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Kindling: Separate vs. Shared Mechanisms in Affective Disorders and Epilepsy

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Review

Abstract
Kindling is discussed in relation to affective illness as a nonhomologous model, which shares the feature of increasing illness severity and evolution over time following repeated exposures to certain forms of stimulation. This progressive aspect of kindling has proven useful in the study of approaches to pharmacotherapeutics, mechanisms and characteristics of drug tolerance, and, most recently, illness suppression through physiological rather than pharmacological strategies. Each of these themes is described and the mechanisms that have been uncovered using the kindling model are discussed in relation to how similar principles might apply in affective illness or epilepsy. 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 neurologic illnesses.

Introduction

Kindling is a model of epileptogenesis, in which repeated, intermittent administration of a subconvulsant stimulus results in the development of generalized motor seizures [1]. Ultimately, after many such seizures are generated, spontaneous seizures can arise [2, 3]. Kindling has been demonstrated in a wide range of vertebrate species [1, 4, 5] and, although not definitively demonstrated in humans, it has been suggested to be a component of certain forms of epilepsy, including the late-onset temporal lobe epilepsy (partial complex seizures with secondary generalization) that can result from cerebral trauma of various origins or from febrile seizures that occur during infancy [6]. Kindling has proven to be a useful model for studying the course and progression of epilepsy and for determining the relative efficacy of antiepileptic agents [7–9]. Finally, since it represents an essentially permanent change in the nervous system, kindling has also been conceptualized and studied as a form of long-term neural plasticity and memory [10, 11].

Affective disorders may be contrasted with epilepsy along a number of dimensions. Affective disorders and epilepsy exhibit different behavioral and physiological manifestations; they have differing etiological precipitants; and, in spite of a common responsivity to electroconvulsive seizures (ECS) [12] and to some anticonvulsive agents [13, 14], affective disorders and epilepsy by and large have different pharmacotherapeutic profiles (table 1). In our view, kindling relates to affective disorders in two important aspects. First, kindling provides a model of a progressive increase in illness severity; and second, aspects of the kindling process mirror the shift from precipitated to spontaneous episodes. Both of these processes can be said to characterize a significant proportion of cases of, e.g. panic disorder, posttraumatic stress disorder, and recurrent bipolar and unipolar illness. Thus, the neurobiological processes involved in kindling may

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Table 1. Pharmacological convergence and divergence in seizure kindling and affective illness progression

	Seizure development	Early affective illness	Full-blown seizures	Mid affective illness	Spontaneous seizures	Late affective illness
Lithium	0	++	0	+++	0	+
Antidepressants	±	±	±	±	–	?
ECT	++	++	++	++	?	?
CBZ	0	?	++	++	?	?
CLZ/DZP	+	+	+	+	0	?
LTG	–	?	+	+	?	?
GPN	?	?	?	+	?	?

ECT = Electroconvulsive seizure therapy; CBZ = carbamazepine; CLZ/DZP = clonazepam/diazepam; LTG = lamotrigine; GPN = gabapentin; ++ = very effective; ± = partially effective; 0 = not effective; ? = not tested.

be relevant to a number of diseases even though not strictly homologous to any of them in terms of symptomatology, etiology, or pharmacoresponsivity [15].

Further, while the mechanisms of kindling can begin to be understood through physiological, pharmacological, and molecular dissections, it is not certain that the changes thus revealed will directly relate to the pathophysiology of affective or other psychiatric illnesses. Our premise is similar to that of Kandel and associates, Alkon and associates, and others: Mechanisms of neural plasticity are likely to be conserved across species and across neural systems; and so, by studying simple systems over condensed time frames, one can begin to uncover mechanisms that may also be important for more complex behaviors and organisms. In the case of kindling, our notion is that by studying a readily controlled and easily measured aspect of an organism's response to repeated stimulus exposures, we can begin to uncover fundamental mechanisms of neural plasticity and syndrome progression. We then will be in a position to determine the degree to which these mechanisms are also relevant to more complex systems and more subtle behaviors.

The fact that kindling is most readily achieved in limbic system structures, the same structures that are thought to be important in affective disorders [16, 17], and that some of the same drugs can alter the course or expression of both kindling and affective illness [14, 17, 18], suggest that there are additional bonuses to using this model. However, the question of how these facts mechanistically connect kindling with affective illness remains an open one at this time, worthy of discussion and investigation. Rather than attempt to directly address this question, we will provide examples of some of the lessons that we have learned from the study of kindling, as they might yield insights into potential mechanisms and treatment strategies for the recurrent affective disorders.

Pharmacology as a Function of Illness Evolution, Etiology, and Route of Drug Administration

Figure 1 illustrates schematically the results of a series of studies from our laboratory and others [19] indicating that, for kindled seizures, the anticonvulsant response to a variety of pharmacological agents is determined by a number of factors including stage of illness progression, illness-inducing agent, and method of drug administration.

Illness Progression

Medications that are effective in one stage of illness evolution can be completely ineffective in another. For example, carbamazepine, while highly effective against fully developed amygdala-kindled seizures, is completely without effect on amygdala kindling development (fig. 2) [20]. Similarly, Pinel [19] demonstrated a double dissociation between diazepam and phenytoin on completed vs. spontaneous kindled seizures, with diazepam highly effective against the former and without effect on the latter. Phenytoin showed the opposite profile, i.e. it inhibited the occurrence of spontaneous seizures, but could not block triggered kindled seizures.

Illness Etiology

We have also observed that kindling by different mechanisms can be associated with differential pharmacological responsivities, e.g. pharmacological kindling using the local anesthetics lidocaine or cocaine (administered

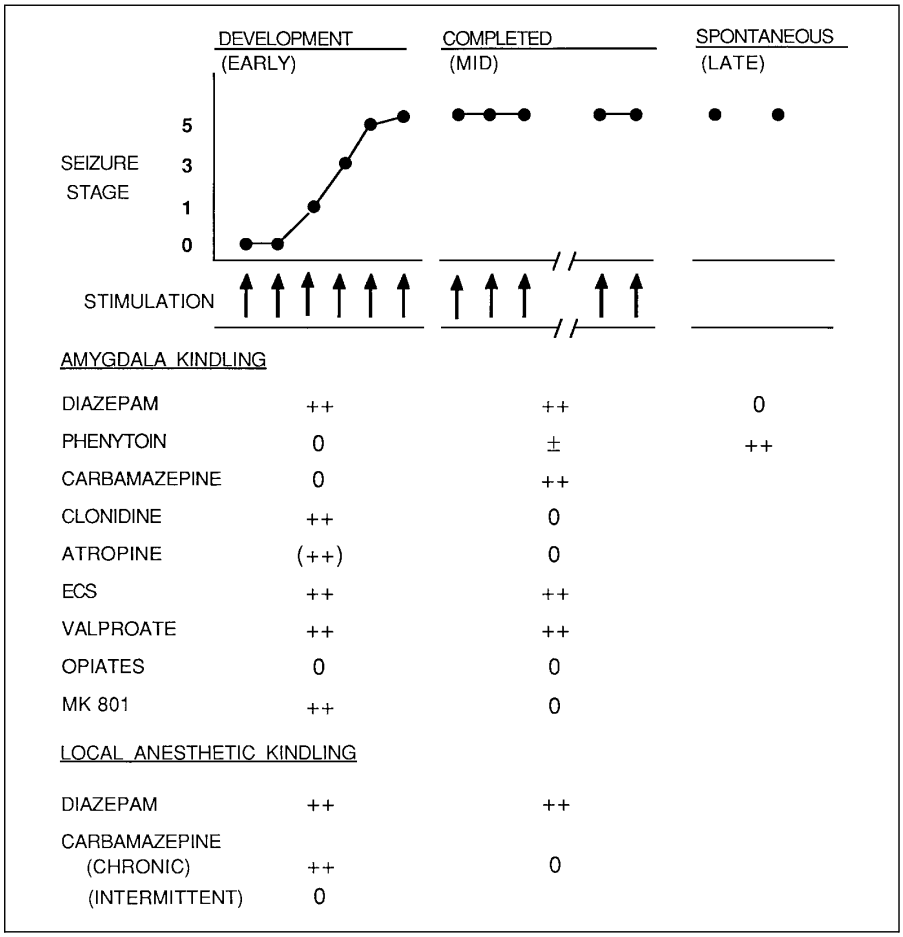

Fig. 1. Pharmacological responsivity as a function of kindling stage. Early (developmental), mid (completed), and late (spontaneous) phases of amygdala (top) or local anesthetic (bottom) kindling evolution show differences in pharmacological responsivity (++ = very effective; ± = partially effective; 0 = not effective). The double dissociation in response to diazepam and phenytoin in the early versus the late phases of amygdala kindling, as described by Pinel [19], are particularly striking. Note also that carbamazepine is effective in inhibiting the developmental phase of local anesthetic but not amygdala kindling, whereas the converse is true for the mid (completed) phase.

repeatedly, intraperitoneally, at subconvulsant doses) can be halted in its development by chronic treatment with carbamazepine (administered orally in the diet), but is not affected by this same treatment once the kindled seizures have developed (fig. 2) [21, 22]. Thus, in this case, the same drug was effective in the development or expression of one type of seizure response but not another. It is notable that the local-anesthetic kindled seizures appear similar to electrically kindled limbic seizures and both seizure types show cross-sensitization to each other. They involve the same behavioral phenomena – oral movements, forepaw clonus, rearing and falling, albeit over different time courses – electrically kindled seizures occur once for about 1 min; local anesthetic seizures recur over the course of about $^1/_2$ h with each seizure lasting approximately 1 min or less [23, 24].

Schedule or Route of Drug Administration

Finally, the method of drug administration can also be important, as indicated in the local anesthetic kindling model (fig. 2) [21, 22]. Carbamazepine's efficacy in this model (but not in electrical kindling of the amygdala) is dependent upon its being administered orally, in the diet. Repeated intraperitoneal administration of doses that produced the same or higher blood levels of the drug were without effect or worsened the course of development of local anesthetic kindling [25]. Thus, the effects of oral vs. intraperitoneal administration of the same drug can also vastly differ and determine whether a response will occur or not.

Clinical Implications

Thus, the efficacy of an anticonvulsant agent appears to depend upon many factors including the stage of illness progression, the method for inducing the disorder, and even the method of drug administration. What this suggests clinically is that there are many factors that need to be considered in drug treatment, determining not only whether or not the drug is effective but also for how long efficacy can be maintained (see tolerance section below).

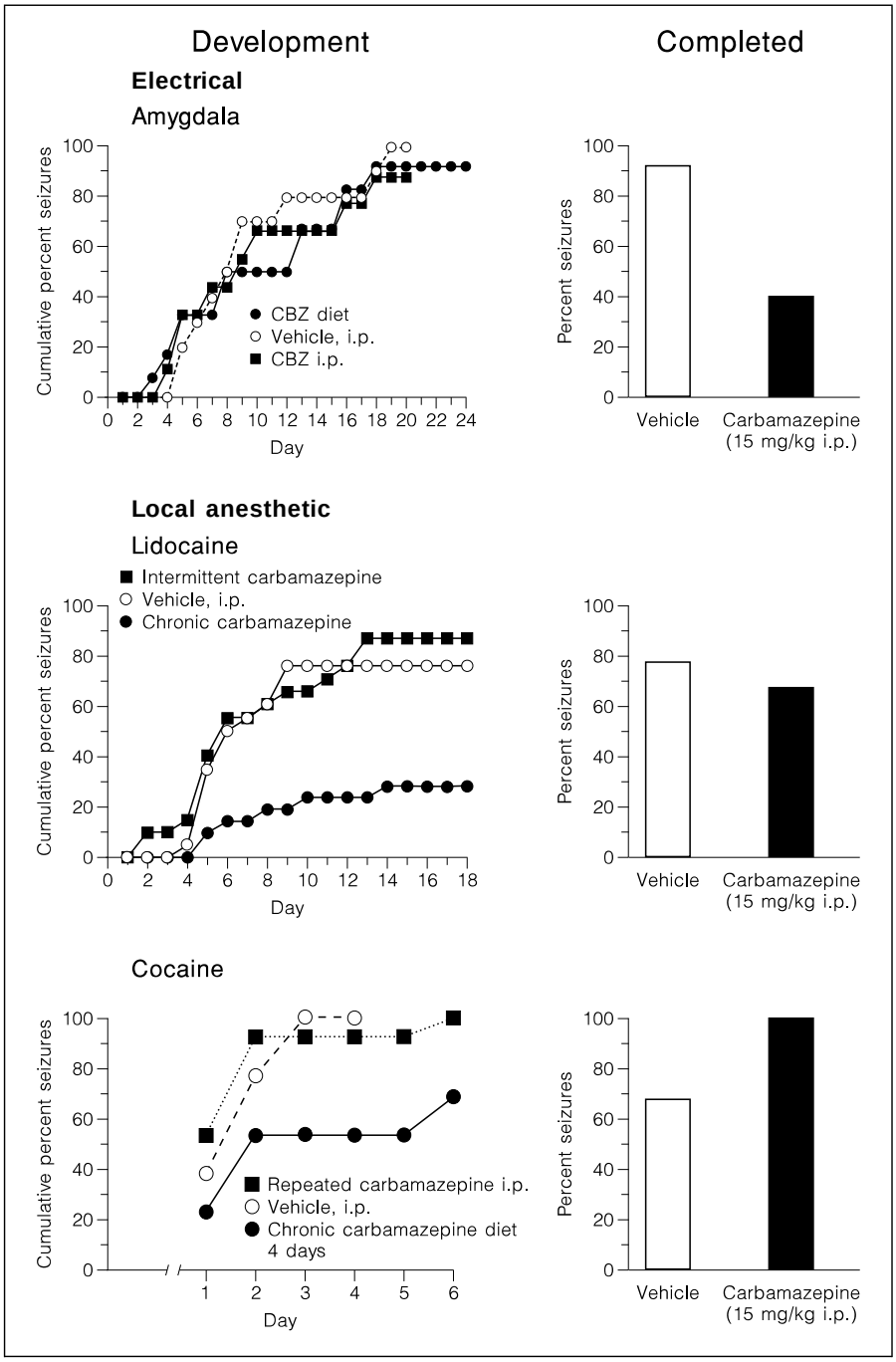

Fig. 2. Dissociations in anticonvulsant efficacy of carbamazepine based on seizure type, stage of kindling, and method of drug administration. Carbamazepine blocks completed amygdala-kindled seizures, but not their development (top). In contrast, chronic carbamazepine in the diet (but not repeated, intermittent, i.p. administration), blocks the development of lidocaine (65 mg/kg middle row)- or cocaine (65 mg/kg bottom row)-kindled seizures, but not completed or high-dose seizures.

How can we explain some of these findings using the kindling model?

There are a variety of data that illustrate some of the molecular and biochemical distinctions that occur between different stages of kindling development as well as between kindled seizure types. Clark et al. [26] have measured mRNA expression for the immediate early gene c-fos as an indicator of activation of the nervous system to map the spread of activity during the kindling process. Initial stimulations of the amygdala produced a predominantly ipsilateral activation of the cortical areas surrounding the amygdala (i.e. piriform, perirhinal, and entorhinal cortices) and the hippocampus if a long afterdischarge was elicited (>30 s). Subsequent stimulations

(associated with behavioral seizure progression) induced a more widespread activation of c-fos bilaterally, although mostly still restricted to limbic regions, and some other cortical areas (e.g. parietal cortex). Remarkably, a spontaneous seizure (assessed in one animal) was found to induce c-fos mRNA expression in the hemisphere contralateral to the stimulation only [Clark, unpubl. observations].

Similar patterns of change in the neuroanatomical distribution of the kindled seizure have been reported using deoxyglucose as a marker of neuronal activity [27, 28], and physiological recording techniques [3, 29, 30]. Pinel [3, 30] found a shift in the recorded seizure activity during a spontaneous seizure from subcortical to cortical regions. Thus, as the kindling process develops, the behavioral manifestations shift, associated with clear changes in gene activation, and pharmacological responsivity.

Our observations that oral vs. intraperitoneal drug administration produce distinct effects are not so surprising when one considers that in many circumstances (including kindling itself), chronic continuous exposure to a stimulus can produce radically different outcomes compared to repeated intermittent exposures. For some drugs (e.g. stimulants), this can result in the behavioral manifestations of sensitization [31–33] or tolerance [34, 35] to the drug's effects. Kindling requires intermittent stimulation and does not occur if continuous trains are applied to the same area [1]. Thus, the brain adaptations to a drug and the effects of the drug itself are likely to be different based on the method of drug administration, resulting in different behavioral and therapeutic profiles. It follows then that different medications, or schedules of drug administration, may be required to target different structures or different physiological pathologies during the course of illness progression, and that etiological differences in the illness can also be important for determining optimal treatment strategies.

Changing Response to Drugs Based on History of Drug Exposure: Tolerance

The response to drugs can change following repeated exposure, resulting in tolerance or sensitization to their behavioral, biochemical, or physiological effects. The nature of this change can also be affected by many factors, including, as mentioned above, e.g., route or schedule of drug administration [36]. In a series of studies described below, we will introduce the notion of contingent tolerance and suggest that this form of tolerance occurs because of a loss of endogenous seizure-dampening modifications of the nervous system. What these data imply for clinical therapeutics is that not only must the direct effects of the drug be considered in evaluating a treatment, but also the indirect or adaptive changes that occur in response to both the drug and the illness. Ultimately, strategies aimed at minimizing the likelihood of tolerance development and enhancing endogenous adaptive responses should be possible.

Functional or Contingent Tolerance

We first observed contingent tolerance to carbamazepine's anticonvulsant effects in an amygdala-kindled seizure model [37], and found this to be the *only* form of tolerance we could produce with this drug. Contingent tolerance occurs when kindled animals are treated with carbamazepine *before* each kindling stimulation for a number of days ($\sim$5–7 days), but not when animals are given comparable amounts of the drug *after* the seizure or stimulation has occurred (fig. 3). Contingent tolerance to anticonvulsant agents has also been demonstrated by other investigators [38–40] using diazepam and alcohol against amygdala-kindled seizures. Further, we have found that contingent tolerance to diazepam's anticonvulsant effects can be demonstrated in a different seizure model – that of lidocaine kindling.

Thus, contingent tolerance appears to be a robust and possibly widespread form of tolerance worthy of consideration in clinical therapeutics. Contingent tolerance represents a functional change in the response to a drug; it is based on what is occurring at the time the drug is present in the brain. If stimulation occurs, tolerance to the drug's anticonvulsant effect develops; if stimulation does not occur (e.g. after the seizure is completed) tolerance to this effect of the drug does not occur. In this regard, contingent tolerance is quite a remarkable phenomena, especially since the response being modulated, i.e. a seizure, is thought of as hard-wired and the same on each occasion. What the tolerance data imply is that with each kindling stimulation, there continues to be a set of brain responses undergoing modulation based on whether or not a drug is present. This occurs even in animals that are fully kindled and have been reliably experiencing seizures on many prior occasions.

Demonstration of Endogenous Anticonvulsant Adaptations

In a series of biochemical and molecular studies, we (and others) have discovered a number of changes in the

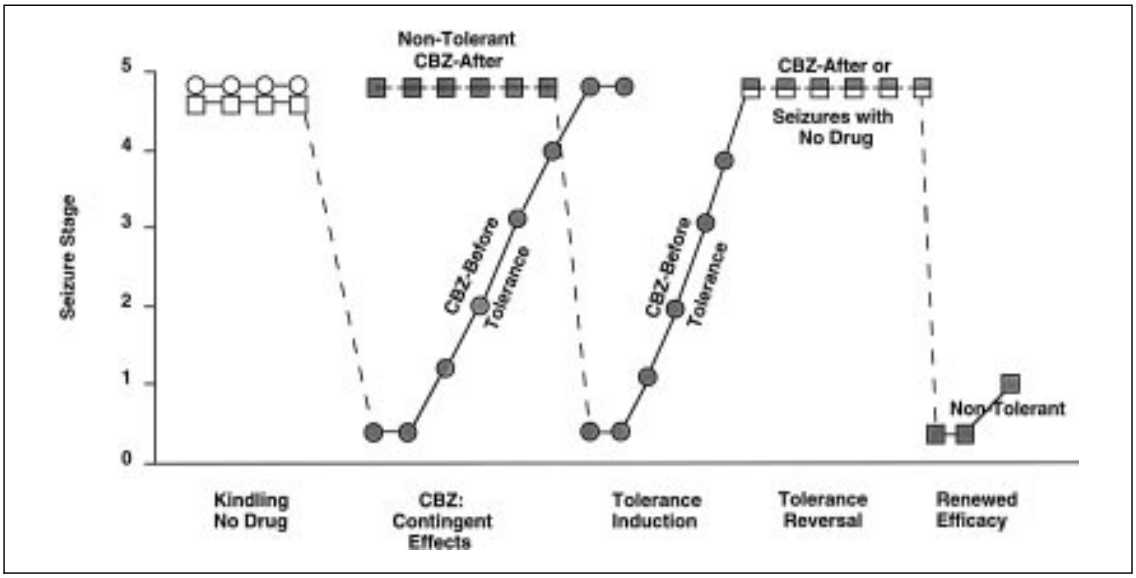

Fig. 3. Schematic illustration of contingent tolerance to carbamazepine: development and reversal. In fully kindled animals (open circles) carbamazepine treatment inhibits kindled seizures (filled circles). Repeated drug administration *before* (filled circles; solid lines), but not *after* (filled squares; dotted lines), stimulation results in tolerance development. Tolerance induced in this manner can be reversed by a period of kindled seizures without drug (open half-squares, dotted lines) or with drug administration *after* each seizure (filled half-squares, dotted lines). Modified from Weiss et al. [41].

brain that are associated with kindled seizures. These include an increase in benzodiazepine and $GABA_A$ receptor binding, and increases in mRNA expression for a number of peptides, growth factors, and immediate early genes [41, 42]. Some of these factors [e.g. thyrotropin-releasing hormone (TRH) or neuropeptide Y (NPY)] have been shown to be anticonvulsant in kindling or other seizure models [43–45]. Thus, their enhancement following a seizure suggests that they may be endogenous adaptations that could alleviate or decrease the seizure response to subsequent stimulation (or prevent the development of status epilepticus).

Remarkably, in animals that have become tolerant to carbamazepine, and are experiencing seizures upon each kindling stimulation, some of these 'seizure-induced' alterations fail to occur (fig. 4) [41]. That is, in animals that are tolerant to carbamazepine, but not those that have received equal amounts of drug after the kindling stimulation occurred (i.e. those that are not tolerant), there is a failure of seizures to upregulate $GABA_A$ receptors and to increase the mRNA expression for TRH and NPY [46, 47]. Therefore, the presence of the drug during the kindling stimulation must have, in some way, signaled the nervous system not to respond by increasing its GABA receptor function, e.g. in the rats treated with vehicle or drug *after* the stimulation, no such signal was present and an upregulation of this system occurred. In other words, the treatment altered the functional response to the stimulation, in part, by diminishing some of the brain's natural therapeutic mechanisms.

Function of Endogenous Anticonvulsant Adaptations

That these mechanisms are functionally important is suggested by other data that we have collected from kindled animals given a time-off period from seizures [41]. Although these animals remain susceptible to the kindling stimulation, they become less responsive to anticonvulsant medication. We have found diminished efficacy of both carbamazepine and diazepam following 4 or 10 days of time off from seizures, respectively. These few days of time off from seizures are also associated with a decrease in the seizure threshold in kindled animals. Thus, these data indicate that some seizure-related adaptations contribute to the maintenance of a stable seizure threshold, in addition to or perhaps leading to greater anticonvulsant responsivity. Moreover, these mechanisms, unlike the kindling process itself, appear to be transient, i.e. they dissipate within days of the last seizure. The reasons for this are unclear, but the consequences are very clear. It appears that there is greater

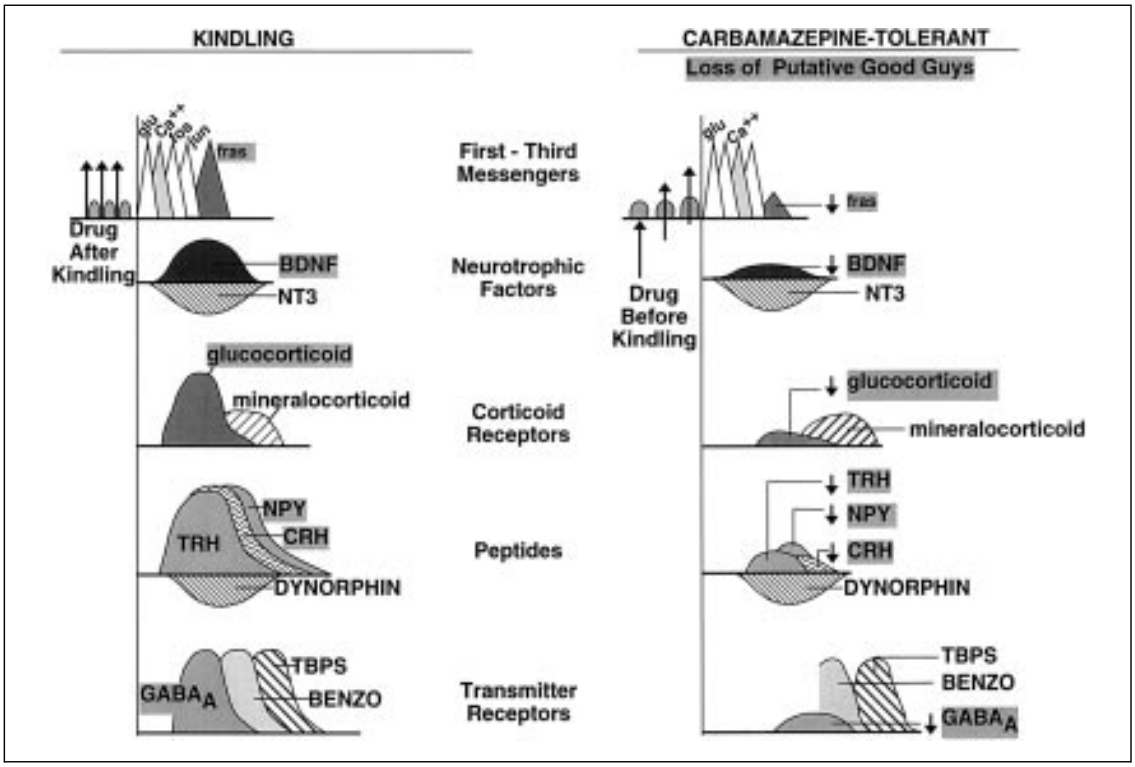

Fig. 4. Schematic illustration of changes in gene expression or receptor binding measured after kindled seizures induced in animals that were (right) or were not (left) tolerant to carbamazepine. Shaded areas represent seizure-induced changes that may be compensatory anticonvulsant adaptations (e.g. increases in $GABA_A$ and benzodiazepine receptor binding). In carbamazepine-tolerant animals, seizures fail to induce a number of biochemical changes including the increases in $GABA_A$ receptor binding as well as the increases in mRNA expression for the peptides TRH and NPY. The loss of these putative anticonvulsant adpatations may be responsible for the development of tolerance to carbamazepine's effects.

stability or longevity to the pathological processes of kindling (ultimately leading to spontaneous epilepsy) than to the adaptive responses aimed at dampening the kindling process.

Based on these data, we would suggest that effective prophylactic treatments may be required for the long-term management of illness to combat the relatively stable pathological processes. The endogenous compensatory mechanisms have already failed (as evidenced by the presence of the illness) and seem preprogrammed to fail again due to their transient nature, unless otherwise enhanced with exogenous treatment.

Functional or Contingent Inefficacy

The fact that some endogenous adaptations fail to occur when drugs are present during an illness-precipitating event (i.e. electrical stimulation in amygdala kindling) also suggests caution in the use of questionable prophylactic treatments aimed at preventing illness development. For example, in the case of post-traumatic epilepsy, the data now indicate that phenytoin is not effective in blocking the development of epilepsy. Our preclinical data, described below, suggest an even more pernicious outcome of ineffective prophylaxis – that of increased subsequent resistance to drug treatment and a more malignant course of illness, due to the failure of endogenous illness-related adaptations to develop.

We have found that carbamazepine treatment administered to rats during amygdala-kindled seizure development (when it is without effect, see fig. 1), not only is unable to alter the course of kindling, but renders the animals subsequently unresponsive to carbamazepine during the phase of the illness when it otherwise would be effective (i.e. on fully developed kindled seizures; fig. 5) [37]. Based on the data from our tolerance studies, we would surmise that during the course of kindling develop-

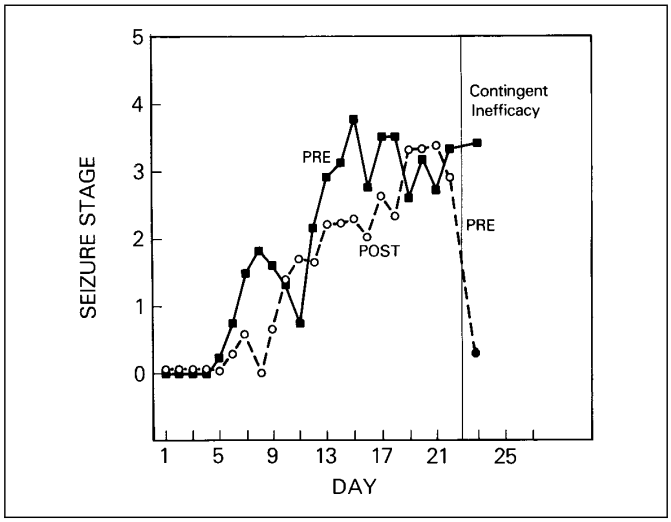

Fig. 5. The development of kindling is illustrated in rats treated with carbamazepine *before* (filled squares; pre) or *after* (open circles; post) electrical stimulation. The group mean seizure stage is plotted as a function of day of stimulation. The group receiving carbamazepine *before* each stimulation did not respond to the drug during any phase of treatment (contingent inefficacy), whereas the group treated with carbamazepine *after* stimulation showed a marked anticonvulsant response when they received carbamazepine before stimulation on day 23 (filled circle). Adapted from Weiss and Post [37].

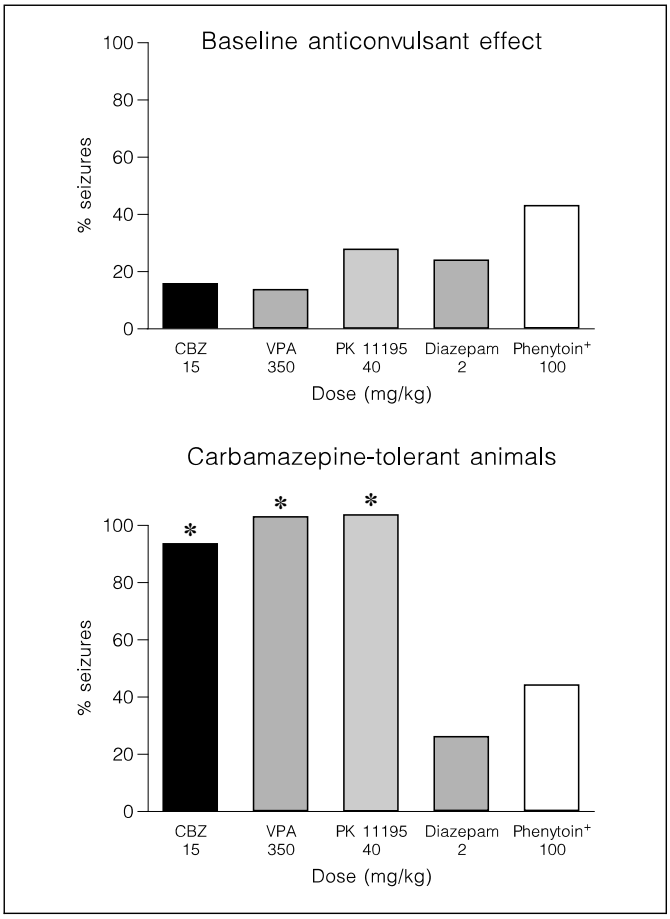

Fig. 6. Differential cross-tolerance to carbamazepine. This figure summarizes a series of studies in which amygdala-kindled animals were evaluated for their anticonvulsant response to various drugs before (top) and after (bottom) tolerance development to carbamazepine. Cross-tolerance was observed to PK 11195 (the peripheral-type benzodiazepine antagonist) and sodium valproate (VPA), but not to clonazepam, diazepam (central-type benzodiazepine agonists) or phenytoin. Note that when testing for cross-tolerance to phenytoin, the stimulation intensity was reduced to the minimum current required to produce a generalized motor seizure in each animal. This procedural change was necessary in order to achieve an anticonvulsant effect of this drug on amygdala-kindled seizures. Even using threshold stimulation current, tolerance to carbamazepine did not alter the response to phenytoin. $^{*}p < 0.05$; $^{+}$threshold kindling stimulation. From Weiss et al. [41].

ment, these animals did not induce the same endogenous seizure-ameliorating mechanisms as those rats not pretreated with carbamazepine. We observed that the control group, which was made up of rats that were administered carbamazepine *after* each electrical stimulation, readily responded to carbamazepine when completed kindled seizures developed. Thus, as in the tolerance studies, contingent application of a drug (*before*, but not *after* stimulation) resulted in diminished efficacy of the drug – in this case on subsequent trials when it otherwise would have become effective.

Cross-Tolerance between Anticonvulsant Treatments

Finally, we have found that in animals rendered contingently tolerant to carbamazepine, cross-tolerance also occurs to some, but not all other anticonvulsant drugs (fig. 6) [41]. Notably, cross-tolerance occurs only when the drug is given *before* and not *after* the kindling stimulation, indicating that it is not based on pharmacokinetic interactions between the drugs, but rather is dependent on pharmacodynamic changes occurring in response to contingent drug administration [48, 49]. We observed cross-tolerance to PK-11195 (which acts at the peripheral-type benzodiazepine receptor), and valproate, but not to diazepam (which acts at the central-type benzodiazepine receptor), or phenytoin.

The reasons for these differential effects are likely related to the biochemical consequences of contingent tolerance, some of which we have already described. For example, although carbamazepine does not directly affect GABA receptor function, it does block the kindling-

induced upregulation of these receptors. To the extent that valproate's anticonvulsant effects are related to this system, this could explain why carbamazepine-tolerant animals show cross-tolerance to valproate. Surprisingly, the seizure-induced upregulation of the benzodiazepine receptors (fig. 4) is not affected by contingent tolerance to carbamazepine (i.e. it still occurs in tolerant animals), perhaps explaining why cross-tolerance to diazepam is not readily observed. Obviously, this is overly simplistic and speculative, being based solely on the findings we have so far obtained. It is likely that other systems are also involved that we have not yet investigated, and that the complexities of the benzodiazepine-GABA receptor complex need to be understood better in this regard. Nevertheless, using this model, we can begin to tease apart and answer some of these questions, and hopefully, we can also formulate clinical predictions, which can then be tested in the appropriate patient populations.

Clinical Implications

Taken together, the tolerance data have multiple clinical ramifications, some of which have already been briefly discussed. However, the most obvious consideration is the potentially higher vulnerable state of the patient upon discontinuation of a partially or formerly therapeutic agent. Increased incapacity would be predicted due not only to the pre-existing illness, but also to the loss of endogenous illness-related adaptations that would have diminished during the course of drug treatment. Therefore, treatment should be withdrawn cautiously with a view toward ameliorating emerging symptomatology using other medication or treatment strategies not likely to show cross-tolerance to the former, now ineffective, agent.

Furthermore, the implications of the tolerance data are *not* to withhold treatment or to remove a currently effective medication. If an illness is evident (as stated above), then the endogenous adaptive mechanisms have already proven insufficient. Instead, attempts should be made to identify and enhance these adaptations if possible, as well as to bring in additional systems that might counter illness occurrence or progression. If a medication is effective, its withdrawal is counterproductive since the current state of the patient is likely dependent upon the adaptations that have occurred (or failed to occur) in response to the medication as well as the illness. Therefore, withdrawal of treatment will result in a reconfiguring of these changes, likely increasing the patient's vulnerability to relapse, possibly to a more refractory form of the illness. This has already been observed in affective disorder patients who were successfully treated with lithium for many years, stopped treatment, and then relapsed with a much more treatment-resistant form of the illness that ended in suicide in a number of cases [50, 51]. Thus, the overall picture emerging from the preclinical and clinical data is that additional factors relating to adaptive responses need to be considered when a treatment is withdrawn, in the use of drugs in general, and particularly if the drugs are of questionable efficacy at the time of use.

On the more positive side, we have found contingent tolerance to be reversible, at least over a few drug-tolerance exposures [37]. In our paradigm, the animals are required to re-experience seizures in the absence of drug (even if the drug continues to be administered *after* the seizure has occurred). Thus, we presume that when the illness is re-experienced in the absence of drug, some of these endogenous factors can be re-elicited, reinstating drug responsivity.

This did not apear to be the case in the lithium-discontinuation-induced refractory patients, but again that situation differed from tolerance since the drug was effective at the time it was discontinued. Therefore, the patients may have already been maximally utilizing their own internal adaptations along with the exogenous effects of the drug to manifest a healthy state. Once the drug was removed, the illness may have gained access to additional neural substrates, much the same way that a malignancy can metastasize in cancer patients, rendering it less susceptible to treatment [50].

The other important notion that emerges from the tolerance data is that of identifying and enhancing endogenous therapeutic mechanisms in a clinically relevant manner [52]. While much of clinical research has focused on ameliorating the differences in behavior, biochemistry, and physiology that are found between patient and normal populations, we would suggest that enhancement of some of these differences could also be beneficial, i.e. those that reflect compensatory rather than pathological mechanisms.

This was the conceptual strategy behind our attempt to administer TRH to depressed patients [53, 54]. TRH has been reported to be elevated in the CSF of some depressed patients [55]. Based on its anticonvulsant properties [44, 45], and several earlier attempts to administer TRH peripherally for the treatment of depression [54–59], we hypothesized that it might be an endogenous adaptation that could be enhanced via exogenous administration. The initial TRH trials using both intracisternal and subcutaneous routes of administration have been very promising in some severely depressed, treatment-refrac-

tory patients [53, 54]. However, the effect has not been sustainable, even with repeated TRH administrations, in a long-term fashion [53]. This may reflect a more general problem with the notion of trying to enhance endogenous adaptive mechanisms, which, as indicated above, appear to be transient, or it may be particular to TRH, indicating that the optimal strategy for its delivery has not yet been discovered. Nevertheless, the hypothesis that an increase in TRH would improve rather than worsen the patients' condition was borne out, indicating that some observed abnormalities in an illness are compensatory rather than damaging.

Novel Physiological Treatment Strategies: Quenching

Our focus on the kindling model has also led to some novel physiological findings which may provide additional insights into treatment strategies for affective illness, as well as adding to the conceptual framework for considering illness progression and/or regression. Because kindling produces a relatively permanent change in neural excitability, the question of whether or not this could be reversed has remained an open and interesting one. Anticonvulsant or anti-epileptogenic agents can clearly block or suppress kindled seizures, but the underlying pathophysiology typically remains intact, and the drugs may become ineffective over time (e.g. with tolerance development). Therefore, we wondered whether different parameters of electrical stimulation might be applied to alter or reverse the kinding process in a long-lasting fashion.

We have recently discovered that electrical stimulation of the amygdala, using low-intensity direct current, can inhibit the development and expression of amygdala-kindled seizures, attributable at least partly to a threshold-increasing effect of the stimulation [Weiss et al., submitted]. The direct current does not appear to reverse the epileptic state in animals already fully kindled. However, it does induce a long-lasting increase in the seizure threshold, which is sufficient to block the seizure response to the previously effective stimulation. We have called this effect quenching, and arrived at these parameters of stimulation through a highly circuitous route briefly described below.

Development of the Quenching Paradigm: Long-Term Potentiation vs. Long-Term Depression

After several aborted physiological manipulations, all of which tended to exacerbate kindling or induce status epilepticus, we turned to a procedure that had been described in the literature to inhibit the effects of high-frequency stimulation in vitro. This procedure, which results in long-term depression (LTD) or depotentiation [60–64], involves the application of low-frequency (1–3 Hz) electrical stimulation for long durations ($\sim$15 min) to block or reverse the effects of brief high-frequency stimulus trains (e.g. 100 Hz for 1 s), used to produce long-term potentiation (LTP). LTP has been suggested as a cellular model of long-term memory since it is characterized by an enhanced physiological response to electrical stimulation, based on prior stimulation activity [65, 66]. LTP has been reported to occur in vivo as well as in vitro and can last for hours, days, or weeks depending upon the paradigm [61, 65, 66]. LTP has also been demonstrated in several brain regions [67–69] although it is most commonly and extensively investigated in the hippocampus, largely due to its relative ease of study based on the clearly defined circuitry in this region.

The stimulation used to produce kindling is similar to that used for LTP (50–100 Hz, $\sim$1 s) although there are some notable differences (e.g. bipolar vs. unipolar stimulation for kindling vs. LTP), and, kindling, in general, can be dissociated from LTP in a number of ways (e.g. longevity, pharmacology, knockout strain responses [70, 71]). Nevertheless, the notion that low-frequency stimulation, when applied after high-frequency stimulation, could reverse the effects of the latter [64, 72, 73], seemed intriguing and worth investigating in the kindling model. Thus, we began a series of studies using low-frequency (LTD-like) stimulation to attempt to block the effects of high frequency (LTP-like) kindling stimulation.

Quenching of Amygdala Kindling

By applying low-frequency stimulation (1 Hz, for 15 min, at the afterdischarge (AD) threshold intensity $+100$ μA) immediately after each kindling stimulation (100 Hz, 0.5 s, at AD threshold intensity), we were able to completely inhibit the development of kindled seizures and produce an increase in the AD threshold. This same stimulation applied for 1 week (15 min/day) to fully kindled animals also inhibited subsequent seizures when the kindling stimulation was delivered at the seizure threshold intensity. We termed this procedure quenching, and found that the inhibitory effects on seizure development and expression were long-lasting (weeks to months) and appeared to be largely related to the increase in afterdischarge and seizure thresholds produced by the stimulation [74].

In a series of follow-up studies, we discovered that quenching could be reliably induced only when certain stimulators were used, leading us to investigate what char-

acteristics of the stimulation were necessary for the quenching effect. Ultimately, we determined that the stimulators that were effective against kindling development and seizure expression were those that were simultaneously delivering a low-level direct current (DC) output in addition to the low-frequency stimulation. When we explored this parameter more systematically, we discovered that suppressive effects on kindling development could be achieved with intensities of direct current as low as 1 μA, administered for 15 min/day. Similarly, seizures could also be inhibited by direct current stimulation using an intensity of 10 μA for 15 min, repeated for 7 or 14 days. The effects of the DC on afterdischarge and seizure threshold were intensity-dependent (i.e. greater at intensities of 10–15 μA) and long-lasting even after the DC treatment was discontinued [Weiss et al., submitted].

Since DC at higher intensities (in the mA range) can produce neuronal damage, we are currently investigating whether such damage could also be a factor in the observed DC quenching effects. Our preliminary observations do not indicate any gross damage at the site of stimulation or elsewhere in the brain; however, careful histological examination of the tissue is still required.

We are pursuing this avenue of investigation to determine how DC could induce the observed changes in seizure and after discharge threshold, as well as how it might produce effects distal to the site of stimulation. In previous studies of the biochemical consequences of quenching, we observed enhanced binding to benzodiazepine receptors in the perirhinal and entorhinal cortices [75], which are projection sites of the amygdala. To the extent that these effects were also dependent upon the DC stimulation, which still needs to be demonstrated, mechanisms of neural or non-neural communication (e.g. via gap junctions) will be explored.

Irrespective of the mechanisms that will ultimately be elucidated for quenching, the observation that some forms of electrical stimulation to the brain can induce compensatory or neuroprotective effects leads to the idea that physiological manipulations could also be developed to treat psychiatric or neurologic illnesses. That these effects of quenching can last for long periods of time after the stimulation is discontinued further suggests its utility. Thus, in addition to the pathophysiological changes that can be induced in a long-lasting manner by kindling, there may also be protective effects that can also be induced by physiological manipulations such as quenching. The question of whether a pathological, evolving process can be reversed once it has been engendered still remains open for further investigation. But these different forms of stimulation may suggest new clinical options as well as providing useful models for the study of long-term neural plasticity and/or pathology.

Clinical Applications

The most direct application of quenching would be in patients with treatment-refractory epilepsy. Often, to remove the damaged, hyperexcitable tissue, these patients require surgery, which is preceded by the intracerebral implantation of electrodes to identify the epileptic focus. Quenching stimulation, if effective in elevating the seizure threshold, may prove to be a less invasive procedure. Moreover, the possibility of combining physiological and pharmacological treatment strategies might also prove useful, especially if procedures can be developed that enhance the positive effects of each treatment and diminish the problematic side effects which could result from the need for high doses or high intensities of stimulation with either method used alone.

In addition, since quenching stimulation has been shown to increase the threshold for a pathological response (in this case, seizures), we would suggest that it may also be possible to develop analogous forms of stimulation to increase the threshold for triggering a pathological psychiatric state, such as anxiety or depression.

The use of physiological stimulation strategies in psychiatric patients is already being explored thanks to the development of high-intensity magnets that can be controlled to produce electrical stimulation of the brain [76–79]. This procedure is called repeated transcranial magnetic stimulation (rTMS), and it can be applied extracranially, allowing for non-invasive targeted brain stimulation.

Among the variables being explored in the use of rTMS is the frequency of stimulation as it relates to illness-type and metabolic activity in the brain as assessed by PET imaging methods. This variable was chosen for study because of the data illustrating a stimulation frequency dependence for LTP and LTD in vitro, as well as for kindling and quenching in vivo (based on our earlier findings prior to the discovery of the DC component of quenching) [80]. Specifically, the hypothesis was that high-frequency rTMS (20–25 Hz) would be effective in depression since it might reverse the hypometabolic frontal cortical state associated with depression [81–83], while low-frequency rTMS (1 Hz) should be effective in posttraumatic stress disorder (PTSD), since it should decrease the temporal cortical hypermetabolism associated with PTSD [84, 85]. Preliminary data using PET imaging techniques support the hypothesis that the high frequency rTMS increased

brain activity and normalized a depressed hypometabolic state [76] and vice versa for low-frequency rTMS [86, 87]. The data also preliminarily indicate a positive therapeutic response to the 1 Hz stimulation in PTSD patients [86, 87], as well as to the 20-Hz stimulation in depressed patients [76]. However, methodologies are still needed to enhance and, particularly, to extend the duration of these clinical effects.

The quenching effect has now been reattributed to the stimulation with direct current rather than low frequency as originally described. Whether direct current will also prove useful in psychiatric illness and, particularly, whether it could be used to enhance the duration or magnitude of effect produced by magnetic stimulation or pharmacological therapies remains an open question. Further technology may be required to optimize its delivery without invasive brain electrode implantation, but these questions for future research all emerged because of preclinical findings and serendipity. The interplay between pharmacological and physiological strategies has not even begun to be explored, and may ultimately prove to be the most worthwhile approach, short of a cure for the illness itself.

Conclusion

Kindling as a shared mechanism for affective illness and epilepsy may or may not ultimately pan out. Kindling as an indirect model for the study of long-term neural plasticity, illness progression, and pharmacological sensitivity has already proven valuable in generating novel questions for clinical therapeutics and for conceptualizing the course of psychiatric illness in evolution.

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