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A Speculative Model of Affective Illness Cyclicity Based on Patterns of Drug Tolerance Observed in Amygdala-Kindled Seizures

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Abstract

In this article, we discuss molecular mechanisms involved in the evolution of amygdala kindling and the episodic loss of response to pharmacological treatments during tolerance development. These phenomena allow us to consider how similar principles (in different neurochemical systems) could account for illness progression, cyclicity, and drug tolerance in affective disorders. We describe the phenomenon of amygdala-kindled seizures episodically breaking through effective daily pharmacotherapy with carbamazepine and valproate, suggesting that these observations could reflect the balance of pathological vs compensatory illness-induced changes in gene expression. Under certain circumstances, amygdala-kindled animals that were initially drug responsive can develop highly individualized patterns of seizure breakthroughs progressing toward a complete loss of drug efficacy. This initial drug efficacy may reflect the combination of drug-related exogenous neurochemical mechanisms and illness-induced endogenous compensatory mechanisms. However, we postulate that when seizures are inhibited, the endogenous illness-induced adaptations dissipate (the "time-off seizure" effect), leading to the re-emergence of seizures, a re-induction of a new, but diminished, set of endogenous compensatory mechanisms, and a temporary period of renewed drug efficacy. As this pattern repeats, an intermittent or cyclic response to the anticonvulsant treatment emerges, leading toward complete drug tolerance.

We also postulate that the cyclic pattern accelerates over time because of both the failure of robust illness-induced endogenous adaptations to emerge and the progression in pathophysiological mechanisms (mediated by long-lasting changes in gene expression and their downstream consequences) as a result of repeated occurrences of seizures. In this seizure model, this pattern can be inhibited and drug responsivity can be temporarily reinstated by several manipulations, including lowering illness drive (decreasing the stimulation current), increasing drug dosage, switching to a new drug that does not show crosstolerance to the original medication, or temporarily discontinuing treatment, allowing the illness to re-emerge in an unmedicated animal. Each of these variables is discussed in relation to the potential relevance to the emergence, progression, and suppression of individual patterns of episodic cyclicity in the recurrent affective disorders. A variety of clinical studies are outlined that specifically test the hypotheses derived

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from this formulation. Data from animal studies suggest that illness cyclicity can develop from the relative ratio between primary pathological processes and secondary endogenous adaptations (assisted by exogenous medications). If this proposition is verified, it further suggests that illness cyclicity is inherent to the neurobiological processes of episode emergence and amelioration, and one does not need to postulate a separate defect in the biological clock. The formulation predicts that early and aggressive long-term interventions may be optimal in order to prevent illness emergence and progression and its associated accumulating neurobiological vulnerability factors.

Index Entries: Manic depressive illness; gene expression; cyclicity; recurrence; time-off effect; endogenous adaptations; contingent tolerance.

Introduction

A major conundrum in unipolar and bipolar affective disorder relates to how episodes of illness are linked to a recurrent mechanism that often develops a pattern of regular or irregular cyclicity. Patterns of cycling tend to be characteristic for each individual, but they can also be variable within individuals. This individual variability in average cycle duration, ranging from days to months to years, makes it unlikely that a given "clock" mechanism or alteration in circadian rhythm accounts for the patterns of recurrence. Despite this irregularity, there is a general tendency for episodes to recur with increasing severity (Maj et al., 1992) and/or rapidity over time; i.e., a decreasing well-interval between successive episodes in either untreated patients or in those refractory to medications (Kraepelin, 1921; Post et al. 1984b). A similar acceleration in episode breakthroughs is observed during the development of tolerance to a previously effective medication (Post et al., 1984b, 1995; Post, 1990b; Weiss et al., 1994).

The response of both manic and depressive phases of bipolar illness to single agents, such as lithium carbonate, carbamazepine, valproate, or, acutely, ECT, also suggests some unitary mechanism underlying the divergent phases. Episodes of mania and depression that are apparently so polar opposite in terms of mood, motor activity, energy, sociability, and vegetative functions (and at times, sleep) would, on superficial consideration, appear unlikely to respond to a single agent. We believe, however, that it is a convergence of these issues in bipolar illnesses; i.e., recurrence, regular or irregular cyclicity, response to single agents, and acceleration in the rate of breakthrough episodes, that may allow one to conceptualize a coherent framework for the mechanisms underlying both generation of individual episodes and their cyclicity.

Our basic formulation is that episodes of illness are associated with two types of opposing neurobiological processes, in part coded at the level of gene expression. One process is related to the primary pathology driving the illness itself and the other process is associated with secondary compensatory endogenous adaptations that occur in the attempt to re-establish homeostasis (Post and Weiss, 1992a; Weiss et al., 1995). Both processes are constantly changing and evolving. For ease of identification and discussion we will sometimes refer to the entire range of putative primary pathological processes that drive the illness as the "bad guys" and the secondary adaptations that attempt to compensate and renew equilibrium as the endogenous "good guys." During periods of illness we postulate that the biochemistry of the primary pathological driving force predominates, but that these and the episodes themselves eventually engender endogenous compensatory mechanisms that then succeed in terminating the episode, particularly if additional exogenous mechanisms (e.g., psychotropic drugs) are added to help the endogenous ones. Following termination of the episode there is a dissipation of the endogenous episode-engendered mechanisms, eventually leading to a renewed dominance of the primary pathophysiological processes and to the re-emer-

gence of a new episode with its subsequent engendering of another round of compensatory adaptations aimed at illness modulation. This iterative process would then result in episode cyclicity.

In the face of maximum pathological illness drive and inadequate endogenous or exogenous therapeutic mechanisms, there would be periods of persistent illness. In contrast, in the face of maximum endogenous compensatory mechanisms and/or exogenous therapeutic effects of medication, there would be a relative absence of illness. When both processes are close to their respective thresholds, however, we postulate that there would be a fragile balance, resulting in intermittent illness suppression and recurrence, i.e., episode cycling would occur. Given the relative permanence of the primary pathological processes because of long-lasting genetic and/or experiential vulnerability and their putative accretion and progression by successive episodes of illness (Post, 1992), and the more transient nature of the endogenous adaptations (and their partial inhibition by some medications during tolerance development), the episodes of illness would fitfully progress toward faster recurrence over time.

Empirical Basis for This Formulation: Findings Observed in Drug Treatment of Amygdala-Kindled Seizures

Kindling is the intermittent (usually once daily) stimulation of the brain that is initially without effect but, with repetition, goes on to evoke a full-blown convulsion to the previously subconvulsant stimulation (Goddard et al., 1969; Racine, 1978). Following sufficient numbers of induced seizures they emerge spontaneously in the absence of exogenous electrical stimulation. The process can be divided roughly into three phases: development, when afterdischarges increase in duration, spread, and complexity; completed, when full-blown seizures reliably occur to each stimulation; and spontaneous, when seizures emerge autonomously. These different phases are associated with biochemical changes in immediate early genes (IEGs) (Morgan and Curran, 1990), related transcription factors, and growth factors (Clark et al., 1991, 1994a; Smith et al., 1995), and late effecter genes (LEGs), such as peptides, receptors, and enzymes (Rosen et al., 1992, 1993). Additionally, different phases of kindling evolution are associated with differential pharmacological responsivity (Wada, 1977; Baltzer et al., 1981; Pinel, 1983; Albertson et al., 1984; Schmutz et al., 1986; Weiss and Post, 1987; Post et al., 1990b) and distinct neuroanatomical reorganization (Hovorka et al., 1989; Geinisman et al., 1990; Sutula, 1991, 1992b; Wallace et al., 1991). For example, in terms of pharmacological responsiveness, carbamazepine is a highly effective anticonvulsant against the completed phase amygdala-kindled seizures, but is ineffective in preventing the early development phase (Weiss and Post, 1987; Post et al., 1991). Conversely, diazepam is effective in the early and completed phases of kindling, but is ineffective against spontaneous seizures, and phenytoin shows the opposite pattern (Pinel, 1983).

Preclinical Model for Tolerance and Seizure Cycling During Anticonvulsant Treatment

Carbamazepine (Post et al., 1990a, 1994) and valproate (Calabrese and Delucchi, 1989; McElroy et al., 1992; Calabrese et al., 1993) are effective in the prevention of manic and depressive recurrences in patients with bipolar illness when used alone or in combination (Keck et al., 1992; Ketter et al., 1995). However, as is the case with lithium (Maj et al., 1989a; Post et al., 1992a, 1993), a subgroup of patients may show a progressive loss of efficacy (perhaps via tolerance) during long-term treatment (Post, 1989; Post et al., 1990a; McElroy, 1992, personal communication). These episodes may break through prophylactic treatment with mood stabilizers, increasing frequency and severity until a complete loss of response is observed. The tolerance phenomenon and poten-

tial ways of preventing or reversing its development have recently begun to be explored.

In the course of our preclinical studies of the efficacy of carbamazepine and valproate against amygdala-kindled seizures, we observed tolerance to the anticonvulsant effects of these agents emerging episodically in a temporal pattern resembling the periodic breakthroughs in affective disorder. A closer examination of the factors influencing and the mechanisms underlying development of tolerance to the anticonvulsant effects of carbamazepine and valproate might provide insights into the types of mechanisms (perhaps in different neuronal systems) involved in the loss of response to these same agents in the treatment of the affective disorders.

Cyclicity in Anticonvulsant Response to Carbamazepine Using Intermediate Intensity Stimulation

Although initial treatment with carbamazepine (15 mg/kg, ip) is highly effective in suppressing seizures in fully kindled animals (i.e., after numerous stage 4 or 5 seizures), repeated once-daily administration of carbamazepine before each stimulation rapidly results in tolerance to its anticonvulsant effects against seizures induced by high or suprathreshold electrical stimulation (800 μA) (Weiss and Post, 1990). However, in animals stimulated at half that current intensity (400 μA), we observed highly individualized patterns of tolerance development to carbamazepine characterized by episodic, and at times, cyclic emergence of seizures. As illustrated in Fig. 1A, most animals appear to show intermittent patterns of seizure breakthroughs with a general progression toward more complete loss of anticonvulsant efficacy. However, even at the outset, some animals were relatively persistently responsive to carbamazepine at this dose and stimulation (Fig. 1A, bottom), whereas others were relatively nonresponsive (Fig. 1A, top). Although some animals showed periods of slower cycle patterns, others showed ultra-fast, essentially 48-h cycling (i.e., seizures on one day and not the next). These data suggest a large interindi-

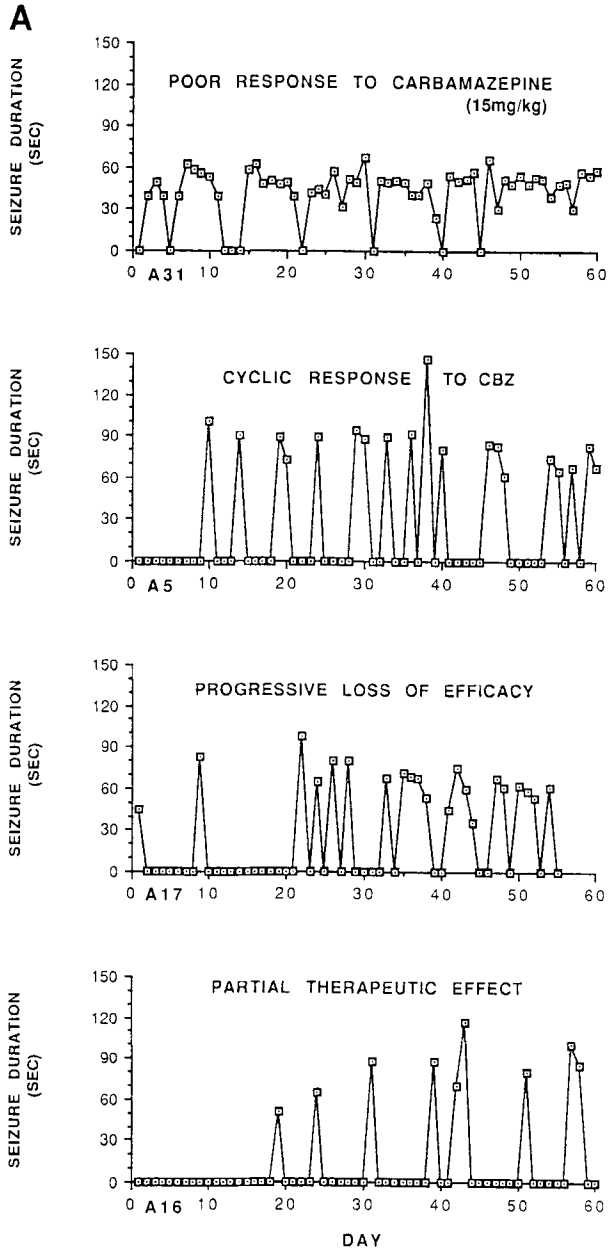
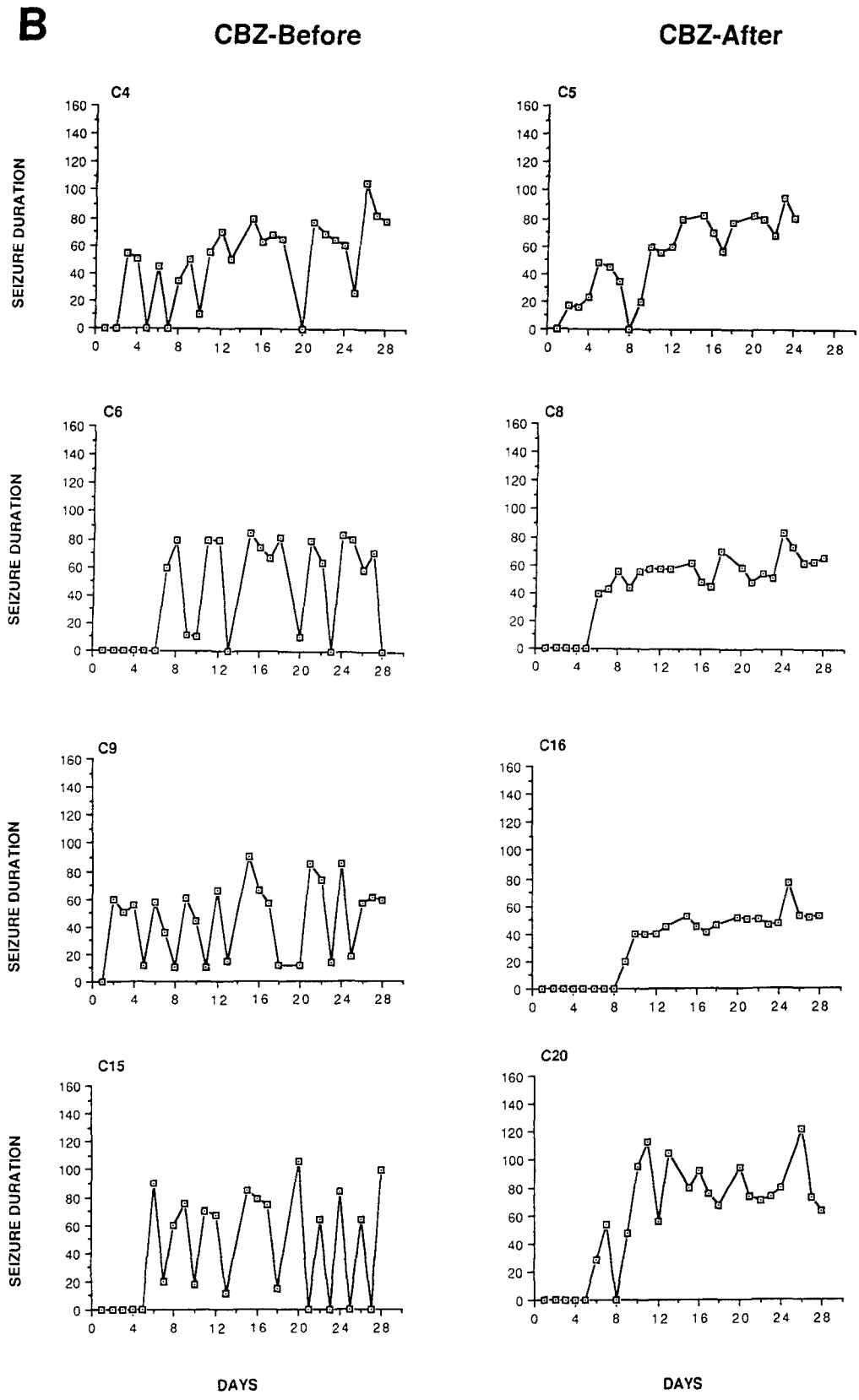


Fig. 1. **(A)** Variable and oscillating patterns of tolerance emergence to carbamazepine's anticonvulsant effects in individual rats. Kindling stimulation was administered at 400 μA. Motor seizure duration is plotted on the ordinate and days of electrical stimulation (with drug treatment) are plotted on the abscissa. **(B)** *(opposite page)* Oscillations in kindling development during contingent treatment with carbamazepine. Seizure duration as a function of day of stimulation is plotted for individual rats. Rats treated with carbamazepine before each stimulation (left column) show an oscillating pattern of seizure development compared to those treated with carbamazepine after stimulation (right column).


B
CBZ-Before
CBZ-After
C4
C5
C6
C8
C9
C16
C15
C20
SEIZURE DURATION
DAYS
0 4 8 12 16 20 24 28
0 20 40 60 80 100 120 140 160

vidual variability in initial responsivity to the drug and the tendency for faster or slower cyclic seizure breakthroughs to occur despite repeated drug administration. Initially, as can be seen across animals, there were relatively longer periods between successive seizures progressing toward a shortening of these intervals, indicating a trend toward loss of efficacy in the group as whole (*see* Fig. 1A).

Another instance of cyclic seizure emergence during carbamazepine treatment was observed when the drug was administered prior to the kindled stimulation during the development of amygdala-kindled seizures. Despite the inability of carbamazepine to influence the rate of amygdala kindling development in the group as a whole, the individual animal's patterns of seizure development were markedly different in those treated with carbamazepine before vs after the stimulation. In ten of the 12 animals receiving carbamazepine before the stimulation, marked oscillating patterns of seizure evolution were observed with an overall tendency toward consistent seizure occurrences (Fig. 1B). When carbamazepine was given after stimulation only two of nine showed this type of oscillatory pattern of seizure evolution. Thus, carbamazepine exposure *per se* (i.e., after the stimulation) during the phase of kindling development was not critical for the cyclic patterns of seizure development, but the presence of the drug during the electrical stimulation appears to be crucial for inducing such cyclic patterns.

Cyclicity in Anticonvulsant Response to Valproate Using High Intensity Kindling Stimulation

At conventional anticonvulsant doses (250 mg/kg) and maximal stimulation current (800 μA), a general pattern of episodic seizure breakthrough progressing toward tolerance was again observed for valproate (Fig. 2). Individual animals also showed marked differences in their patterns of cyclicity of seizure occurrence alternating with seizure suppression. The distinct patterns of cyclicity in individual animals were demonstrated across all seizure parameters including afterdischarge duration and seizure stage although only the seizure

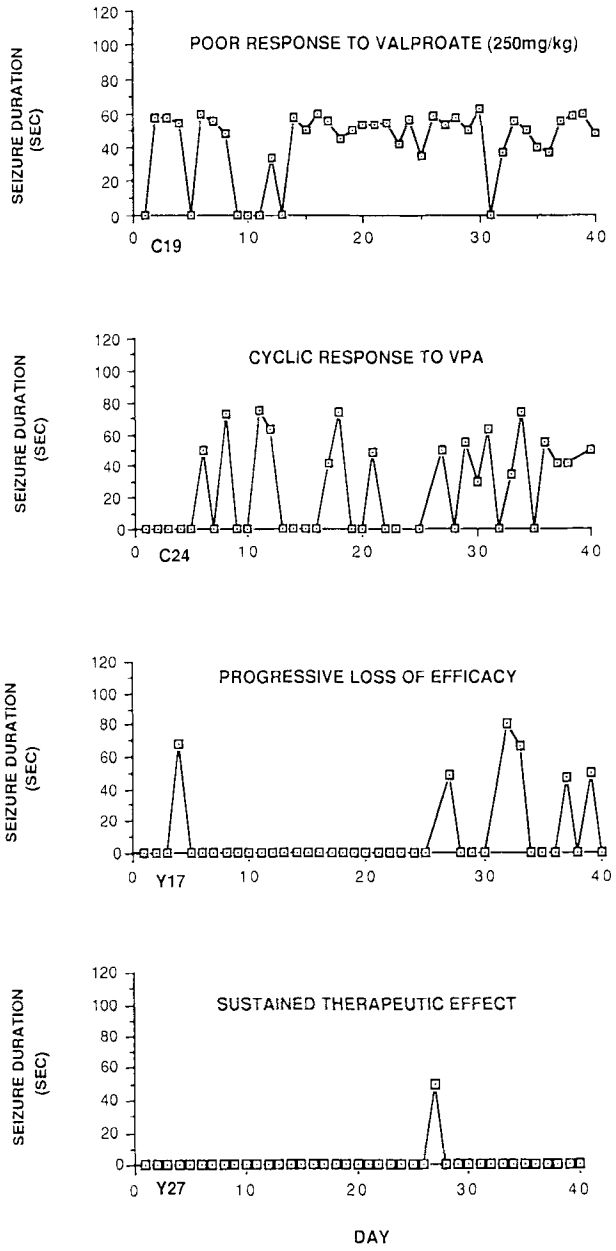


Fig. 2. Variable and oscillating patterns of tolerance emergence to valproate's anticonvulsant effects in individual rats. In fully kindled rats; stimulation was administered at 800 μA (i.e., at twice the intensity of that in Fig. 1A since animals are generally less prone to tolerance development on VPA compared to CBZ). Seizure duration is plotted in individual rats as a function of day of stimulation (with drug treatment).

duration data are illustrated in Fig. 2. They are representative of the relative all-or-none seizure occurrence, or lack thereof, typically evi-

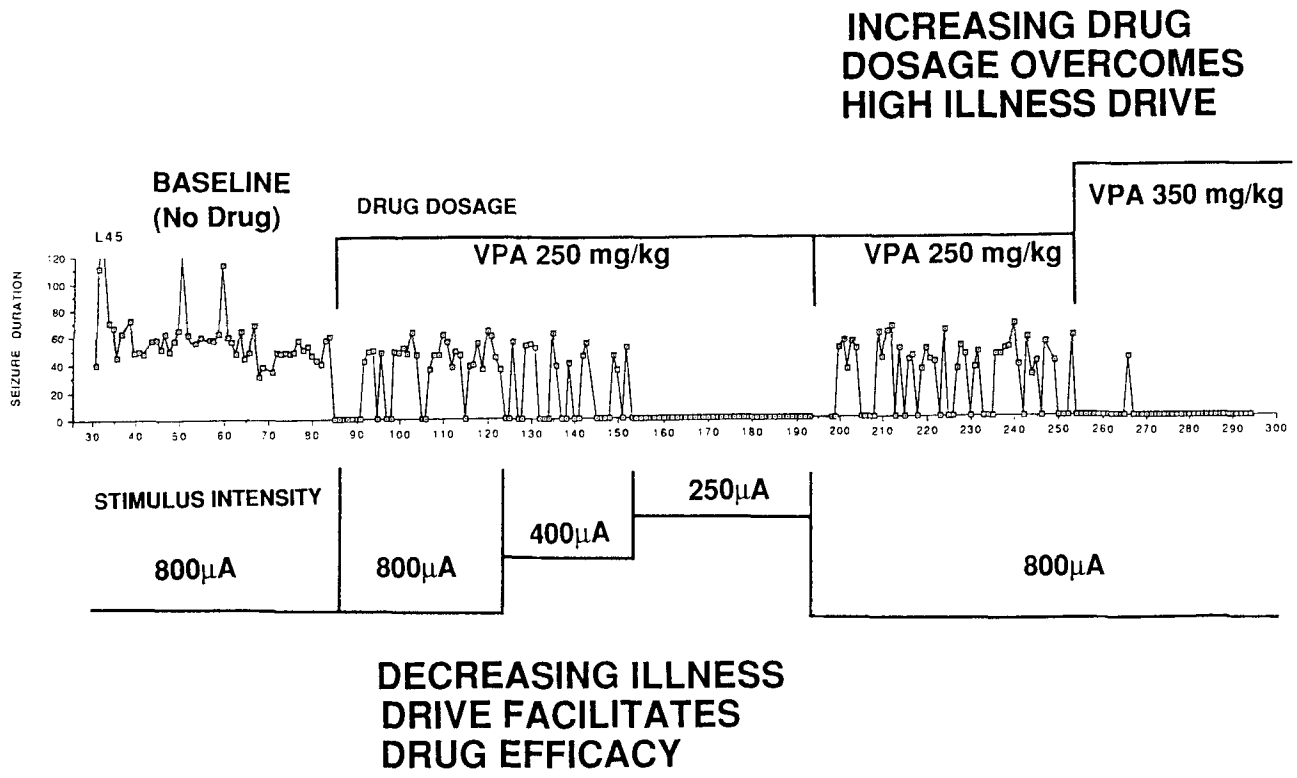


Fig. 3. The seizure duration is plotted by day in a single animal exposed to varying dosages of drug **(top)** and varying stimulation intensities **(bottom)**. Decreasing illness drive can facilitate drug efficacy; increasing drug dosage can overcome high illness drive.

denced within individual animal's seizure cyclicity patterns.

Dose and Stimulation Intensity as it Effects Cyclic Progression Toward Tolerance

With typical initial anticonvulsant doses of valproate (250 mg/kg) and high stimulation currents (800 μA) we did not observe the rapid and consistent pattern of complete loss of efficacy seen with carbamazepine (15 mg/kg and 800 μA). Raising the dose of carbamazepine to 25 mg/kg ip did not effectively delay tolerance development. This suggests that valproate at moderate doses is less likely than carbamazepine to be associated with tolerance, although full-dose response studies remain to be explored. Instead, it appeared that there were individualized rhythmic or cyclic patterns of seizure breakthroughs with a general tendency for progression toward more seizures from a period of relatively good anticonvulsant efficacy (Fig. 2). Preliminary evidence (Fig. 3) suggests that raising the dose of valproate (from 250 to 350 mg/kg) or decreasing the intensity of stimulation (from 800 to 400 or 250 μA) can reinstate drug efficacy and slow the progression toward tolerance.

Before discussing the potential mechanisms and implications of these findings of different patterns of seizure cycling in individual animals, it is necessary to present background information on two other phenomena also observed with drug treatment of amygdala-kindled seizures. These are the time-off seizure effect and contingent tolerance. We postulate that it is the combination and sequential occurrence of these two phenomena that help to account for seizure cyclicity during drug treatment.

Time-Off Seizure Effect

This phenomenon of loss of response to an effective acute dose of drug was observed in

kindled animals given a "vacation" or a period of time off from seizures (Post and Weiss, 1992a; Weiss et al., 1995). Following four or more days without kindled seizures, the anticonvulsant effects of carbamazepine were significantly diminished, suggesting that seizures themselves potentiated the anticonvulsant drug response. A similar time-off seizure effect was observed for diazepam. However, a different time-course was required for the two drugs, and 10 d without a seizure was the time after which diazepam became less effective. Control animals given daily seizures during these 4- or 10-d intervals remained responsive to both anticonvulsants (Weiss et al., 1995). These data have been confirmed in a crossover study and, further, have been shown not to be dependent on prior experience with the drug; that is, the time-off seizure effect can be demonstrated in drug-naive animals. These observations and others in the literature (Adamec and Stark-Adamec, 1983; Tuff et al., 1983; Dragunow, 1986; Caldecott-Hazard and Engel, 1987; Sackheim, 1988; Spiller and Racine, 1994) form the bulwark of the suggestion that seizure episodes are capable of evoking biological effects that are compensatory or adaptive (Post and Weiss, 1992a; Weiss et al., 1995) and that when these endogenous mechanisms dissipate, the animals become less responsive to exogenous drugs. This loss of endogenous, seizure-induced, anticonvulsant mechanisms is also manifested as a decrease in the seizure threshold (i.e., an increase in seizure susceptibility) (Weiss et al., 1995).

Although the neurochemical substrates mediating this time-off effect have not been definitively identified, seizure-induced adaptations have been demonstrated in many instances in inhibitory neurotransmitter ($GABA_A$ and benzodiazepines) and neuropeptide (TRH, CCK, NPY, and endogenous opiate) systems that could serve to enhance anticonvulsant effects of exogenous drugs or provide sufficient endogenous mechanisms to produce anticonvulsant effects of their own (Post and Weiss, 1992a; Weiss et al., 1995; Adamec and Stark-Adamec, 1983; Tuff et al., 1983; Dragunow, 1986; Caldecott-Hazard and Engel, 1987; Sackheim, 1988; Spiller and Racine, 1994).

Previous data revealed that animals given suprathreshold-kindled seizure stimulation (with 800 μA), perhaps evoking greater seizure-induced biological adaptations than low stimulation currents, do not experience seizures to less intense kindling stimulation (Weiss et al., 1995). These observations are convergent with earlier data showing that the major motor seizures of electroconvulsive therapy are sufficient to prevent both the development and the transient reversal of fully expressed amygdala-kindled seizures (Post et al., 1984a; 1986a). Thus, evidence of seizure-induced neurobiological substrate includes:

1. Anticonvulsant drugs become less effective when seizures do not occur;
2. There is an associated lowering of the medication-free seizure threshold; and
3. Seizures driven by high-intensity stimulation are themselves anticonvulsant to low-intensity stimulation; i.e., direct evidence of an endogenous seizure-induced suppressing mechanism.

Contingent Tolerance

A second phenomenon of importance for this discussion is contingent tolerance and its putative neurobiological substrates. As stated previously, carbamazepine initially is highly effective in suppressing seizures kindled with suprathreshold stimulation, but over a brief period of time the anticonvulsant loses effectiveness; i.e., tolerance occurs (Weiss et al., 1991). This tolerance is not observed in animals treated with similar doses of carbamazepine given after each seizure has occurred (Fig. 4A). This loss of efficacy is thus an associative phenomenon; i.e., it is contingent on the pairing or co-occurrence of drug and seizure stimulation and does not occur if these two events are temporally dissociated; i.e., when the drug is given after the seizure has already occurred. (Note that carbamazepine has a very short half-life in the rat and no drug is present the day following a seizure.) This type of tolerance differs from that observed when animals are merely repeatedly or continuously

exposed to a drug; i.e., conventional pharmacodynamic or pharmacokinetic tolerance.

When animals have become tolerant to the anticonvulsant effects of carbamazepine, a period of seizures without the drug or, even more remarkably, seizures and drug (if the drug is administered after a seizure has occurred), is sufficient to reverse tolerance and to renew the anticonvulsant effects of carbamazepine (Weiss and Post, 1990). Merely waiting (no seizures or drug) or giving the drug alone in the absence of seizures does not reverse tolerance (Weiss and Post, 1990). However, this latter observation is confounded with the time-off seizure effect, in which the absence of seizures can also diminish drug efficacy. Nevertheless, the data indicate that contingent tolerance can be reversed if seizures are induced in the absence of drug.

The development of this type of tolerance also appears to reflect endogenous biological alterations since the medication-free seizure threshold is decreased (i.e., animals are more seizure-prone) when animals are tolerant to the drug and returns to the kindled baseline level when tolerance is reversed (Weiss et al., 1991). Weiss and associates (Weiss et al., 1995) have found that a variety of biochemical alterations that typically occur following kindled seizures fail to occur in animals that are tolerant to the anticonvulsant effects of carbamazepine. These effects are selective to tolerant animals because controls (that experience the same number and dosages of carbamazepine but given after the seizures [Fig. 4B]) demonstrate seizure-induced increases in these factors. In tolerant animals, seizures selectively fail to increase *fos*-related antigens (FRAS), binding to $GABA_A$ receptors (specifically the α-4 subunit), (Clark et al., 1994b), mRNA expression for TRH (Rosen et al., 1993, 1994), CRH, and CRH-binding protein, NPY, BDNF, and glucocorticoid receptors (Smith et al., 1995; Weiss et al., 1995) (Fig. 4C). However, other seizure-induced adaptations continue to occur, including the increases in benzodiazepine and t-butylbicyclophosphorothionate (TBPS) binding.

TRH and NPY are candidates for endogenous anticonvulsant mechanisms (Fig. 5) as they are reported to exert anticonvulsant effects when administered to animals. Similarly, GABA is the major inhibitory neurotransmitter in brain and GABA-active manipulations are anticonvulsant. To the extent that some of these seizure-induced increases enhance the anticonvulsant effects of a drug (Post and Weiss, 1992a; Weiss et al., 1995), it is possible that the loss of these putative endogenous, anticonvulsant adaptations, i.e., the increases in TRH, NPY, and GABA receptors, could contribute to the loss of efficacy as well as the observed decreases in seizure threshold observed in conjunction with tolerance. The seizure thresholds again increase when tolerance is reversed by giving seizures in the absence of drug. This would be expected to reinduce the full range of seizure-induced adaptations and render the animal responsive to the drug once again.

We have previously observed crosstolerance between carbamazepine and valproate (Weiss et al., 1993). This was unexpected since valproate's anticonvulsant actions are thought to be exerted mostly through different mechanisms than those of carbamazepine and to importantly involve GABAergic systems (Post and Weiss, 1992b). Thus, it is possible that the failure of carbamazepine-tolerant animals to show seizure-induced upregulation of $GABA_A$ receptors (which valproate can effect indirectly) could account for this cross tolerance (Clark et al., 1994b; Weiss et al., 1995). When animals are tolerant to the anticonvulsant effects of both carbamazepine and valproate, renewed response to either drug can be achieved following a period of giving seizures without drug.

Potential Mechanisms Involved in the Expression of Individual Patterns of Rhythmicity in Amygdala-Kindled Animals Treated with Anticonvulsant Drugs

To summarize, when animals are stimulated with high intensities (800 μA), they rapidly and consistently become tolerant to the anticonvul-

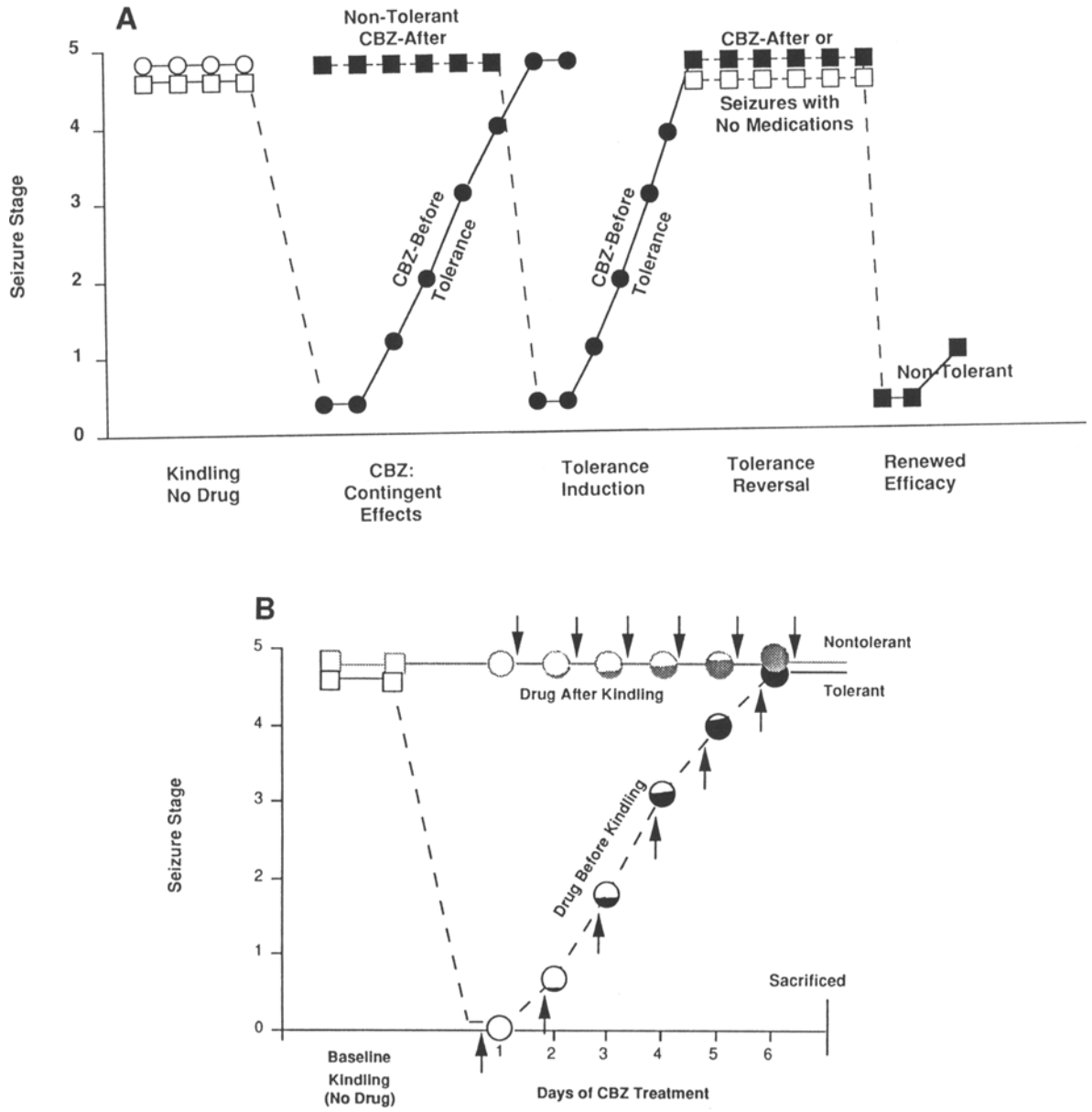


Fig. 4. **(A)** Schematic illustration of contingent tolerance development and reversal. In fully kindled animals (open symbols), carbamazepine treatment inhibits kindled seizures (filled circles). Repeated drug administration before (solid lines), but not after (dotted lines), kindling stimulation results in tolerance development. Tolerance induced in this manner can be reversed by a period of kindled seizures without drug administration (open squares; right side) or even with continued drug administration but after each seizure (filled squares; right side). **(B)** Schematic illustration of procedure used to examine the biochemistry of contingent tolerance. Fully kindled animals were divided into groups receiving vehicle (not illustrated) carbamazepine (CBZ) after stimulation ○ ↓, or CBZ before stimulation ↑ ○. In order to match animals for number and patterns of seizure occurrences, as well as drug administrations, the rats that received CBZ before stimulation were kindled first. If a CBZ-before rat did not have a seizure on that day (e.g., d 1, 2) then its matched cohort, receiving CBZ after, would be sham stimulated so that it would also not experience a seizure on that day. If the rat had a seizure (i.e., as tolerance developed), then its matched cohort would also be stimulated (e.g., d 4–6). When a CBZ-before animal had experienced at least three seizures in the previous 4 d it was considered to have developed tolerance and was sacrificed along with its matched nontolerant control, which had now received the same number of seizures and drug treatments. Percent of rats with seizures: ○ None; ◒ 50%; ● 100%.

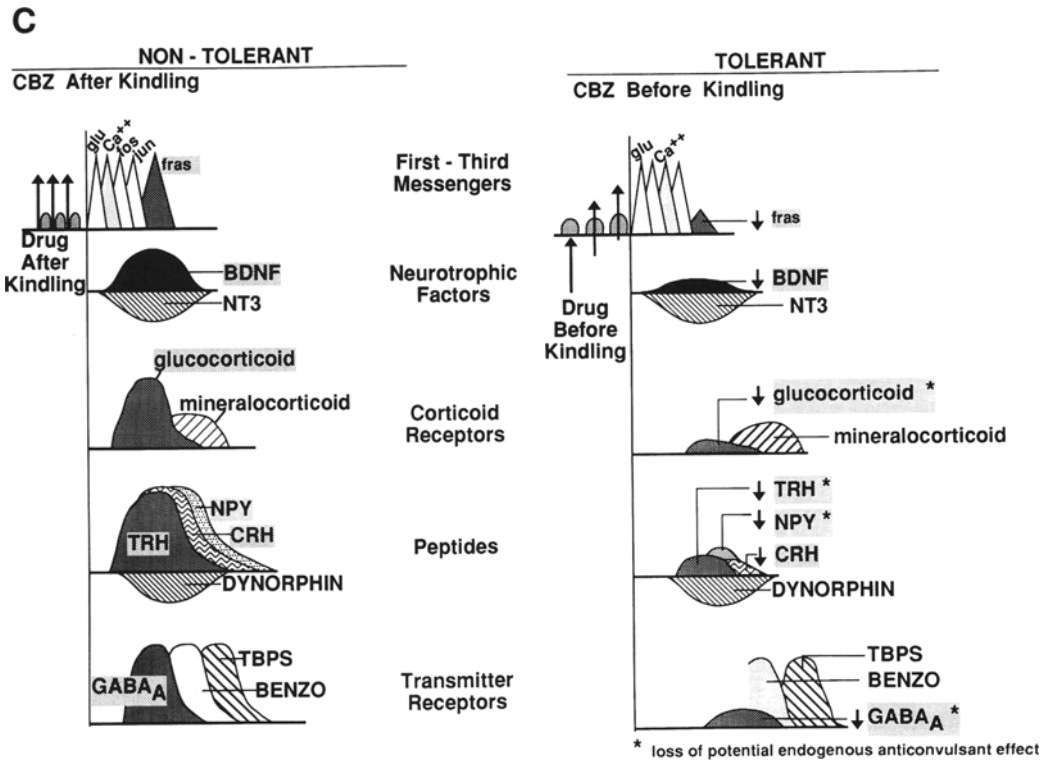


Fig. 4. *(continued)* **(C)** Alterations in gene expression produced by kindling and carbamazepine tolerance. Changes in immediate early genes (e.g., *fos, fras*) and their targets or late effector genes (e.g., growth factors, corticoid receptors, peptides, and receptors) have been demonstrated after kindled seizures (left column). These changes, which have varying time-courses and anatomical distributions, may be related to either seizure-promoting ("bad guys"; e.g., CRH) or endogenous seizure-suppressing mechanisms ("good guys"; e.g., TRH, $GABA_A$ receptors, NPY). In kindled rats that have become tolerant to carbamazepine (and are experiencing seizures) many of the seizure-induced adaptations fail to occur (right column). We hypothesize that the loss of some of the seizure-induced compensatory mechanisms contributes to the loss of anticonvulsant drug efficacy in tolerant animals. CBZ = carbamazepine; CRH = corticotropin-releasing hormone; GABA = γ-aminobutyric acid; TBPS = t-butylbicyclophosphorothionate; TRH = thyrotropin-releasing hormone; NPY = neuropeptide Y; BDNF = brain derived neurotrophic factor; NT_3 = neurotrophin-3; *fras* = *fos*-related antigens.

sant effects of carbamazepine at moderate doses (15–25 mg/kg, ip). When they are stimulated at lower intensities (400 μA) the rate of tolerance development is substantially slower and individualized rhythmic patterns are more readily observed (Fig. 1). With valproate (250 mg/kg), seizures slowly and episodically emerge over time when suprathreshold (800 μA) stimulation is used (Fig. 2). Higher valproate doses or lower stimulation intensities result in more sustained anticonvulsant effects (Fig. 3) (Weiss et al., 1995).

Taken together, these data suggest that when animals are near the threshold or margin for effective anticonvulsant treatment they are prone to episodic breakthrough seizures. These are likely to occur more rapidly and consistently (complete tolerance) when stimulation intensity is higher. Under the condition of marginal anticonvulsant effects (weighted toward relative efficacy of the drug) seizure breakthroughs appear to emerge in a rhythmic pattern (Fig. 6). This may be partially independent of drug mechanism of action as it occurs for both carbamazepine and valproate, although at different stimulation intensities.

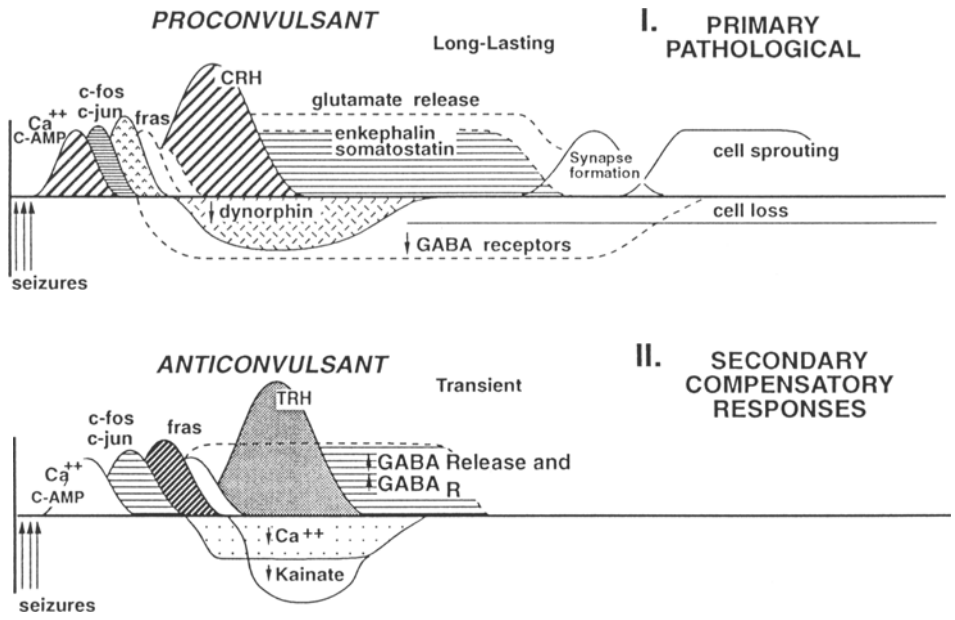


Fig. 5. Schematic illustration of potential genomic, neurotransmitter, and peptidergic alterations that follow repeated kindled seizures. Putative mechanisms related to the primary pathological drive (i.e., kindled seizure evolution) are illustrated on top, and those thought to be related to the secondary compensatory responses (i.e., anticonvulsant effects) are shown on the bottom. The horizontal line represents time. Sequential transient increases in second messengers and IEGs are followed by longer-lasting alterations in peptides, neurotransmitters, and receptors or their mRNAs, as illustrated above the line, whereas decreases are shown below the line. Given the potential unfolding of these competing mechanisms in the evolution of seizure disorders, the question arises regarding whether parallel opposing processes also occur in the course of affective illness of other psychiatric disorders. Such endogenous adaptive changes may be exploited in the design of the new treatment strategies.

We postulate that it is the multiple occurrences of the "time-off seizure" effect superimposed on an overall progressing tolerance mechanism that contributes to the cycling pattern. That is, after a sufficient period of time without a seizure occurring because of the anticonvulsant drug's effect, previous seizure-induced endogenous anticonvulsant adaptations dissipate (Fig. 5). To the extent that these endogenous anticonvulsant adaptations had assisted the efficacy of the drugs, their loss may be associated with seizures erupting through an otherwise effective dose of drug. The re-emergence of the full-blown seizure, in addition to re-engendering the primary pathological processes (i.e., the putative "bad guys"), may have its potential secondary benefits in the reinduction of seizure-induced anticonvulsant adaptations (i.e., the putative "good guys"). However, the illness breakthroughs are now occurring in the presence of drug treatment, and, therefore, might induce a diminished "good guy" response (e.g., no upregulated $GABA_A$ receptor binding or TRH and NPY mRNA) as in Fig. 4C. Nevertheless, the seizures during drug treatment are still able to induce at least some of the endogenous adaptations (e.g., benzodiazepine receptor and TBPS upregulation; Fig. 4C). Anticonvulsant effectiveness may then be renewed, at least for a brief period of time, until these putative seizure-induced adaptations are again dissipated by another "time-off seizure" effect, in this case achieved because the combined effect of the endogenous mechanism and exogenous drug are transiently sufficient to block seizures for one or more days (Fig. 7).

To the extent that this type of iterative mechanism accounts for the cyclicity patterns, the question arises about what factors deter-

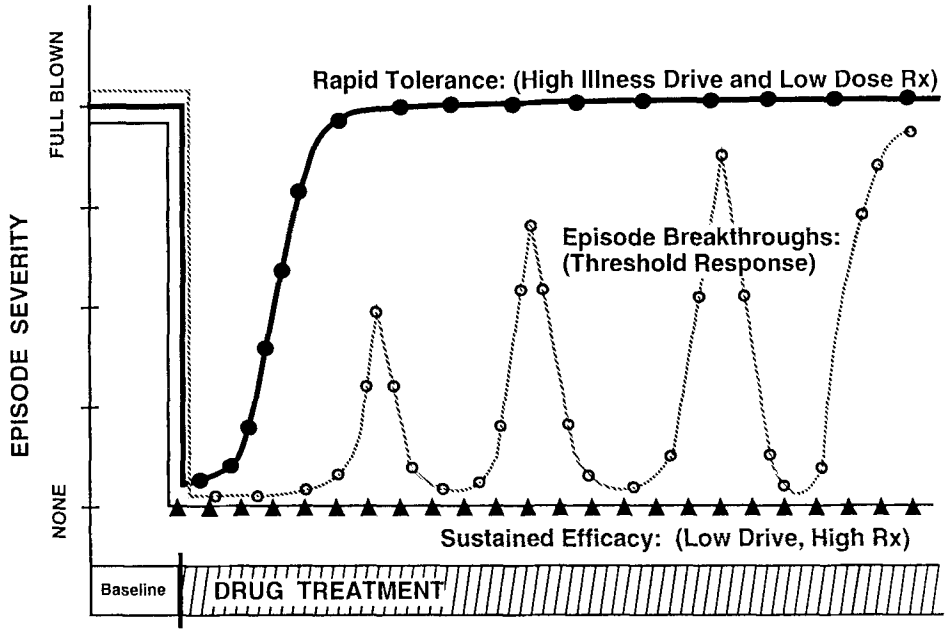


Fig. 6. Schematic summary of the interaction of intensity of illness drive and drug dosage in treatment outcome. In cases of high illness drive and low drug dose or efficacy (●), tolerance develops rapidly. In cases of low illness drive or high drug dose or efficacy (▲), the treatment remains effective and tolerance is slow or does not develop at all. However, in cases where illness drive is closely balanced by drug dosage or efficacy, tolerance emergence is cyclic, but progressive as illustrated (○), and in Figs. 1A and 2.

mine each rat's adoption of a given pattern of seizure cycling, ranging from almost complete anticonvulsant effectiveness (Figs. 1A and 2 bottom) or slow oscillations vs more rapid oscillations progressing to the rapid development of tolerance with complete loss of anticonvulsant effectiveness (Figs. 1A and 2 top). Based on the above observations we postulate that it is the relative balance of the putative "good guys" and "bad guys" within each individual animal that determines this patterning. This would depend on the magnitude and duration of the compensatory adaptations (assisted by exogenous drug) balanced against the frequency, intensity, and number of stimulated seizures; (i.e., variables that would be highly influenced by both genetic and experimental predispositions and influences).

Inherent in this conceptual viewpoint is the notion that the kindled "memory trace" is long-lasting and the primary pathological processes of kindling (i.e., the bad guys) are relatively preponderant compared with the more transient compensatory adaptive mechanisms that episode re-emergence evokes (i.e., the good guys) (Figs. 5 and 7). That this is likely to be the case is based on other evidence from the kindling process. The kindling memory trace is relatively permanent, as observed in the original descriptions of kindling by Graham Goddard and his associates (1969), and as reviewed by Racine (1978) and McNamara (1988). One or two stimulations are all that are required to reinvoke a full-blown kindled seizure after many months of no stimulation. This may be based on long-term biochemical adaptations, which have been reviewed elsewhere (McNamara, 1988), as well as changes occurring at the level of synaptic and neuronal microstructural rearrangement (Sutula, 1992a). Perhaps these occur through the induction of N-Cams and related adhesion molecules shown to be involved in other types of learning, such as LTP (Edelman, 1984; Bailey et al., 1992; Mayford et al., 1992; Kandel, 1993), and/or the modulation of a variety of growth fac-

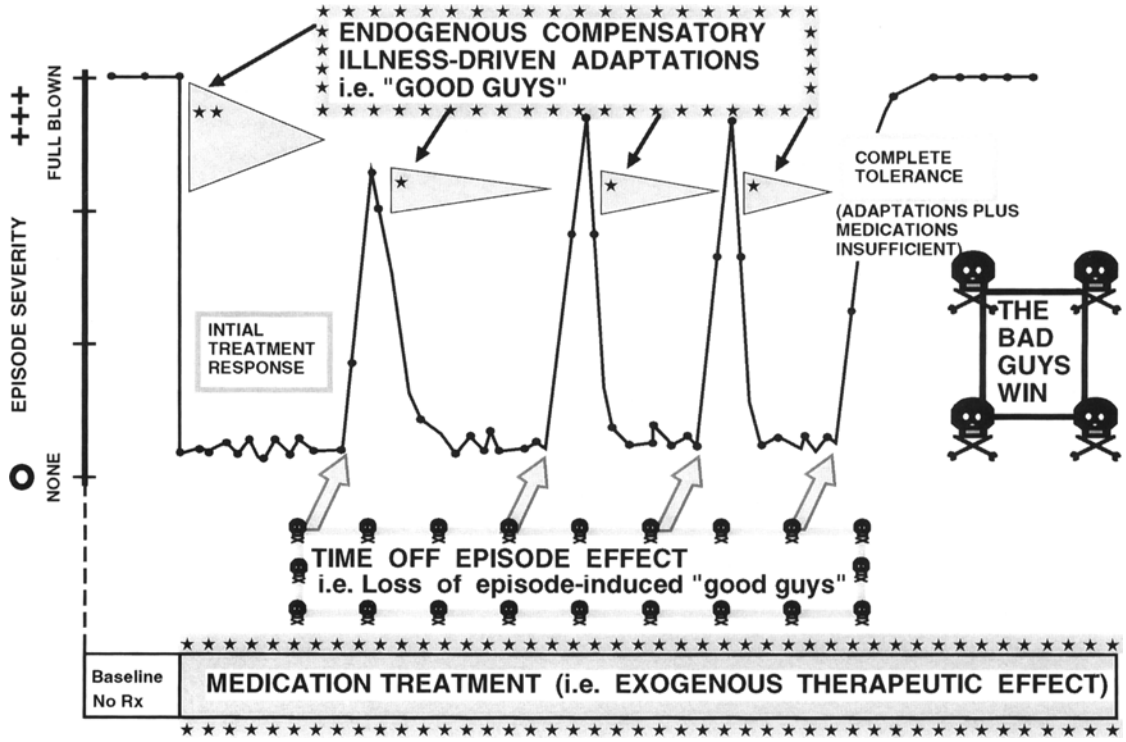


Fig. 7. Hypothetical schema of the role of endogenous regulatory factors in the generation and progression of illness cyclicity. Following an illness episode, adaptive compensatory mechanisms are induced (i.e., "good guys"; triangles), which together with drug treatment suppress the illness (initial treatment response; box). The "good guys" dissipate with time (i.e., the time-off seizure effect), and episodes of illness re-emerge. Although this re-elicits illness-related compensatory mechanisms, the concurrent drug treatment prevents some of the illness-induced adaptive responses from occurring (smaller triangles). As tolerance proceeds (associated with the loss of adaptive mechanisms) faster illness re-emergence occurs. Thus, the drug is becoming less effective in the face of less robust compensatory adaptive mechanisms. The primary pathology is progressively re-emerging, driven both by additional stimulations and episodes (i.e., the kindled memory trace or the "bad guys") along with a loss of illness-induced adaptations. Since this cyclic process is presumably driven by the ratio of the "bad vs good guys" at the level of changes in gene expression, we postulate that such fluctuations in the "battle of the oncogenes" arising out of illness- and treatment-related variables could account for individual patterns in illness cyclicity. An inherent abnormality in clock function is then not necessary to postulate. The illness is the clock that drives cyclicity.

tors, such as increases in BDNF and nerve growth factor itself, and/or the suppression of NT3, which has also been reported with kindling (Rocamora et al., 1992; Weiss et al., 1995). Sutula and colleagues (Sutula et al., 1992b) have emphasized that there is not only sprouting in the mossy fiber system of the dentate granule cells with kindling evolution that occurs relatively early in the process of afterdischarge generation, but a progressive loss of cells in the dentate hilus region. The magnitude of this cell loss correlates with the number of prior kindling stimulations.

As in other types of learning and memory paradigms in which the neurobiological substrates progressively evolve (Zola-Morgan, 1994), it is clear from electrophysiological evidence, regional glucose utilization, and *in situ* hybridization (of IEGs, such as c-*fos* and their targets LEGs, peptides, transmitters, and enzymes]) that the process of kindling is not a static one, but also evolves with stimulus and

seizure episode repetition (Post et al., 1991). Whereas the kindled "trace" is relatively permanent and progressively evolving toward spontaneity and automaticity (perhaps through the development of mirror foci), the compensatory adaptations (Fig. 5) that are also evoked at the level of alterations in gene expression would appear to be more transient (Post and Weiss, 1992a; Weiss et al., 1995). Their shorter duration is suggested by the relatively brief period of time required for the "time-off seizure" effect on anticonvulsant responsivity and seizure threshold of approx 4 d in the case of carbamazepine and 10 d for diazepam. Thus, in the face of inadequate pharmacoprophylaxis, kindling proceeds inexorably with transient, partial, but inadequate resistance occurring in a more fitful or cyclic fashion. This, in concert with the overall strengthening of the kindled trace with each stimulation, might account for the general tendency for intervals between seizure episodes to shorten (Figs. 1A and 2), and for there to be a gradually increasing proportion of days with full-blown seizures (Fig. 8, bottom).

If an adequate or high dose of drug is utilized, kindled seizures can remain suppressed for a considerable period of time with only an occasional day of seizure re-emergence (Fig. 3). In the case of inadequate or marginal doses or treatments, particularly if there is a high illness drive as manifested by increased intensity of stimulation in the kindling paradigm, then more oscillatory patterns emerge or complete tolerance may rapidly be acquired with loss of efficacy in a relatively short period of time. Thus, the process of illness evolution and cyclicity generated in the face of inadequate treatment interventions may be partially based on a battle of the oncogenes and the relative balance of transcriptional regulation of IEGs, LEGs (Fig. 5), and their downstream consequences (Fig. 9). In the case of oscillations toward the loss of anticonvulsant effects of a drug, tolerance may be a relative term depending on where the animal is in its cyclic pattern; the associated underlying biological mechanisms may be changing and evolving accordingly. To the extent that tolerance is, in part, associated with an impaired induction of c-*fos* and other transcription factors (FRAS) (Weiss et al., 1995) and their downstream effects, one could conceptualize how this relative lack of immediate early gene induction could be translated into a failure of other more long-term mechanisms.

This possibility is not without parallels in other areas of medicine in which c-*fos* and related IEGs have already been postulated to be master switches in the development of tolerance or multidrug resistance to the cancer chemotherapeutic agents (Adams and Cory, 1991; Funato et al., 1992; Harnevo and Agur, 1992; Lowe et al., 1993; Hennigan et al., 1994; Mansouri et al., 1994). Moreover, some analogies that can be drawn from cancer evolution also suggest that there may be abrupt changes, not only in increases in oncogenes that are driving cells toward increased self-replication and malignancy, but also in the loss of suppressor factors that are associated with progression and metastasis formation. The relative malignancy of a tumor line may be a consequence of genetic predisposition and environmental alterations based on sequential impacts of somatic mutations. In a somewhat comparable fashion, it would appear that kindling evolution is based on sequential alterations in gene expression driven not by somatic mutation, but by environmental stimulation and its contingencies.

Implications for Mechanisms Underlying Cyclicity in the Affective Disorders

Episode Cyclicity

To the extent that processes underlying the unfolding of kindling have some formal neurobiological similarities with affective illness evolution despite the fact that they do not share precise homologies (Weiss and Post, 1995), it is possible to envision affective illness progression in a similar fashion (*see* Post and Weiss, 1989, 1992a; Post et al., 1984a, 1986b, 1994). This framework could assist in formulating mecha-

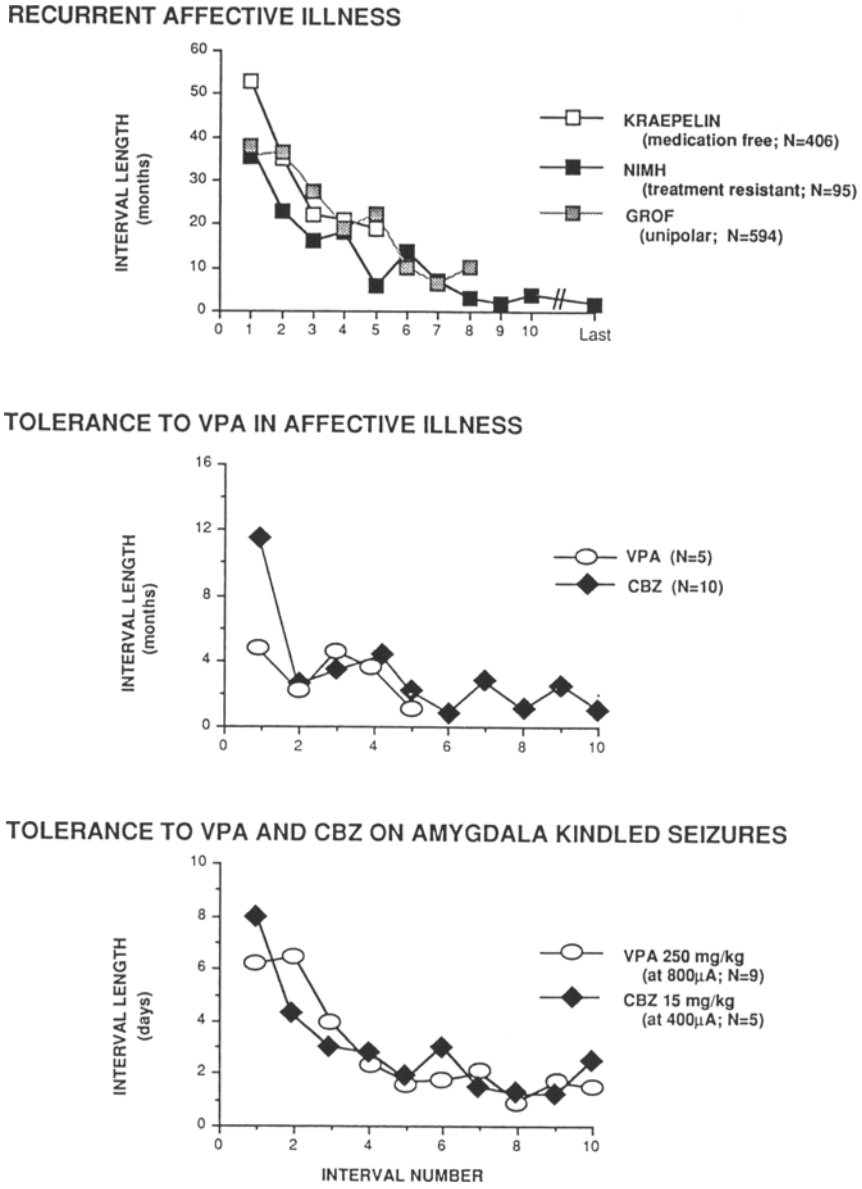


Fig. 8. Decreasing well intervals between successive episodes in the emergence of recurrent affective illness is illustrated **(top)**. Plotted on the abscissa is the interval number between successive episodes of affective illness or seizures. Plotted on the ordinate is the duration of that interval. A similar progressive pattern (over different time frames) is observed during the development of tolerance to the psychotropic effects of anticonvulsants in patients with affective illness **(middle)** and anticonvulsant effects in kindled animals **(bottom)** treated with carbamazepine or valproate. Following emergence of an illness episode, subsequent episodes occur with rapid onset propelling the illness toward deterioration and the drug effect toward tolerance.

nisms related to several elements of illness evolution, including: the development of more severe episodes from minor episodes; the faster recurrence of full-blown episodes; the greater likelihood of episodes to occur spontaneously without precipitation by psychosocial stress; as well as the current postulate of how illness episodes could manifest in highly individualized cyclic patterns during tolerance development and, by inference, also during primary

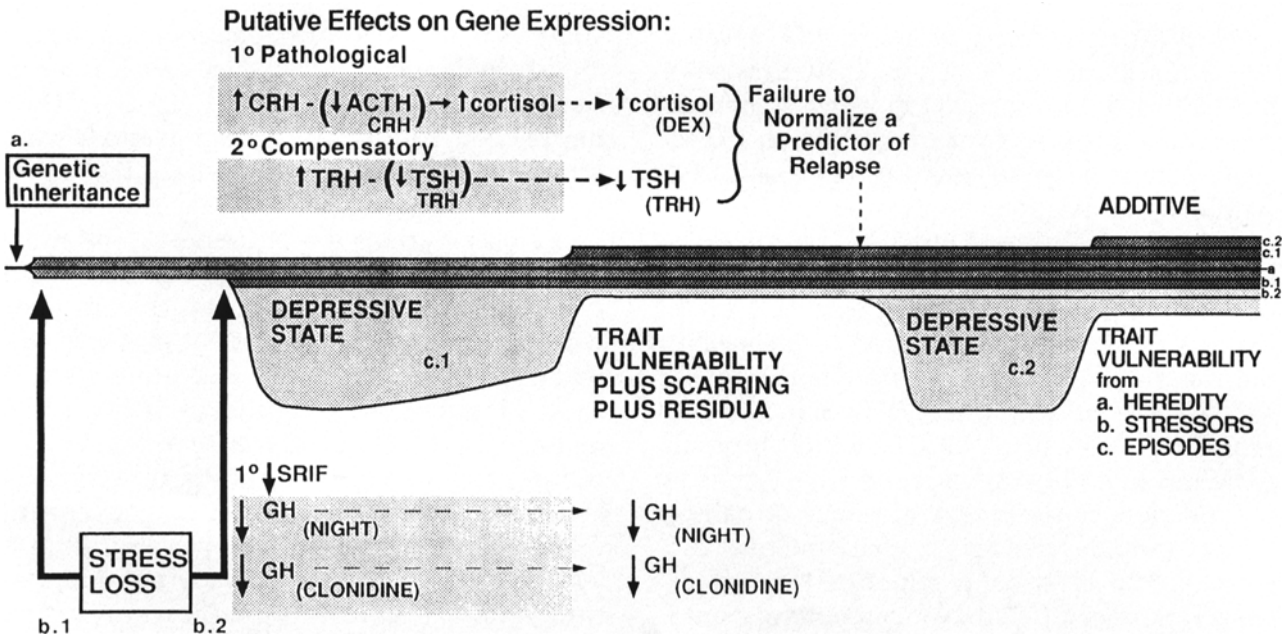


Fig. 9. Accumulating experiential genetic vulnerability in recurrent affective illness. Schematic of how initial stressors may leave behind trait vulnerabilities (at the level of alterations in gene expression). With appropriate reactivation by stress of relevant neurobiological systems, the threshold for neuropeptide and hormonal changes associated with a depressive episode may be exceeded. These episode-related alterations may be normalized with the termination of episode, but in some instances may persist and add further trait vulnerabilities toward recurrence in addition to the genetic **(A)** and stressor **(B)** changes.

illness evolution not involving exogenous medications.

Thus, one would postulate that in addition to genetic predisposition, experiential factors are sequentially affecting gene expression in the unfolding affective illness in which both stresses (analogous to kindled stimulation) and episodes themselves (analogous to seizures) leave behind long-lasting neurobiological memory traces propelling the illness toward recurrence and spontaneity, as illustrated in Fig. 9. In seizure kindling, some of these changes in gene expression could be compensatory and adaptive. For example, we have observed that TRH, which is hypersecreted in some depressed patients (Banki et al., 1988), may have positive effects on mood and behavior (Callahan et al., 1995; Marangell et al., 1996). Conversely, blockade of glucocorticoid excesses in depression that are presumably driven, in part, by increases in CRH (a putative "bad guy") (Nemeroff et al., 1984; Banki et al., 1988; Arana and Forbes, 1991; McEwen et al., 1992) can improve depressed mood (Arana et al., 1995). This identification of differential mechanistic components of the illness (Fig. 9) and targeting them for individualized treatment may ultimately lead to novel therapeutic interventions.

Treatment of Bipolar Patients with Unimodal (Antidepressant or Antimanic) Therapies

In bipolar illness endogenous adaptations and exogenous treatments of a given mood phase may overshoot their optimum level, and the putative "good guys" of one phase could become the "bad guys" of the next, opposite phase. For example, the tricyclic antidepressants may alleviate the depressive phase but potentiate the next manic phase or induce cycle acceleration, as has been demonstrated in some studies (Wehr and Goodwin, 1979; Kukopulos et al., 1983; Rouillon et al., 1989, 1991; Geller et al.,

1993; Hurowitz and Leibowitz, 1993; Wehr, 1993) but not in all (*see* Schou, 1979; Kupfer et al., 1989, 1992; Winokur et al., 1993). There is perhaps a greater consensus that in rapid cycling patients these agents can be associated with a higher proportion of patients with very fast cycling patterns. Similarly, neuroleptics may increase frequency or severity of the next depressive episode (Kukopulos et al., 1980; Ahlfors et al., 1981) in addition to increasing the risk for tardive dyskinesia (Hamra et al., 1983; Yassa et al., 1983, 1990; Kane, 1988; Waddington et al., 1989) to which bipolar patients are highly predisposed.

This view of the relative balance of pathological and adaptive factors changing over the course of an episode, is supported by recent observations of differential therapeutic response to sleep deprivation as a function of episode duration in rapid cycling bipolar patients. Gill et al. (Gill et al., 1993) observed, in a small series of bipolar patients, that sleep deprivation early in a depressive episode was largely ineffective; in mid phases it was transiently effective; and toward the end of an episode, it was markedly effective. In many cases, when administered late in an episode it would be able to entirely switch the patient out of the episode. The relative preponderance of endogenous adaptation activity in concert with the effects of sleep deprivation may thus combine for a more maximal effect late compared to early in an episode.

To the extent that at the end of an episode endogenous mechanisms are already primed or entrained for episode termination, utilization of unimodal antidepressants may propel a more rapid termination of a depressive episode, but at the potential cost of a more rapid or major onset of the next manic episode and the subsequent re-emergence of the next depressive episode. In contrast, lithium or the mood stabilizing anticonvulsants do not appear to share this proclivity.

Effect of Mood Stabilizers on Cyclicity

Recent data from several studies are supportive of the notion that lithium is more effective in patients with a pattern of mania followed by depression and then a well interval (mania-depression-interval [M-D-I) than depression followed by mania and a well interval (D-M-I) (Kukopulos et al., 1980; Grof et al., 1987; Haag et al., 1987; Maj et al., 1989b). These observations are of interest in relationship to the greater efficacy of lithium in the treatment of acute manic episodes compared with acute depressive episodes. Given the current discussion, it is possible that lithium's ability to dampen the magnitude of an initial manic episode to a greater extent than an initial depressive episode results in a smaller endogenous compensatory set of mechanisms in the former instance. Moreover, if lithium is less likely to be effective as an acute antidepressant and to require augmentation with a unimodal antidepressant agent (Kukopulos et al., 1980; 1983), such exogenous treatment of a severe depressive episode, together with a bigger evoked endogenous antidepressant response, could increase the liability of switching the patient into the next manic episode.

To the extent that lithium and the mood stabilizing anticonvulsants carbamazepine and valproate are able to dampen the severity of both the mania and depressive poles of the illness, one could see how this might result in a decreased cycling pattern because of the lesser evocation of endogenous compensatory mechanisms propelling the illness toward the next phase. Inasmuch as lithium and the mood-stabilizing anticonvulsants have both antimanic and antidepressant properties in long-term prophylaxis, the current theoretical formulation helps envision how this could occur via the process of inhibiting neurobiological systems that tend to overswing both in terms of the primary pathological, and secondarily compensatory mechanisms. The comparative mechanisms of action of lithium and the mood-stabilizing anticonvulsants carbamazepine and valproate and how they may be capable of dampening overexcursions in both excitatory and inhibitory systems, are discussed in more detail elsewhere (Post et al., 1991, 1992b, 1994).

Factors Affecting Illness Drive and the Rate of Tolerance Development

The current analysis of cyclic phenomena emerging out of treatment paradigms that are only marginally effective emphasizes the potential continuity between early episodic minor or major breakthroughs and the eventual complete loss of drug efficacy via tolerance (Kessler et al., 1995, unpublished observations). Tolerance in recurrent affective illness often appears in an intermittent and progressive fashion (Figs. 8 and 10). The current perspective leads to the prediction that patients with greater illness drive and only marginal drug efficacy (because of low doses, low efficacy, or lack of combination treatment) may be more prone to developing breakthrough episodes and eventual tolerance.

It is of interest that our preliminary observations in patients who developed tolerance to carbamazepine showed a faster progression of cycle acceleration in the 4 yr prior to carbamazepine treatment (compared with those who did not become tolerant) (Post and Chuang 1991). Perhaps this rapid deterioration during the baseline in spite of best attempts at treatment in the community is an indicator of greater illness drive. Similarly, Calabrese et al., (1994) reported better antimanic prophylaxis with valproate in those patients without a pattern of cycle acceleration. This could be based on either greater genetic or accumulated experiential predispositions (Post, 1992).

Thus, one would predict that patients at highest risk for malignant illness progression might have:

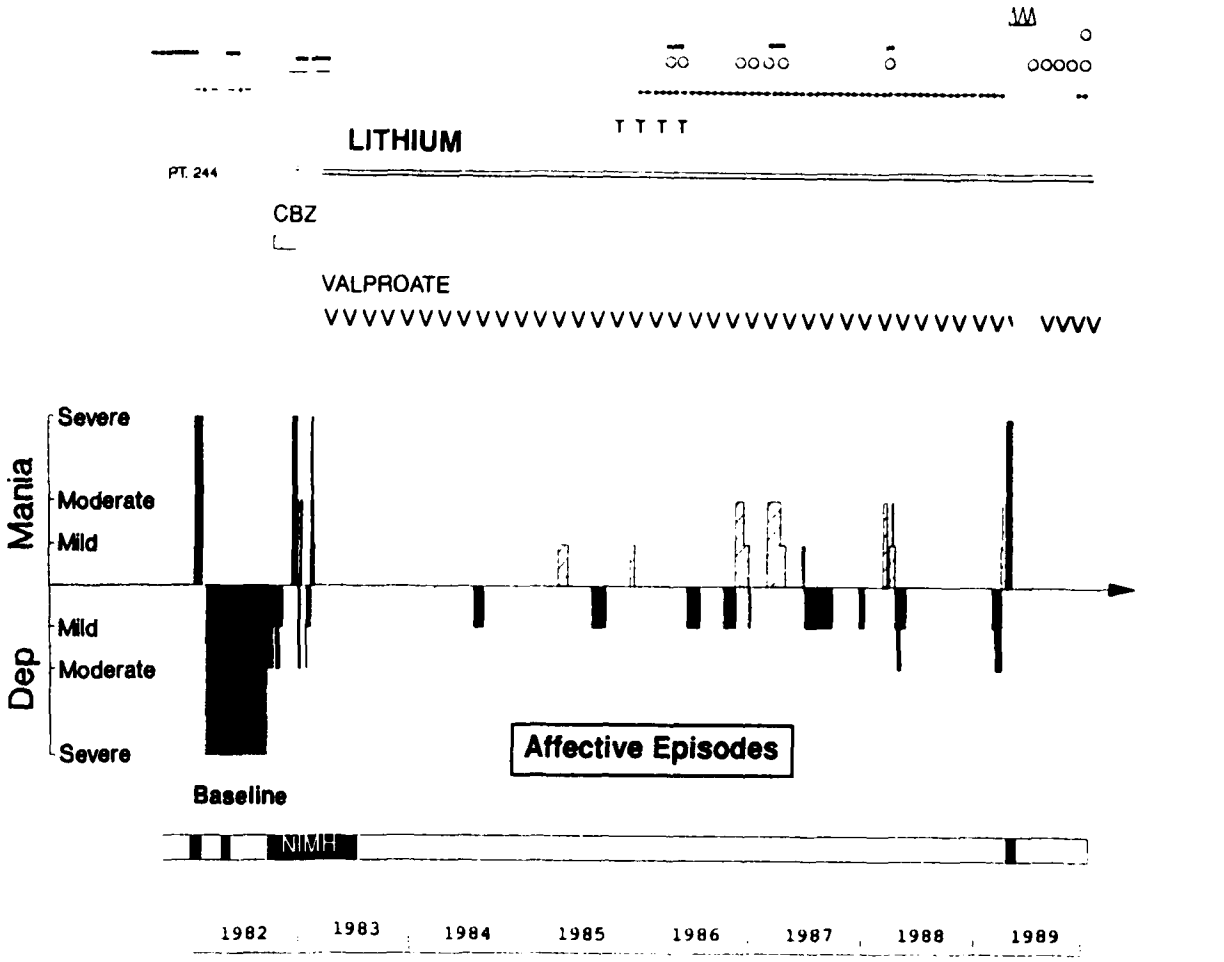
1. Greater numbers of severe psychosocial stresses early in life that recur in adulthood (Breier, 1989);
2. Lack of social support (Brown and Harris, 1978; Breier, 1989);
3. High episode recurrence prior to initiating long-term prophylaxis (Gelenberg et al., 1989; O'Connell et al., 1991; Winokur et al., 1993);
4. Noncompliance-related episodes (Jamison and Akiskal, 1983; Post et al., 1992a, 1993);
5. Drug and alcohol abuse comorbidity (Post et al., unpublished observations); and
6. Comorbid psychiatric illness and personality disorders (Mellman and Uhde, 1989) as well as comorbid medical illness (Weissman et al., 1988; Kessler et al., 1994).

If such patients with multiple risk factors (perhaps indicative of a high degree of "illness drive") were at higher risk for cycle acceleration and tolerance development, earlier, more aggressive interventions might be indicated.

Potential Treatment Implications for Affective Illness

Keller and associates (1992) have found that breakthrough of mild symptoms (what they have called "flurries") was a precursor to the subsequent occurrence of more full-blown episodes requiring major intervention or hospitalization. This is consistent with our clinical observations of the way tolerance appears to emerge through previously effective treatment with lithium (Post et al., 1992a, 1993), carbamazepine (Post et al., 1990a), or valproate (Post, 1990a), i.e., smaller intermittent episodes may herald larger and more frequently occurring breakthroughs.

The data of Gelenberg et al., (1989) suggests that in the face of greater illness drive, as manifested by greater number of prior episodes, even high-dose lithium treatment may not be sufficient to prevent episode recurrence. If a patient is already at or near their side-effects threshold, it may behoove the clinician to add another mood-stabilizing agent rather than attempting to push lithium to toxicity, which may either be ineffective or engender noncompliance and secondarily propel the illness toward further breakthrough episodes. A reanalysis of the Gelenberg et al., (1989) study also indicates that rapid decreases in lithium dose propel many of the relapses in the group randomized to the change from high- to low-dose lithium (Sachs et al., 1994). Although some of these may have been preventable using a slower drug taper to the lower level (Faedda et al., 1993), they nonetheless emphasize the view that marginalizing treatment efficacy, either purposely or inadvertently via noncompliance, may increase proneness to breakthrough episodes and possibly complete loss of efficacy.


LITHIUM
PT. 244
CBZ
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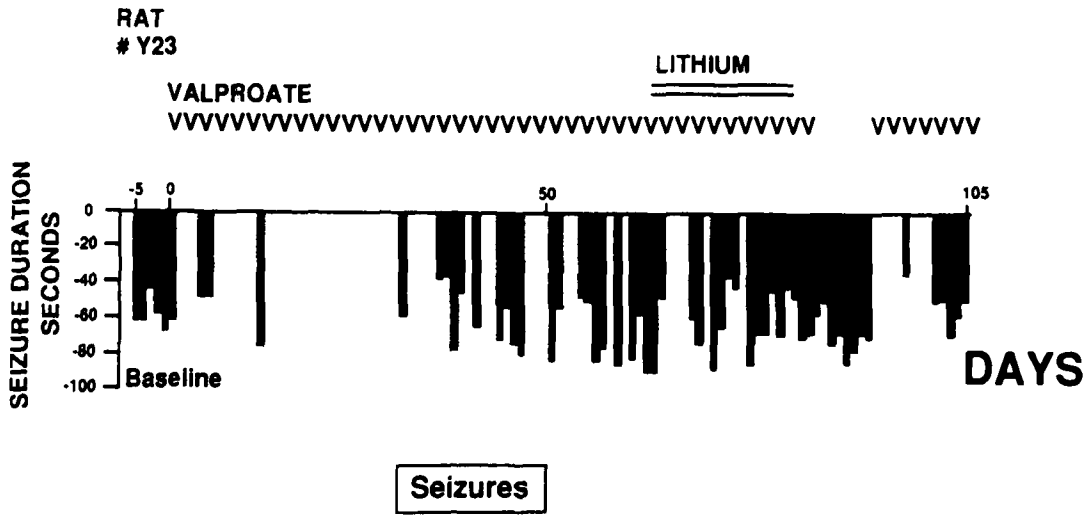
RAT
Y23
LITHIUM
VALPROATE
SEIZURE DURATION
SECONDS
0
-20
-40
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-80
-100
-5
0
50
105
Baseline
DAYS
Seizures

The potential importance of mood-stabilizer combination treatment is also suggested by preclinical models. For example, when carbamazepine and valproate are used in combination (at doses that were ineffective as monotherapy) they inhibit seizure cycling and the rate of tolerance development (Weiss et al., unpublished data, 1994) (Fig. 11). Whether this would also be the case for the affective disorders remains to be directly studied. However, in situations of initial inefficacy, the carbamazepine/valproate combination may be more effective than either drug alone in refractory cycling patients (Keck et al., 1992; Ketter et al., 1992). Would more aggressive treatment of "flurries" (Keller et al., 1992) with either a high dose of a mood stabilizer or combination therapy prevent the eventual occurrence of more full-blown episodes?

Kalynchuk et al. (1994) reported that animals given gradual increases in dosages of anticonvulsant drugs against amygdala-kindled seizures showed a more rapid onset of tolerance than animals maintained on stable doses, either higher or lower. These data raise the question of whether the typical clinical strategy of targeting affective symptomatology with the lowest or minimally effective dose should be re-evaluated, particularly in patients with indices of high illness drive. Applying the higher or maximal tolerated dose may be more effective in preventing the eventual development of recurrences associated with tolerance. A full dose strategy was effective in the 3- (Frank et al., 1990) and 5-yr (Kupfer et al., 1992) prophylaxis studies with imipramine (200 mg/d) for recurrent unipolar depression. When Kupfer and associates (Kupfer et al., 1992) reduced this dosage they began to see a higher incidence of relapse. Halving the dosage of lithium prophylaxis also results in breakthrough episodes (Lafer et al., 1994). While in the prophylactic trial of maprotiline for unipolar depression, a dosage that was twice that of the lowest effective dose showed greater therapeutic efficacy (Rouillon et al., 1989).

Patients with extreme rapidity of cycling, (ultra rapid and ultradian cycling) (Kramlinger and Post, 1996; George et al., 1996) appear particularly refractory to mood-stabilizer monotherapy with lithium, carbamazepine, or valproate. In some instances, they respond to mood-stabilizer combination therapy or the calcium channel antagonists nimodipine or isradipine alone or in combination with carbamazepine (Pazzaglia et al., 1993; McDermut et al., 1995). The relative efficacy of these dihydropyridine vs other L-type calcium channel blockers, such as verapamil (Dubovsky et al., 1982; Hoschl et al., 1992), and their use in monotherapy and combination therapy (Post et al., 1996) remain to be explored.

A further prediction and caveat from this model would be that a period of time-off drug in the face of tolerance development (and only in instances of tolerance development) might be of clinical value (Pazzaglia and Post, 1992; Weiss et al., 1995). However, it should be re-emphasized that discontinuation of a treatment that continues to show efficacy raises a series of hazards. These include: the high risk for relapse (Suppes et al., 1991); the attendant morbidity; the potential, small but not trivial, discontinuation-induced refractoriness (Post et al., 1992a, 1993); and the increased risk of suicide (Muller-Oerlinghausen et al., 1991, 1992). Thus, the model predicts a very differential impact of treatment discontinuations based on the history and pattern of illness responsiveness to a given drug.

Fig. 10. *(previous page)* Loss of efficacy to valproate via tolerance: Comparative progressive evolution in syndrome breakthroughs. **(Top)** Course of tolerance development in a patient. **(Bottom)** Course of tolerance development in an amygdala-kindled rat. In both instances, although over vastly different time scales, there is a progression of episodic breakthroughs leading to complete tolerance. Interestingly, for both the patient and the kindled animal, drug efficacy was reinstated by a period of time off from the drug treatment (patient; right side ≈ 1989, rat; right side ≈ d 88–94).

Conclusions

Given these preliminary empirical data and theoretical formulations, the importance of

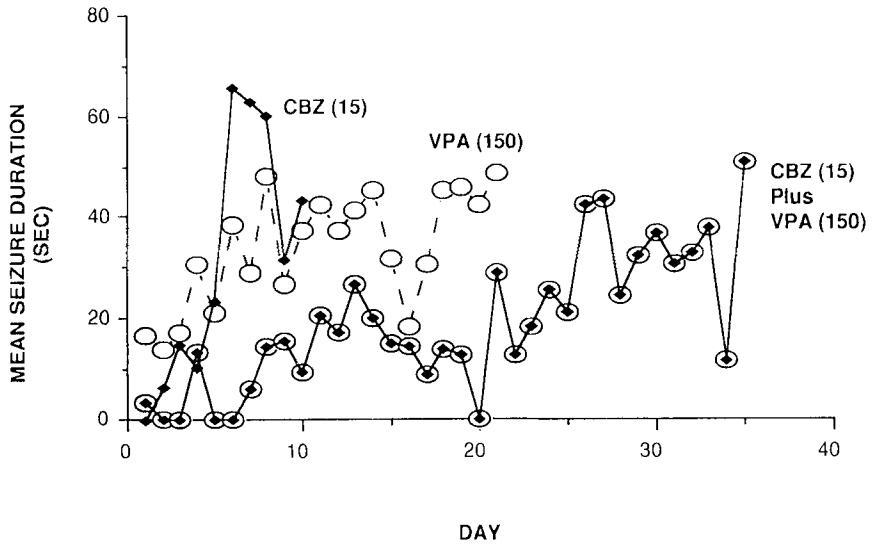

Fig. 11. Enhanced anticonvulsant efficacy of carbamazepine plus valproate compared to monotherapy in amygdala-kindled rats. Group mean seizure duration is plotted over days in rats treated with carbamazepine (CBZ) alone (15 mg/kg) (filled symbols), valproate (VPA) alone (150 mg/kg) (open circles), or the combination (filled circles). Tolerance was slowest to develop and anticonvulsant efficacy was best and most prolonged in the group receiving the combined CBZ-VPA treatment.

conducting systematic trials of long-term prophylaxis with different agents, at different doses, and in various combinations is highlighted. One could hypothesize on the basis of the very indirect preclinical extrapolations presented here that patients with higher indices of "illness drive" should be more aggressively treated from the outset using the most effective treatment regimens, including combination therapies. Targeted psychotherapies, therapeutic approaches to comorbid problems of substance abuse, and behavioral treatments directed toward compliance might also help prevent accumulation of experiential risk factors and further cycle progression. Therefore, a wide range of prospective clinical trials with specific outcome predictions are suggested by this therapeutic view of initial illness emergence and reemergence via progression and drug tolerance. The potential for better therapeutic targeting of endogenous adaptive mechanisms for enhancement as well as the putative primary pathological mechanisms for suppression is also suggested.

This conceptual view may also help to bridge one of the fundamental problems in the recurrent affective disorders—how episode recurrence can become linked to both highly individualized and variable patterns of cyclicity both among and within individuals. Further preclinical studies are needed to more precisely identify the variables and molecular principles involved in the individualized patterns of cyclicity, but the current preliminary view suggests that the factors involved in the induction and remission of acute episodes themselves may be the same ones inherently linked to cyclicity. If this proves to be the case, then one does not need to postulate a second abnormality in "clock function" in the illness. Rather, based on this analysis, we suggest that rhythmic abnormalities emerge directly out of illness-related variables and that the illness provides its own individualized clock function based on the balance of primary pathophysiological mechanisms and compensatory adaptations (Figs. 5 and 7).

The prediction from this formulation is that the illness is the clock and one that can be highly variable between individuals and even within individuals. If this were to prove valid, it would lead to very different biological and genetic explanations of the basic abnormalities

in bipolar illness. Rather than one abnormality in mood regulation and another in a circadian or clock function, one could conceptualize a more integrated set of abnormalities with liability to illness progression. These could ultimately involve loss of regulation in multiple systems similar to that observed in seizure evolution, or in cancer evolution, where dysfunction exists at many steps in otherwise normal regulatory pathways involving both transcriptional and oncogenic activation on the one hand and loss of suppressor factors on the other.

If some of these preclinical concepts prove helpful in formulating, prioritizing, and designing specific prophylactic clinical trials as suggested, this in itself would help certify this type of indirect model building (Weiss and Post, 1995) as worthwhile and heuristically useful. Although kindling is not homologous to the behaviors involved in affective disorders and seizures are not thought to underlie affective dysregulation of primary affective disorder, the current specific analysis of some of the factors involved in seizure progression and cyclicity may help in the identification and assessment of related phenomena in affective illness evolution. These might include a differential and progressively changing neurobiology and psychopharmacology of different stages of illness development, progression to full-blown episodes, tolerance, renewed response following time-off, loss of responsiveness via tolerance, and renewal of responsivity. Many of the predictions derived from this conceptual view of illness evolution and cycling can now be subjected to further direct preclinical study and evaluation in appropriate clinical trials in affectively ill patients.

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