THE KINDLING EFFECT IN PSYCHIATRIC DISORDERS

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Abstract:
The kindling effect is generally thought to be highly persistent and possibly permanent, but little direct evidence is available to support this idea. The term kindling originally referred to a very specific type of sensitization process: the development of behavioral seizures in response to repeated electrical or chemical stimuli. Likewise, an understanding of some of the molecular substrates identified in the kindling model of epilepsy should serve to assist in the development of hypotheses regarding sensitization mechanisms in psychiatric illnesses. It is hoped that some of the lessons from the kindling model will provide useful and novel insights into aspects of treatment and mechanisms of psychiatric and neurological illnesses.

Key words: kindling, psychiatric disorders, neurotransmitters

Kindling originally referred to a very specific type of sensitization process: the development of behavioral seizures as response to repeated electrical or chemical stimuli. The kindling effect has been discovered accidentally in epilepsy by researcher Graham Goddard in 1967, while he was studying learning in rats. He found that a sustained, periodic, low-intensity stimulation of the limbic region of mammalian brains eventually sets up a cumulative resonance which increases in magnitude until the entire organism is in sympathetic resonance. Eventually these bursts of electrical activity induce similar patterns in nearby brain regions, and the seizure threshold progressively lowered. While normally the electrical stimulation he used was too low to cause any type of convulsing, he discovered that repeated exposure of brain areas to small electric shocks seem to make subsequent episodes of spontaneous seizure-like electrical events more likely to occur. After repeated stimulation at the same intensity, their brains had become sensitized to electricity, and even months later the rat would convulse when stimulated. Goddard demonstrated that it was possible to induce kindling chemically as well through repeated small exposures to inhaled toxins; or single overwhelming exposures of chemical, visual, auditory, electrical stimulation.

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Kindling may start in the limbic brain where it progresses from the amygdala to the hippocampus, to the occipital cortex, and finally to the frontal cortex. For several reasons, the hippocampus represents a model for the study of the molecular mechanisms of kindling. First, it is this structure, along with other parts of the limbic system that has been most strongly implicated as the focus of abnormal neuronal activity in the majority of human complex partial seizures. Second, the circuitry of the principal neurons of the hippocampus is well established, and thus potential alterations in biochemical or physiological properties of subtypes of hippocampal neurons can be appreciated in light of their impact on information flow through this circuit. Measurements of neurotransmitter receptor density and neuro-anatomical lesion studies have implicated the hippocampus as an important structure in kindling. Early studies of the hippocampus provided molecular evidence for a modification, following kindling, of neurotransmitter receptors intrinsic to discrete populations of neurons. These studies identified changes in the density of muscarinic cholinergeric receptors and benzodiazepine receptors on dentate granule cells. The importance of the hippocampus was further indicated by the observation that selective elimination of hippocampal dentate granule cells resulted in a marked slowing of the rate of kindling development. Likewise, disruption of the excitatory input into the hippocampus profoundly slowed the rate of kindling development. Electrophysiological studies of hippocampal slices in vitro showed that the hippocampus, in addition to facilitating the development of kindling, also displayed abnormal excitability after kindling developed. In slices examined one day or one month following the last kindled seizure, hyperexcitability was identified in all three principal neuronal populations of the hippocampus: the dentate granule cells, the CA2/3 pyramidal cells, and the CA1 pyramidal cells. These studies clearly implicated the hippocampus as one structure of the kindled brain having abnormal excitability. Although it is generally accepted that synapses using glutamate and related excitatory amino acids represent the principal excitatory synapses in the mammalian central nervous system, it took many years of experimentation before this idea gained widespread approval. Of all the glutamate receptor subtypes the NMDA receptor is best characterized, because of the relatively large number of selective agonists and antagonists that recognize it. The receptor has multiple regulatory and pharmacological domains. Given the role of NMDA receptor–mediated responses in both in vitro and in vivo models of seizure activity, it is possible that enhanced function of synapses using this receptor is a mechanism underlying the enduring hyperexcitability of a "kindled" brain.

The fact that NMDA receptor antagonists inhibit seizures during kindling initiation indicates the importance of NMDA receptor-mediated responses in the development of kindling. The discovery of enhanced sensitivity of NMDA receptor-mediated responses following the induction of kindling
suggests that these receptors play a role in the expression of neuronal hyperexcitability. A lasting enhancement of NMDA receptor–mediated activity may underlie diverse sensitization models, where neuro-anatomical locale of the receptor may be the determinant of the expressed behavior.

The development of kindled seizures is contingent on the repeated application of a stimulus over time. During kindling, the strength of the repeated stimulus does not vary; however, the behavioral response to the stimulus becomes progressively more severe over time. By analogy, repeated stimuli in psychiatric illness (be it an episode of affective illness, exacerbation of psychosis, environmental or physical stress, or exogenous substances) may over time lead to a progressively more severe clinical presentation. For example, such a kindling-like effect is seen in the increased vulnerability of alcoholics to alcohol withdrawal, manifested in adverse withdrawal effects, in the setting of a prior history of withdrawal from alcohol.

The kindling effect is generally thought to be highly persistent and possibly permanent, but little direct evidence is available to support this idea. Sensitization or "kindling-like" phenomena have been implicated in the pathophysiology of a number of psychiatric illnesses. A basic understanding of the prototypical sensitization phenomenon, the kindling model of epilepsy, is thus of increasing significance for the psychiatrist. Pathophysiological models of psychiatric diseases as seemingly diverse as mood disorders, schizophrenia, drug addiction-posttraumatic stress disorder, multiple chemical sensitivity, and pain have all implicated sensitization mechanisms. The most common analogy is between an epileptic seizure and a manic episode of bipolar disorder. Like seizures, manic episodes can occur without obvious triggers, and have fairly abrupt beginnings and endings. In the case of bipolar disorder, the “kindling” is theoretically provided by stressful life events, which may produce certain kinds of electrical brain stimulations. At first, these events are not sufficient to cause a manic episode, but over time, they may accumulate to trigger such an episode. Furthermore, “episodes may beget episodes,” meaning that the manic episodes themselves may damage the brain in some way, making it more vulnerable, so that eventually the episodes may begin to occur spontaneously, without a trigger.

In addition, it has been shown that substances such as cocaine and alcohol have their own kindling effects which can contribute to bipolar kindling. In fact, it was the knowledge that cocaine causes seizures that led Dr. Post to connect kindling in epilepsy with mood disorders, after he had studied the unexpected effects of cocaine on severely depressed patients (NARSAD).

A study led by Dr. Joseph Goldberg found that patients diagnosed with both bipolar disorder and substance abuse were much likely to respond to treatment that included an anticonvulsivant/mood stabilizer, divalproex or carbamazepine, with or without Lithium, than
treatment with Lithium alone. At the same time, patients who had bipolar disorder but no history of substance abuse had similar remission rates with both types of treatment. Dr. Goldberg did note that more controlled studies are needed on the role of anticonvulsants in treating dual diagnosis patients (Substance Abuse, 2000).

Conclusions

Kindling phenomena is relevant both in psychiatry disorders and in epilepsy, the implicated structures are common - mamillary bodies, hippocampus and limbic structures.

The kindling model represents the prototypical model of sensitization. Because sensitization has been proposed as a pathophysiological mechanism in a number of psychiatric illnesses, a basic understanding of the kindling model of epilepsy is essential.

References


