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Neurobiological links between epilepsy and mood disorders

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Abstract

With increasing realization of the extent and consequences of depressive comorbidity in epilepsy, much human and animal research has focussed on its explanation. Recent studies tackle all three explanatory possibilities: that epilepsy leads to depression; that depression contributes to causation of epilepsy; or that shared causal factors or processes lead to both epilepsy and depression. These are not mutually exclusive; all three probably contribute. Animal models have provided many insights into the interplay between epilepsy and depressive-like behaviours, both associations and mechanisms. Notably, experimental stress potently affects epilepsy endpoints, as well as depressive-like behaviour, having actions at multiple relevant biological levels. Current general (nonepilepsy) depression modelling is biopsychosocial in nature, integrating insights from genetics, epidemiology, psychology and neurobiology; and takes a lifespan developmental perspective, as the causation of depression is a multistage process with origins in early life - as is the case for many epilepsies. These perspectives need to be more fully adopted in the epilepsy/depression field.

INTRODUCTION

With increasing realization of the extent of depressive comorbidity in epilepsy[1,2] and its serious adverse consequences, much human and animal research has focussed on its explanation. These consequences include the distress and impaired function of the depressed state itself, suicide, reduced adherence to antiepileptic medication and lifestyle measures, and impaired quality of life.[2] Several issues remain un- or under-explored: depression is linked to other chronic physical diseases, such as diabetes, obesity and ischemic heart disease, all of which occur in patients with epilepsy and add to their disability; there are important biological pathways that may link depression to SUDEP that deserve further scrutiny[3]; and recently the possibility has been considered, on the basis of animal studies, that depression aggravates epileptogenesis.

NEUROBIOLOGICAL LINKS

Recent studies tackle all three main explanatory possibilities:

1. *Epilepsy as cause of depression*: The everyday experience of patients and clinicians, combined with an extensive psychosocial literature, testify to the multiple stresses and indignities of living with epilepsy. These include the distress of seizures, anxiety about seizures, risk of injury, effects on memory, the burden of medical assessment and antiepileptic medication, coping with stigma and discrimination, financial stress, and impacts on relationships, work, mobility, education and leisure. For many, such factors alone are sufficient to explain the depression. However, there is great interindividual variation in resilience and in the psychiatric impact of life stress, some of which can be thought of as neurobiological[4], and this is the case too for the depression that occurs in people with epilepsy, although little studied to date.

2. *Depression as cause of epilepsy:* Evidence for the reverse direction, the idea that depression has a causal role in epilepsy, comes from epidemiological studies[5,6] and from animal studies showing that stress states not dissimilar to depression in humans can aggravate epileptogenesis.[7]

3. *Shared causation:* The richest data suggesting shared causal factors and processes leading to both epilepsy and depression derives from animal models. Animals with genetically driven epilepsy, such as GEPRS[8] and GAERS[9] rats, also demonstrate elevated depressive and/or anxiety-like behaviours, often before

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emergence of seizures. Early life stress, a causal contributor to depression vulnerability in humans and depression-like behaviour in animals[10], has robust effects in aggravating epilepsy in several animal models.[11]

What follows is a very brief, selective sketch of some current prominent lines of human and animal research into mechanisms. Neurotransmitters implicated in both epilepsy and depression include 5-HT, norepinephine (NE), GABA and glutamate (Glu). 5-HT and NE neurotransmission are abnormal in GEPRS rats[8] and, in humans, PET studies show altered 5HT1A receptor binding in depressed patients with mesial temporal lobe epilepsy.[12] Structural brain changes associated with depression, for example in hippocampus[13] may well have implications for temporal lobe epilepsy, a general hypothesis as yet untested. Glutamate, the major excitatory neurotransmitter with a key role in the epileptic state, is implicated in the biology of depression. Ketamine, an NMDA receptor antagonist, has a rapid antidepressant action in humans and animals. Recently, it was shown that the mTOR pathway is involved in this action.[14] Interestingly, the mTOR pathway is implicated causally in several animal models of epilepsy.[15,16]

A key feature of limbic epileptogenesis is abnormal neurogenesis[17]; hippocampal neurogenesis has been invoked in depression causation and the action of antidepressant medications.[18] This intersection has been little studied, although a recent study suggested that second generation antidepressants have *antiseizure* activity.[19]

Inflammation and cytokines, the subject of energetic research in both the epilepsy[20] and depression[21] fields, are prime suspects for playing a part in shared causation. Only recently has initial supportive experimental evidence emerged.[22,23]

THREE THEMES

1. Stress biology

In animal models, experimental stress potently affects epilepsy endpoints, like kindling rates, and has actions at several biological levels that might explain its effects: gene expression, ion channels, neurotransmitter systems, inflammation and epilepsy-relevant neuroplasticity.[11] In addition, stress can act at several *stages* in the epileptogenesis process. Furthermore, a great deal is known about how stressors, at various life stages, contribute to depressive- and anxiety-like behaviours and impaired cognition[24]; this knowledge can inform hypotheses about the behavioural comorbidities of experimental epilepsy. Stressors and glucocorticoids aggravate experimental epilepsy[7]; conversely, inducing epilepsy (in the status epilepticus model) potently increases HPA axis reactivity[25,26], as well as causing depressive behaviour and diminished hippocampal serotonergic release.

2. Epilepsy genetics

The extraordinary recent developments in epilepsy genetics[27] open up new approaches - not yet exploited - to the study of epilepsy and depression. For example, various genetically-based ion channel disorders have been characterised, but their psychiatric phenotypes are largely neglected. In addition, it's clear there can be wide phenotypic variation stemming from a single genetic abnormality.[28] Epistasis explains some of this variation; some is due to as yet unknown environmental exposures[29] which themselves may act via a range of mechanisms, include epigenetically. In thinking about possible environmental agents, stress, particularly stress in early life, should be seriously considered. Although the human evidence remains sparse, the experimental animal evidence for neuroplastic effects of stress is overwhelming.[30] Unfortunately, children and their developing brains are often exposed to chronic stress: in the Dunedin birth cohort study, which had multiple, detailed measures, 27% of children suffered some form of maltreatment.[31] In many less developed countries, affected by many forms of widespread stress and trauma, the figures are far worse.[32]

3. The need for a life-course approach to explaining the epilepsy/depression nexus

Current general (nonepilepsy) depression modelling is biopsychosocial in nature, integrating insights from genetics, epidemiology, psychology and neurobiology; and takes a lifespan developmental perspective[33], as the causation of depression is a multistage process with origins in early life - as is the case for many epilepsies. These essential perspectives have not been adopted in the epilepsy/depression field as fully as they need to be. One neglected approach is prospective cohort studies addressing epilepsy causation and doing so in a way that carefully examines psychosocial exposures at key developmental stages as well as psychiatric and cognitive comorbidity.[34]

CONCLUSION

The last point is the main one this paper seeks to make: progress in understanding, preventing and treating depression in epilepsy requires a biopsychosocial, life-course perspective.[33] This entails close collaboration between neurologists, psychiatrists, psychologists, epidemiologists and social researchers. Thankfully such collaboration is occurring to some extent and hopefully will grow.

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