Psychiatry*, 1983; 7: 309-333.
- Lesch KP, Disselkamp-Tietze J, Schmidtke A. 5-HT-1a receptor function in depression: effect of chronic Amitriptyline treatment. *J Neural Transm*, 1990; 80: 157-161.
- Leuchter AF, Cook IA, Uijdehaage SH, Dunkin J, Lufkin RB, Anderson-Hanley C, Abrams M, Rosenberg-Thompson S, O'Hara R, Simon SL, Osato S, Babaie A. Brain structure and function and the outcomes of treatment for depression. *J Clin Psychiatry*, 1997; 58 (Suppl 16): 22-31.
- Lindfors N, Brodin E, Metsis M. Spatiotemporal selective effects on brain-derived neurotrophic factor and TrkB messenger RNA in rat hippocampus by electroconvulsive shock. *Neuroscience*, 1995; 65:661-70.
- Lindsay RM, Wiegand SJ, Anthony Altar C.A, Di Stefano PS. Neurotrophic factors: from molecule to man. *TINS*, 1994;17:182-90.
- Linnoila M, Karoum F, Potter WZ. Effects of antidepressant treatments on dopamine turnover in depressed patients. *Arch Gen Psychiatry*, 1983; 40: 1015-1017.
- Linnoila M, Litovitz G, Scheinin M, Chang M-D, Cutler NR. Effects of electroconvulsive treatment on monoamine metabolites, growth hormone, and prolactin in plasma. *Biol Psychiatry*, 1984a;19: 79-84.
- Linnoila M, Miller TL, Bartko H, Potter WZ. Five antidepressant treatments in depressed patients. Effects on urinary serotonin and 5-hydroxyindoleacetic acid output. *Arch Gen Psychiatry*, 1984b; 41: 688-692.
- Lisanby SH, Devanand DP, Prudic J, Pierson D, Nobler MS, Fitzsimons L, Sackeim HA. Prolactin response to electroconvulsive therapy: effect of electrode placement and stimulus dosage. *Biol Psychiatry*, 1998; 43: 146-155.
- MacNeil A & Gower M. Do antidepressants induce dopamine autoreceptor subsensitivity? *Nature*, 1982; 298:302.
- Madsen TM, Treschow A, Bengzon J, Bolwig TG, Lindvall O, Tingstrom A. Increased Neurogenesis in a model of electroconvulsive therapy. *Biol Psychiatry*, 2000;47:1043-1049.
- Maj M, Mastrorardi P, Cerrera A, Romano M, Mazzarella B, Kemali D. Changes in platelet 3H-imipramine binding in depressed patients receiving electroconvulsive therapy. *Biol Psychiatry*, 1988; 24: 469-472.
- Malaspina D, Devanand DP, Krueger RB, Prudic J, Sackeim HA. The significance of clinical EEG abnormalities in depressed patients treated with ECT. *Convulsive Ther*, 1994;10: 259-266.
- Mann JJ, Mahler JC, Wilner PJ, et al. Normalisation of blunted lymphocyte  $\beta$ -adrenergic responsiveness in melancholic inpatients by a course of electroconvulsive therapy. *Arch Gen Psychiatry*, 1990; 47: 461-464.
- Mann JJ, Stanley M, McBride PA, McEwen BS. Increased serotonin and beta adrenergic receptor binding in the frontal cortices of suicide victims. *Arch Gen Psychiatry*, 1986; 43: 945-959.
- Mann JJ. Neurobiological correlates of the antidepressant action of electroconvulsive therapy. *J ECT*, 1998; 14: 172-180.
- Mathe AA. Neuropeptides and electroconvulsive treatment. *J ECT*. 1999 Mar;15(1):60-75.
- McCall WV, Reid S, Rosenquist P, Foreman A, Kiesow-Webb N. A reappraisal of the role of caffeine in ECT. *Am J Psychiatry*, 1993; 150: 1543-1545.

- McCall WV, Robinette GD, Hardesty D. Relationship of seizure morphology to the convulsive threshold. *Convulsive Ther*, 1996; 12:147-151.
- McGarvey KA, Zis AP, Brown EE, Nomikos GG, Fibiger HC. ECS-induced dopamine release: effects of electrode placement, anticonvulsant treatment, and stimulus intensity. *Biol Psychiatry*, 1993; 34: 152-157.
- Meldrum BS. Neuropathological consequences of chemically and electrically induced seizures. *Ann N Y Acad Sci*, 1986; 462:186-193.
- Menken M, Safer J, Goldfarb C, Varga E. Multiple ECT: morphological effects. *Am J Psychiatry*, 1979; 136: 453.
- Metsis M, Timmusk T, Arenas E, Persson H. Differential usage of multiple brain-derived neurotrophic factor promoters in the rat brain following neuronal activation. *Proc Natl Acad Sci USA*, 1993; 90:8802-8806.
- Mikkelsen JD, Woldbye D, Kragh J, Larsen PJ, Bolwig TG. Electroconvulsive shocks increase the expression of neuropeptide Y (NPY) mRNA in the piriform cortex and the dentate gyrus. *Brain Res Mol Brain Res*. 1994;23(4):317-22.
- Miller E. Psychological theories of ECT: A Review. *Br J Psychiatry*, 1967; 113: 301-311.
- Minchin MCW, Williams J, Bowdler JM, Green AR. The effect of electroconvulsive shock on the uptake and release of noradrenaline and 5-hydroxytryptamine in rat brain slices. *J. Neurochem*, 1983; 40: 765-768.
- Modigh K, Balldin J, Eriksson E, Granerus A. K, Walinder J. In : B. Lerer, R.D. Weiner, R.H. Belmaker (Eds) *ECT: Basic Mechanisms*, London., John Libbey, 1984. pp 18-27.
- Modigh K. Long term effects of electroconvulsive shock therapy on synthesis, turnover and uptake of brain monoamines. *Psychopharmacology*, 1976; 49: 179-185.
- Mongeau R, de Montigny C, Blier P. Effects of long term alpha 2 adrenergic antagonists and electroconvulsive treatments on the alpha 2 adrenoceptors modulating serotonergic neurotransmission. *J Pharmacol Exp Ther*, 1994; 269: 1152
- Monteleone P, D'Istria M, De Luca B, Serino I, Maj M, Kemali D. Pineal response to isoproterenol in rats chronically treated with electroconvulsive shock. *Brain Res Bull*, 1993; 31:257-259.
- Monteleone P, Steardo L, D'Istria M, Serino I, Maj M. Effects of single and repeated electroconvulsive shock on isoproterenol-stimulated pineal N-acetyltransferase activity and melatonin production in rats. *Pharmacol Biochem Behav*, 1995; 50:241-4.
- Morinbu S, Nibuya M, Duman RS. Chronic antidepressant treatment down regulates the induction of c-fos mRNA in response to acute stress in rat frontal cortex. *Neuropsychopharmacology*, 1995; 12: 221-228.
- Mukherjee S. Mechanisms of the antimanic effect of electroconvulsive therapy. *Convulsive Ther*, 1989; 5: 227-243.
- Musacchio JM, Julou L, Ketty SS, Glowinski J. Increase in rat brain tyrosine hydroxylase activity produced by electroconvulsive shock. *Proc Natl Acad Sci USA*, 1969; 63:1117-1119.
- Naylor P, Stewart CA, Wright SR, Pearson RC, Reid IC. Repeated ECS induces GluR1 mRNA but not NMDAR1A-G mRNA in the rat hippocampus. *Brain Res Mol Brain Res*, 1996; 351-2:349-53.
- Nibuya M, Morinobu S, Duman RS. Regulation of BDNF and TrkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments. *J Neurosci*, 1995a; 15:7539-47.
- Nibuya M, Nestler EJ, Duman RS. Chronic antidepressant administration increases the expression of cAMP response element binding protein (CREB) in rat hippocampus. *J Neurosci*. 1996 Apr 1; 16(7):2365-72.
- Nibuya M, Nestler EJ, Duman RS. Chronic antidepressant administration increases the expression of cAMP response element binding protein CREB in rat hippocampus. *J Neurosci*, 1995b; 16: 2365-2372.
- Nobler MS, Sackeim HA, Prohovnik I, Moeller JR, Mukherjee S, Schnur DB, Prudic J, Devanand DP. Regional cerebral blood flow in mood disorders. III. Treatment and clinical response. *Arch Gen Psychiatry*, 1994; 51:884-897.
- Nobler MS, Sackeim HA, Solomou M, Luber B, Devanand DP, Prudic J. EEG manifestations during ECT: effects of electrode placement and stimulus intensity. *Biol Psychiatry*, 1993; 34:321-330.
- Nordin G, Ottosson J-O, Roos B-E. Influence of convulsive therapy on 5-hydroxyindoleacetic acid and homovanillic acid cerebrospinal fluid in endogenous depression. *Psychopharmacology Berlin*, 1971; 20: 320.
- Nowak G & Dulinski J. Effect of repeated treatment with electroconvulsive shock ECS on serotonin receptor density and turnover in the rat cortex. *Pharmacol Biochem Behav*, 1991; 38: 691-694.
- Nutt DJ, Cowen PJ, Green AR. Studies on the post-ictal rise in seizure threshold. *Eur J Pharmacol*. 1981; 71(2-3):287-95.
- Orzi F, Zoli M, Passarelli F, Ferraguti F, Fieschi C, Agnati LF. Repeated electroconvulsive shock increases glial fibrillary acidic protein, ornithine decarboxylase, somatostatin and cholecystokinin immunoreactivities in the hippocampal formation of the rat. *Brain Res*. 1990; 533(2):223-31.
- Pande AC, Grunhaus L, Aisen AM, Haskett RF. A preliminary MRI study of ECT-treated depressed patients. *Biol Psychiatry*, 1990; 27:102-104.
- Pandey GN, Heinze WJ, Brown BD, Davis JM. Electroconvulsive shock treatment decreases beta-adrenergic receptor sensitivity in rat brain. *Nature*, 1979; 280:234-235.
- Pandey GN, Pandey SC, Dwivedi Y, Sharma RP, Janicak PG, Davis JM. Platelet serotonin 2a receptors a potential biological marker for suicidal behaviour. *Am J Pharmacol*, 1995; 152: 850-855.
- Pandey GN, Pandey SC, Janicak PG, Marks RC, Davis JM. Platelet serotonin-2 binding sites in depression and suicide. *Biol Psychiatry*, 1990; 28:215-222.
- Pandey SC, Issac L, Davis JM, Pandey GN. Similar effect of treatment with Desipramine and electroconvulsive shock on 5-hydroxytryptamine 1A receptors in rat brain. *Eur J Pharmacol*, 1991; 202:221-225.
- Parent JM, Janumpalli S, McNamara JO, Lowenstein DH. Increased dentate granule cell neurogenesis following

- amygdala kindling in the adult rat. *Neurosci Lett*, 1998 ; 247: 9-12.
- Passarelli F & Orzi F. Somatostatin mRNA in the hippocampal formation following electroconvulsive shock in the rat. *Neurosci Lett.*, 1993;153(2):197-201.
- Paul IA, Duncan GE, Mueller RA, Hong J-S, Breese GR. Neural adaptation in response to chronic imipramine and electroconvulsive shock: evidence for separate mechanisms. *Eur J Pharmacol*, 1991; 205:135-143.
- Paul IA, Layer RT, Skolnick P, Nowak G. Adaptation of the NMDA receptor in rat cortex following chronic electroconvulsive shock or imipramine. *Eur J Pharmacol* , 1993; 247: 305-11.
- Paul IA, Nowak G, Layer RT, Popik P, Skolnick P. Adaptation of the N-methyl-D-aspartate receptor complex following chronic antidepressant treatments. *J Pharmacol Exp Ther* , 1994; 269,95-102.
- Petty F, Kramer GL, Gullion CM, Rush AJ. Low plasma GABA levels in male patients with depression. *Biol Psychiatry* , 1992; 32: 354-63.
- Pilc A. & Vetulani J. Depression by chronic electroconvulsive treatment of clonidine hypothermia and 3H-clonidine binding to rat cortical membranes. *Eur J Pharmacol* , 1982; 80: 109-113.
- Post RM, Kotin J, Goodwin FK, Gordon E. Psychomotor activity and cerebrospinal fluid metabolites in affective illness. *Am J Psychiatry*, 1973; 130: 67-72.
- Post RM, Putnam F, Uhde TW, Weiss SR. Electroconvulsive therapy as an anticonvulsant: implications for its mechanism of action in affective illness. *Ann N Y Acad Sci*, 1986; 462:376-88.
- Post RM. ECT : the anticonvulsant connection [see comments]. *Neuropsychopharmacology*, 1990;3:89-92.
- Price LH, Charney DS, Delgado PL, Anderson GM, Heninger GR. Effects of Desipramine and fluvoxamine: a microdialysis study. *Arch Gen Psychiatry*, 1989; 46:625-631.
- Roemer RA, Dubin WR, Jaffe R, Lipschutz L, Sharon D. An efficacy study of single – versus double-seizure induction with ECT in major depression. *J Clin Psychiatry*, 1990; 51:473-478.
- Roemer RA, Shagass C, Dubin W, Jaffe R, Katz R. Relationship between pretreatment electroencephalographic coherence measures and subsequent response to electroconvulsive therapy, *Neuropsychobiology*, 1991; 24:121-124.
- Rosenberg R, Vorstrup S, Anderson A, Bolwig TG. Effects of ECT on cerebral blood flow in melancholia assessed with SPECT. *Convulsive Ther*, 1988; 4: 62-73.
- Rubin RT, Heist EK, McGeoy SS, Hanada K, Lesser IM. Neuroendocrine aspects of primary endogenous depression. XI. Serum melatonin measures in patients and matched control subjects. *Arch Gen Psychiatry*, 1992 ;49:558-67.
- Rudorfer MV, Risby ED, Osman OT, Gold PW, Potter WZ. Hypothalamic-pituitary-adrenal axis and monoamine transmitter activity in depression: a pilot study of central and peripheral effects of electroconvulsive therapy. *Biol Psychiatry*, 1991; 29: 253-64.
- Sackeim HA, Luber B, Katzman GP, Moeller JR, Prudic J, Devanand DP, Nobler MS. The effects of electroconvulsive therapy on quantitative electroencephalogram: relationship to clinical outcome. *Arch Gen Psychiatry*, 1996;53:814-824.
- Sackeim HA, Decina P, Kanzler M, Kerr B, Malitz S. Effects of electrode placement on the efficacy of titrated, low dose ECT. *Am J Psychiatry*, 1987a; 144: 1449-1455.
- Sackeim HA, Decina P, Prohovnik I, Malitz S, Resor SR. Anticonvulsant and antidepressant properties of electroconvulsive therapy : a proposed mechanism of action. *Biol Psychiatry*, 1983; 18:1301-1310.
- Sackeim HA, Decina P, Prohovnik I, Malitz S. Seizure threshold in electroconvulsive therapy: effect of sex, age, electrode placement, and number of treatments. *Arch Gen Psychiatry*, 1987b; 44:355-360
- Sackeim HA, Decina P, Prohovnik I, Portnoy S, Kanzler M, Malitz S. Dosage, seizure threshold and the antidepressant efficacy of electroconvulsive therapy. *Ann N Y Acad Sci*, 1986;462:398-410.
- Sackeim HA, Decina P, Portnoy S, Neeley P, Malitz S. Studies of dosage seizure threshold, and seizure duration in ECT. *Biol Psychiatry*, 1987c; 22: 249-268.
- Sackeim HA, Devanand DP, Prudic J. Stimulus intensity seizure threshold and seizure duration: impact on the efficacy and safety of electroconvulsive therapy. *Psychiatr Clin North Am*, 1991; 14:803-43.
- Sackeim HA, Prudic J, Devanand DP, Kiersky JE, Fitzsimons L, Moody BJ, McElhiney MC, Coleman EA, Settembriono JM. Effects of stimulus intensity and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy, *New Eng J Med*, 1993; 61:233-44.
- Sackeim HA. Central issues regarding the mechanisms of action of electroconvulsive therapy: directions for future research. *Psychopharmacol Bull*, 1994;30:281-308.
- Sackeim HA. The anticonvulsant hypothesis of the mechanism of action of ECT: Current status. *J ECT*, 1999;15:5-26
- Schildkraut JJ. The catecholamine hypothesis of affective disorders: a review of supporting evidence. *Am J Psychiatry*, 1965, 122:509-522.
- Schwindt PC, Spain WJ, Crill WE. Long lasting reduction of excitability by a sodium dependent potassium current in cat neocortical neurons. *J Neurophysiology*, 1989;61:233-244.
- Scott AI, Whalley LJ, Bennie J, Bowler G. Oestrogen-stimulated neurophysin and outcome after electroconvulsive therapy. *Lancet*. 1986 Jun 21;1(8495):1411-4.
- Serra G, Argiolas A, Fadda F, Melis MR, Gessa GL. Repeated electroconvulsive shock prevents the sedative effect of small doses of apomorphine. *Psychopharmacology*, 1981; 73: 194-196.
- Sestoft D, Meden P, Hemmingsen R, Hancke B, Madsen PL, Freberg L. Disparity in regional cerebral blood flow during electrically induced seizure. *Acta Psychiatr Scand*, 1993; 88:140-143.
- Shah PJ, Ebmeier KP, Glabus MF, Goodwin GM. Cortical grey matter reductions associated with treatment – resistant chronic unipolar depression. Controlled magnetic resonance imaging study. *Br J Psychiatry*, 1998; 172: 527-532.

- Shapira B, Lerer B, Kindler S, Lichtenberg P, Gropp C, Cooper T, Calev A. Enhanced serotonergic responsiveness following electroconvulsive therapy in patients with major depression. *Br J Psychiatry*, 1992; 160:223-229.
- Shapira B, Lidsky D, Gorfine M, Lerer B. Electroconvulsive therapy and resistant depression: clinical implications of seizure threshold. *J Clin Psychiatry*, 1996; 57: 32-38.
- Shapira B, Reiss A, Kaiser N, Kindler S, Lerer B. Effect of imipramine treatment on the prolactin response to fenfluramine and placebo challenge in depressed patients. *J Affect Disord*, 1989;16:1-4.
- Sheline YI, Sanghavi M, Mintun MA, Gado MH. Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. *J Neurosci*, 1999; 19: 5034-5043.
- Siever LJ, Trestman RL, Coccaro E, Bernstein D, Gabriel SM, Owen K, Moran M, Lawrence T, Rosenthal J, Horvath TB. The growth hormone response to clonidine in acute and remitted depressed male patients. *Neuropsychopharmacology*, 1992; 6: 165-177.
- Silfverskiold P, Gustafson L, Risberg J, Rosen I. Acute and late effects of electroconvulsive therapy: clinical outcome, regional cerebral blood flow, and electroencephalogram. *Ann N Y Acad Sci*, 1986; 462:236-48.
- Skolinick P, Miller R, Young A, Boje K, Trullas R. Chronic treatment with L-aminocyclopropanecarboxylic acid desensitizes behavioural responses to compounds acting at the NMDA receptor complex. *Psychopharmacology*, 1992; 107: 489-96.
- Slade AP & Checkley SA. A neuroendocrine study of the mechanism of action of ECT. *Br J Psychiatry*, 1980; 137: 217-221.
- Sleight AJ, Marsden CA, Palfreyman MG, Mir AK, Lovenberg. Chronic MAO A and MAO B inhibition decreases the 5 HT<sub>1A</sub> receptor mediated inhibition of forskolin-stimulated adenylate cyclase. *Eur J Pharmacol*, 1988; 154:255-261.
- Smith MA, Makino S, Kvetnansky R, Post RM. Stress alters the expression of brain derived neurotrophic factor and neurotrophin-3 mRNA in the hippocampus. *J Neurosci*, 1995; 15: 1768-1777.
- Smith CB, Hollingworth PJ, Garcia-Sevilla JA, Zis AP. Platelet alpha<sub>2</sub> adrenoceptors are decreased in number after antidepressant therapy. *Prog. Neuropsychopharmacol Biol Psychiatry*, 1983; 7: 241-247.
- Stahl MS. *Essential Psychopharmacology. Neuroscientific basis and practical application.* Cambridge university press, 2nd edition, 2000.
- Stainbrook E. Shock therapy : psychological theory and research. *Psychol Bull*, 1946 ; 43:21-60.
- Stain-Malmgren R, Tham A, Aberg-Wistedt A. Increased platelet 5-HT<sub>2</sub> receptor binding after electroconvulsive therapy in depression. *J ECT*, 1998; 14:15-24.
- Standford SC & Nutt DJ. Comparison of the effects of repeated electroconvulsive shock on alpha 2 and beta adrenoceptors in different regions of rat brain. *Neuroscience*, 1982;7:1753-1757.
- Stanley M & Mann JJ. Increased serotonin-2 binding sites in frontal cortex of suicide victims, *Lancet*, 1983 ;1:214-216.
- Stockmeier CA, Wingenfeld P, Gudelsky GA. Effects of repeated electroconvulsive shock on serotonin 1A receptor binding and receptor-mediated hypothermia in the rat. *Neuropharmacology*, 1992; 31:1039-94.
- Stone TW. *Neuropharmacology of quinolinic and kynurenic acids.* *Pharmacol Rev*, 1993; 45:309-379.
- Summerskill J, Seeman W, Meals DW. An evaluation of postelectroshock confusion with the Reiter apparatus. *Am J Psychiatry*, 1952; 108: 835-838.
- Suppes T, Webb A, Carmody T, Gordon E, Gutierrez-Esteinou R, Hudson JI, Pope HG Jr. Is postictal electrical silence a predictor of response to electroconvulsive therapy? *J Affect Disord*, 1996, 41: 55-58.
- Tepper JM, Nakamura S, Spanis CW, Squire LR, Young SJ, Groves PM. Subsensitivity of catecholaminergic neurons to direct acting agonists after single or repeated electroconvulsive shock. *Biol Psychiatry*, 1982; 17: 1059-1070.
- Thoenen H. Neurotrophins and neuronal plasticity. *Science*, 1995; 270:593-8.
- Thomas DN, Nutt DJ, Holman RB. Effects of chronic electroconvulsive shock on noradrenaline release in the rat hippocampus and frontal cortex. *Br J Pharmacol*, 1992; 106: 430-434.
- Thompson C, Franey C, Arendt J, Checkley SA. A comparison of melatonin secretion in depressed patients and normal subjects. *Br J Psychiatry*, 1988,152:260-5.
- Tortella FC, Long JB, Hong J, Haladay JW. Modulation of endogenous opioid systems by electroconvulsive shock. *Convulsive Ther*, 1989, 5:261-73.
- Tortella, F.C, Long, J.B. Characterisation of opioid peptide-like anticonvulsant activity in rat cerebrospinal fluid. *Brain Res*, 1988, 456:139-46.
- Tortella, F.C, Long, J.B. Endogenous anticonvulsant substance in rat cerebrospinal fluid after a generalised seizure. *Science*. 1985;228(4703):1106-8.
- Vaidya VA, Marek GJ, Aghajanian GK, Duman RS. 5HT<sub>2A</sub> receptor mediated regulation of brain derived neurotrophic factor mRNA in the hippocampus and neocortex. *J Neurosci*, 1997;17:2785-95.
- Vetulani J & Antkiewicz-Michaluk L. Alpha-adrenergic receptor changes during antidepressant treatment. *Acta Pharmacol. Toxicol.*, 1985; (Suppl.56) :55-65.
- Vetulani J & Sulser F. Action of various antidepressant treatments reduces reactivity of noradrenergic cAMP generating system in limbic forebrain. *Nature*, 1975; 257:495-496.
- Vetulani J, Antkiewicz-Michaluk L, Rokosz-Pelc A, Pilc A. Chronic electroconvulsive treatment enhances the density of [<sup>3</sup>H] prazosin binding sites in the central nervous system of the rat. *Brain Res*, 1983; 275:392-395.
- Vetulani J, Lebrecht U, Pilc A. Enhancement of responsiveness of the central serotonergic system and serotonin-2 receptor density in rat frontal cortex by electroconvulsive treatment. *Eur J Pharmacol*, 1981; 76:81-85.
- Vetulani J, Stawarz RJ, Dingell JV, Sulser F. A possible common mechanism of action of antidepressant treatments. *Arch of Pharmacol*, 1976, 293:109-14.
- Volkow ND, Bellar S, Mullani N, Jould L, Dewey S. Effects of electroconvulsive therapy on brain glucose me-

- tabolism: a preliminary study. *Convulsive Ther*, 1988; 4:199-205.
- Wahlestedt C, Blendy JA, Kellar KJ, Heilig M, Widerlov E, Ekman R. Electroconvulsive shocks increase the concentration of neocortical and hippocampal neuropeptide Y (NPY)-like immunoreactivity in the rat. *Brain Res*. 1990;507(1):65-8.
- Weiner RD, Rogers HJ, Davidson JR, Kahn EM. Effects of electroconvulsive therapy upon brain electrical activity. *Ann N Y Acad Sci*, 1986; 462:270-81.
- Weiner RD. Does ECT cause brain damage? *Behav Brain Sci*, 1984 ;7:1-53.
- Welch J, Kim H, Fallon S, Liebman J. Do antidepressant induce dopamine autoreceptor subsensitivity? *Nature*, 1982 ; 298: 301-302.
- Whalley LJ, Rosie R, Dick H, Levy G, Watts AG, Sheward WJ, Christie JE, Fink G. Immediate increases in plasma prolactin and neurophysin but not other hormones after electroconvulsive therapy. *Lancet* 1982;28307:1064-1068.
- Widdowson PS, Ordway GA, Halaris AE. Reduced neuropeptide Y concentrations in suicide brain. *J Neurochem*. 1992;59:73-80.
- Yates M, Leake A, Candy JM, Fairbairn AF, Mckeith IG, Ferrier IN. 5 HT2 receptor changes-depression. *Biol Psychiatry*, 1990,27:489-96.
- Yatham LN, Barry S, Dinan TG, Webb M. Which patients will respond to ECT? *Br J Psychiatry*, 1989; 154:879-80.
- Yoshida K, Higuchi H, Kamata M, Yoshimoto M, Shimizu T, Hishikawa Y. Dopamine releasing response in rat striatum to single and repeated electroconvulsive shock treatment. *Prog Neuropsychopharmacol Biol Psychiatry* , 1997; 21: 707-15.
- Young EA, Haskett RF, Murphy-weinberg V, Watson SJ, Akil H. Loss of glucocorticoid fast feedback in depression. *Arch Gen Psychiatry*, 1991;48: 693-699.
- Zachrisson O, Mathe AA, Stenfors C, Lindefors N. Limbic effects of repeated electroconvulsive stimulation on neuropeptide Y and somatostatin mRNA expression in the rat brain. *Brain Res. Mol Brain Res*. 1995;31(1-2):71-85.
- Zafra, F, Lindholm, D, Castren, E, Htikka, J, Thoenen, H. Regulation of brain-derived neurotrophic factor and nerve growth factor mRNA in primary cultures of hippocampal neurons and astrocytes. *J. Neurosci* 1992;12: 4793-9.