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Electroconvulsive therapy in melancholia: the role of hippocampal neurogenesis

Bolwig TG, Madsen TM. Electroconvulsive therapy in melancholia: the role of hippocampal neurogenesis.

Objective: To elucidate the relationship between the effects of electroconvulsive therapy (ECT) on hippocampal anatomy and function in the therapy of melancholic depression and preclinical observations of increased neurogenesis in the hippocampus of experimental animals receiving electroconvulsive seizures (ECS). We emphasize the role of hypercortisolaemia in melancholic depression and in experimental hippocampal neurogenesis.
Method: Our statements are based on a variety of studies pointing to i) ECT being superior to all other treatment modalities in the therapy of melancholia, ii) melancholia being associated with hypercortisolaemia and iii) evidence of hippocampal neurogenesis being relevant for understanding both melancholia and ECT.
Results: The increased neurogenesis found in animal studies shows stronger effect of seizures than of antidepressant drugs. The onset of effect is not only faster but is also sustained. Newborn cells are found to be functional. Suppression of neurogenesis by chronic treatment with corticosterone is associated with depression-like biology and behaviour making comparison with human depression and its response to ECT relevant.
Conclusion: We hypothesize that the superior antimelancholic effect of induced seizures may be understood in the light of the powerful control of neural plasticity exerted by the regulation of the hypothalamic–pituitary–adrenal axis and, perhaps, other regulatory factors.

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Key words: electroconvulsive therapy; depression; hippocampus; dentate gyrus; neurogenesis; corticosterone

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Introduction

Efficacy of ECT

Electroconvulsive therapy (ECT) is the most efficacious treatment in severe depression. Although a number of conditions can be treated successfully with ECT, for instance mania, catatonia/neuroleptic malignant syndrome, delirium and certain types of schizophrenia, the main indication for ECT is major depression with vegetative symptoms (melancholia) with or without psychotic features.

Various meta-analyses document the superiority of ECT compared with other treatment modalities (1–3). Recent multi-centre studies by the Consortium for Research in ECT (CORE) further underline important aspects of ECT. In this four-hospital collaborative study of a cohort of 253 patients given ECT for severe major depression, rigorous criteria for remission were applied. An overall remission rate of 87% was found. Of the total patient population those with psychotic depression had a remission rate of 95%, those with non-psychotic depression 83% (4). Further, response occurred at a faster rate than found in studies of antidepressant drugs (5), and a rapid relief of expressed suicidal intent was reported (6).

Mechanisms of action

The neurobiological events underlying the therapeutic effects of ECT are far from elucidated, a fact often held against clinicians using ECT (unjustly, considering the similar lack of knowledge regarding mechanisms of psychotropic drugs and psychotherapy).

Pursuing current ideas of a paramount importance of monoamines in the aetiology and therapy of affective disorders, numerous studies of monoamines and their metabolites in blood, urine and cerebrospinal fluid (CSF) have been conducted. These have, however, yielded conflicting results,

insufficiently consistent for the development of coherent theories of depression and antidepressants agents, especially ECT.

The observation of elevated plasma cortisol in patients with severe depression and the lack of inhibition of release of cortisol found in healthy subjects (7) led Carroll et al. to develop the dexamethasone suppression test (DST) as a formal test of hypothalamic–pituitary–adrenal (HPA) function (8).

Dexamethasone suppression test proved useful in many studies of different types of depression, both with respect to classification and as a predictor of suicidality. The more patients met criteria for endogenous depression (with weight loss, agitation, suicide risk and psychosis) the higher was the percentage of DST abnormality. The test fell out of favour for various reasons, among them the revision of classificatory systems in the 1980s (DSM-III), and today it is rarely used in clinical psychopharmacology (for a comment on this issue, see Fink 2005) (9). However, recent work by Yerevianian et al. (10) has again demonstrated DST's usefulness in predicting suicidal behaviour, and, relevant for the present considerations, Yuuki et al. (11) in a study of ECT in severe depression unresponsive to drug therapy applied DST/CRH (modified DST), and clearly demonstrated the reversal of abnormal HPA functioning following remission.

A theory of ECT

Based on differences between ECT with unilateral and bilateral electrode placement Abrams and Taylor suggested an involvement of diencephalic structures (12), but it was against the background of the striking normalization of neuroendocrine disturbances (vegetative symptoms) occurring in melancholic patients undergoing ECT that Fink and Ottosson proposed a coherent theory for the working action of ECT (13).

They concluded: 'Hypothalamic dysfunction is the basis for an endogenous depressive psychosis. The antidepressant efficacy of convulsive therapy results from the persistent release of hypothalamic substances that mediate mood changes from depression to normal mood states with attendant modifications in vegetative functions'.

Brain protein markers and ECT/ECS

Inspired by the ideas of a diencephalic involvement in ECT and by newly developed methods (quantitative immunoelectrophoresis) Jørgensen et al. (14) measured brain-specific proteins in the CSF in a series of severely depressed (melancholic) patients successfully treated with tricyclic antidepressants or ECT. They found increased concentrations in the CSF of the protein marker neural cell adhesion molecule (NCAM) which is assumed to be involved in intercellular recognition during synaptogenesis. Further, in a postmortem study of nine endogenously depressed (ICD-8 criteria) patients treated with tricyclic antidepressants who died in hospital from non-cerebral fatalities (heart failure, pneumonia, sepsis) a significantly increased concentration of NCAM was found in the hippocampus (but not in the frontal cortex) compared with patients with Parkinson's disease and to controls with no neuro-psychiatric illness (15).

The described findings in CSF and tissue both point to an increased synaptic turnover during endogenous depression after treatment, and based on this assumption the same group began studies of a variety of brain-specific protein markers in rats receiving electroconvulsive seizures (ECS) of similar clinical frequency three times weekly for 4 and 8 weeks respectively. Using quantitative immunoelectrophoresis Jørgensen and Bolwig (16) measured postECS changes in specific markers suggesting i) an increase in the number of synaptic vesicles, ii) a neuronal preparedness for glycolytic demands and iii) a delayed development of some areas (occipital cortex) in the brain. This demonstration of an effect on the formation of new synapses was sustained for several weeks, and not a transient epiphenomenon of seizure activity. The observation is thus relevant for considerations regarding ECT in humans.

Inspired by the Fink and Ottosson theory (13) with its emphasis on the significance of hypothalamic functions, the initial study of brain protein markers(17) was expanded to investigate several discrete brain regions, including the hypothalamus. In this study (17) sustained increases in both NCAM and the marker protein synaptin, which plays a functional role in the exo-endocytotic process of synaptic nerve transmission, were significantly more pronounced in the hypothalamus compared with the rest of the forebrain.

The fact that seizure activity did not exert identical effect on synaptic proteins in different regions of the brain, might reflect the phenomenon of a simultaneous stimulatory and inhibitory effect as a result of generalized seizure activity seen in patients given ECT: alleviation of depressive inhibition – mnemic dysfunction. This dual action might also be understood in the light of the variety of functions linked to various regions of the brain (e.g 'vegetative' functions and the hypothalamus, memory function and the hippocampus). A

homogeneous synaptic response to seizure activity therefore may have grossly different effects on the complex interplay between facilitating and inhibiting neuronal systems.

A third series of protein marker studies and ECS (18) addressed the question whether seizures occurring in limbic areas might stimulate the synthesis and release of nerve-growth factors, which again might trigger sprouting of axons. The group looked at the possibility that the demonstrated synaptic remodelling following ECS is preceded by a seizure-induced release of neurotrophic factors from glial cells and neurons.

Using the same seizure paradigm as in the two previous brain protein studies ECS was found to significantly increase the concentration of the glial marker Glial Fibrillary Acidic Protein (GFAP) in the following limbic areas: hippocampus, amygdala and piriform cortex. Again, the observed increases were sustained.

To compare astrocyte activation in two different seizure models, a separate series of experiments with repeated (12–30) injections of lidocaine in subconvulsive doses, eventually leading to seizures ('kindling'), was conducted. Lidocaine in itself did not induce astrocyte activation, but with occurrence of seizures GFAP-concentrations rose to levels similar to the postECS situation.

The study thus showed that it is the seizure activity, whether electrically or pharmacologically induced, that activates astrocytes in certain brain regions.

Summary of the protein marker studies

The reviewed studies conducted decades ago are included in this presentation as they anticipate subsequent investigations of seizure effects on neurogenesis.

Repeated ECS activated both neurons and glia. ECS induced i) synaptic remodelling (synaptogenesis) in especially the hypothalamus, ii) a decrease of synaptic activity in occipital cortex and iii) an increased activation of astrocytes in limbic areas, including the hippocampus, supposedly preceding release of a number of trophic factors including nerve growth factor.

The most significant findings were in the hypothalamus and in the hippocampus.

Depression and hippocampal volume

During recent years magnetic (MRI) studies have pointed to a reduction in hippocampal volume in patients with severe unipolar depression. (19–21). Others report similar findings. A meta-analysis of 12 studies comprising 351 patients and 279 healthy subjects found a considerable heterogeneity regarding age and gender distribution, onset of the disorder, average number of episodes and responsiveness to treatment. The meta-analysis found a weighted average reduction of hippocampal volume of 8% on the left and 10% on the right side (22). After analyses of the causes of heterogeneity the total number of depressive episodes was significantly correlated to right but not left hippocampal volume reduction.

Moreover, volumetric changes reflect the actual number of days that individuals have been depressed with prolonged symptomatic periods corresponding to smaller hippocampi (19, 20).

These findings have heightened interest in studying the hippocampal structure and function in experimental animals (see below).

The nature of the volume reduction of hippocampus in severe depression is not known. It may be speculated that the decreased hippocampal volume accompanying depression *per se* could be the result of a toxic effect of cortisol. The human studies do not allow estimates of mechanisms of putative neuronal loss by, for instance, apoptosis (programmed cell death) or inhibition of neurogenesis. Nor do human studies at present enable measurements of the volume of individual neurons or a possible reduction in the volume of glial tissue.

Depression and hippocampal function

Various animal models of stress/'depression' have been developed during the last 40 years. The most widely applied in testing acute antidepressant response are the Seligman 'learned helplessness' paradigm and (23) the Porsolt 'forced swim test' (24), both of which have shown excellent face validity and reasonably good reliability. Such models allow a closer look at cellular and subcellular components of hippocampal neuroplasticity and may therefore be useful in the search of mechanisms of stress/'depression'. For the same reasons they are also relevant in studies of the effects of ECS/ECT.

The role of the hypothalamus in understanding the biology of melancholia, supported by numerous neuroendocrine findings, not least the demonstration of hypercortisolaemia and of the usefulness of the DST is well demonstrated.

The hippocampus, however, also seems to play an important role in understanding melancholia and the working action of ECT.

A central function of the hippocampus is its involvement in episodic, declarative, contextual and spatial learning and memory, functions which

are disturbed in melancholic depression, and also influenced markedly by ECT. Extensive rodent and human research have demonstrated a relation between the mnemonic functions and neuroplasticity of the hippocampus, which are highly sensitive to stress, i.e. increased glucocorticoid levels (25), found in most animal models of depression, and in humans with melancholic depression.

A combination of several factors has focused research on the hippocampus as one of several limbic brain structures involved in the aetiology and treatment of depression. First, the hippocampus expresses high levels of receptors for the stress-responsive adrenal–glucocorticoids and soutan elevated HPA axis function is a hallmark neuroendocrine marker of depression (26). Secondly, the hippocampus plays a significant role in the negative feedback regulation of the HPA axis, which controls glucocorticoid release and thirdly, chronic stress or elevated glucocorticoids induce atrophy or loss of hippocampal neurons; which in turn may lead to further loss of the feedback inhibition of the HPA axis provided by this structure (27, 28). Important anatomical pathways connect hippocampus, the amygdala and prefrontal cortex, regions which several studies have implicated in mood and cognition. Besides the critical role of hippocampus in learning and memory, it is important in the brain's response to psychosocial stress by regulating the release of hypothalamic corticotropin-releasing factor with subsequent release of adrenocorticotropic hormone by the anterior pituitary (28).

Hippocampal neurogenesis, stress and ECS

The findings by Altman and Das (29) that neuronal cells are continually added to the adult brain was a finding long rejected by the scientific community. Accumulating data, however, have shown that adult-born neurons make functional connections, and modern techniques to detect DNA replication and thus cell division, combined with immunohistochemistry, confirmed that cells from brains of adult rodents and other mammals may assume a neuronal phenotype. In mammals neurogenesis occurs mainly in subregions of the dentate gyrus of the hippocampus; in humans (30) neurogenesis has been conclusively demonstrated only in the hippocampus (for review see Dranovsky and Hen 2006) (31).

The 'neurogenesis' hypothesis

The biology and psychology of depression intersect with stress. Major stressors precede many depressions, and pathologic or pharmacologic excesses of glucocorticoids may elicit depression. Many patients with melancholic depression have some version of glucocorticoid excess, and antiglucocorticoids may act as antidepressants. Both stress and glucocorticoids are among the strongest inhibitors of hippocampal neurogenesis.

Changes in the level of several neurotrophic factors, especially brain-derived neurotrophic factor precede changes in the rate of neurogenesis (for review see Duman 2004, 32). Interventions with antidepressant effect in humans counteract a stress/'depression'-induced suppression of hippocampal neurogenesis. Tricyclic antidepressants, serotonin selective reuptake inhibitors (SSRI), serotonin-noradrenaline reuptake inhibitors (SNRI), mono amine oxidase (MAO)-inhibitors and ECS counteract this suppression, with ECS showing the significantly strongest effect (33).

The time course of the stimulation of neurogenesis fits with the delayed time course of clinical efficacy of antidepressant principles and therefore explains the time-course paradox of antidepressant action, namely that drugs have relatively rapid effect upon monoamine signalling, while the latency to clinical efficacy is far longer. These findings represent strong evidence in favour of the 'neurogenesis' hypothesis.

The experimental data on the role of neurogenesis and stress come from analyses of brains of animals exposed to behavioural paradigms designed to model psychosocial stress and antidepressant response. As it is not possible to model the subjective feeling of depressed mood in rodents, it is unlikely that animal models are representative of melancholic depression in humans. Still many aspects of behavioural responses to antidepressant intervention in 'depressed' animals are of relevance.

In spite of the wealth of evidence supporting the 'neurogenesis' hypothesis of depression and mechanisms of antidepressants, the hypothesis has been an area of debate (34, 35).

A major criticism was raised by Henn and Vollmayr (35) who argued that in an animal model of depression (learned helplessness) 'depressive' behaviour could be induced without suppression of neurogenesis, and further that transcranial magnetic stimulation (TMS) in rhesus monkeys does not induce neurogenesis (S. Scalia 2004, unpublished data). It should, however, be noted that the 'learned helplessness' model has yielded conflicting results, and findings from several other studies suggest that it is mounting a neurogenic response, and not the baseline that is important in models of depression and effects of antidepressants (31) The lack of such mounting a response after

TMS in monkeys may explain why the effects of TMS in treating severe depression in humans remain a matter of dispute.

ECS and hippocampal neurogenesis

In the first published study of ECS showing an effect on hippocampal neurogenesis in rodents Madsen et al. (36) applied advanced labelling techniques to test the phenotype of different cells detected by immunohistochemistry. They demonstrated that both a single and a series of ECS induced solid neurogenesis in the dentate gyrus of the hippocampus in a dose-response manner, and, importantly, they found this effect was sustained and still observable for at least 3 months. Remarkable also was that apoptosis (programmed cell death) could not be detected.

Independent studies with the same findings were published in the same year (33, 37). Common in these first demonstrations of ECS mounting a neurogenesis response in the rat hippocampus was that they were conducted in animals not challenged with stress.

Hellsten et al. in 2002 (38) using similar labelling techniques conducted experiments applying both single and repeated ECS in rats exposed to chronic corticosterone treatment, and reporting massive suppression of neurogenesis. A decrease by 75% of neurogenesis was counteracted by a single, and further, by multiple ECS. Expanding the experiments, the same group (39), in a similar experimental paradigm studied the effect of ECS on both the volume of hippocampus and the proliferation of glia cells in corticosterone-treated rats. They found that the volume of sub-regions of the dentate gyrus of the hippocampus increased following ECS, and that a corticosterone-induced reduction of a subgroup of glia cells (NG2) ECS shows proliferation after ECS that reached the levels of normal controls.

Finally, in recent studies using unbiased stereology (40) C. Fengùa and TM Madsen et al. found a highly significant amount of synapses and an increased synaptic density in the CA1 area of the hippocampus in unchallenged rats given single and repeated ECS (personal communication), substantiating the earlier assumptions of synaptoneogenesis resulting from ECS (16, 17) and pointing clearly to the newly formed cells in the hippocampus being functional.

To conclude electroconvulsive therapy has superior efficacy in the therapy of melancholic depression. The hypercortisolaemia associated with melancholia and the diagnostic quality of the DST form the basis for a neuroendocrine theory of ECT emphasizing the role of the hypothalamus.

Observations of a decreased hippocampal volume in severe depression and neurochemical findings in patients and in animal experiments suggest an involvement also of the hippocampus. A variety of stress paradigms and models of depression are accompanied by hypercortisolaemia and a suppression of hippocampal neurogenesis. This suppression is strongly counteracted by ECS.

Antidepressant medications but not neuroleptics have a similar, yet clearly weaker, effect on hippocampal neurogenesis in animal stress paradigms, and we find it justified to hypothesize that the superior antimelancholic effect of induced seizures may be understood in the light of their powerful control of neural plasticity by the regulation of the HPA axis and perhaps, other regulatory factors.

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