Sensitization and Kindling Perspectives for the Course of Affective Illness: Toward a New Treatment with the Anticonvulsant Carbamazepine

R. M. Post
Biological Psychiatry Branch, National Institute of Mental Health, Bethesda, Maryland, USA

Summary

Successive episodes of affective illness often show an accelerating frequency of recurrence. Two very different preclinical models (behavioral sensitization to psychomotor stimulants and electrophysiological kindling) may be used as indirect analogies or non-homologous models for conceptualizing mechanisms underlying the progressive and evolving aspects of manic-depressive illness. These models focus on phenomena involved in the longitudinal course of illness and on novel treatment implications. Literature is reviewed on the acute and long-term effectiveness of the anticonvulsant carbamazepine, particularly in treatment of lithium-refractory bipolar illness. Potential mechanisms of carbamazepine's acute anticonvulsant and antinociceptive and delayed psychotropic actions are discussed. α-2 adrenergic and peripheral-type benzodiazepine receptors, and stabilization of type-2 sodium channels are likely involved in the anticonvulsant effects of carbamazepine. $GABA_B$ mechanisms are thought to be related to the antinociceptive but not anticonvulsant or psychotropic effects of carbamazepine. A large number of neurotransmitters remain candidates for the psychotropic effects and a novel animal model requiring chronic administration of carbamazepine in order to show efficacy is reported (*Weiss* et al., 1989). It is hoped that further understanding of the mechanism of action of the anticonvulsant agents in comparison and contrast with traditional psychotropic agents will help in generating new treatments and in uncovering the basic defects of manic-depressive illness.

Verbesserung der Behandlungsmöglichkeit der affektiven Erkrankungen durch Pharmakotherapie mit dem Antiepileptikum Carbamazepin

Seit der Zeit *Kraepelins* ist bekannt, daß bei Gemütserkrankungen häufig immer rascher folgende Krankheitsphasen aufeinander folgen. Zwei unterschiedliche Modelle (Sensibilisierung von Verhaltensmustern auf psychomotorische Stimuli und elektrophysiologisches „Kindling") könnten als Vergleiche für die Entstehungsmechanismen dienen, welche dem sich progressiv entwickelnden Krankheitsbild zugrunde liegen. Diese Modelle sind von begrenztem klinischem Wert, beleuchten jedoch Phänomene, welche den Langzeitverlauf und die Behandlungsmöglichkeiten beeinflussen. Die Literatur über Sofort- und Langzeitwirkungen des Antikonvulsivums Carbamazepin, v. a. bei der Behandlung von Lithiumresistenten bipolaren Erkrankungen wurde zusammengefaßt, mögliche antikonvulsive und psychotrope Wirkungsmechanismen werden diskutiert. α2-adrenerge und periphere Benzodiazepin-Rezeptoren sowie Stabilisierung der Typ 2 Natrium-Kanäle sind wahrscheinlich an der antikonvulsiven Wirkung des Carbamazepin beteiligt. Es wird angenommen, daß $GABA_B$-Mechanismen mit der antinociceptiven Wirkung zusammenhängen (*Terrence* et al., 1983), auch wenn neuere Erkenntnisse nahelegen, daß dieses Neurotransmittersystem für die antikonvulsive Wirkung nicht so wichtig ist. Viele Neurotransmitter bleiben als Erklärungsmöglichkeit für die psychotropen Effekte übrig, und es wird über ein neues Tiermodell berichtet, welches eine Langzeitgabe von Carbamazepin voraussetzt, um die Wirksamkeit zu zeigen (*Weiss* et al., 1989). Es bleibt zu hoffen, daß ein verbessertes Verständnis der Wirkungsmechanismen von antikonvulsiven Substanzen im Vergleich zu den traditionellen psychotropen Substanzen helfen wird, neue Behandlungsmöglichkeiten der manisch-depressiven Krankheit zu entwickeln.

Introduction

Acceleration of the Course of Affective Illness

This manuscript focuses on the temporal evolution of affective illness and two different animal models, sensitization and kindling, that may be useful in conceptualizing this process and its underlying pharmacology and mechanisms. Studies using these animal models led to our initiation

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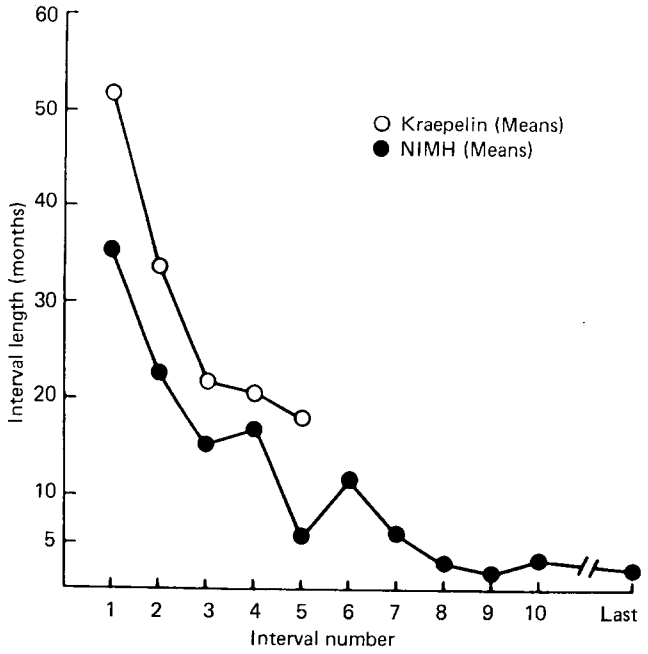

Fig. 1 Decreasing Well Intervals in Recurrent Affective Illness

of investigations of carbamazepine in affective illness. The clinical effectiveness of this anticonvulsant in the acute and prophylactic treatment of manic-depressive illness is briefly reviewed and possible mechanisms of its psychotropic action are considered.

Kraepelin was among the first to observe that successive episodes of affective disorder on the average tended to occur with an increasingly short "well-interval" between them (*Kraepelin*, 1921). Numerous studies have documented the potential for the illness to speed up in cycle frequency, if not also in severity of episodes and rapidity of onset of individual episodes (*Grof* et al., 1974; *Cutler* and *Post*, 1982; *Squillace* et al., 1984). While the minority of patients may experience only a single episode of affective illness, in the better controlled studies with longer follow-ups (*Angst*, 1978; *Grof* et al., 1974; *Perris*, 1966), it is now recognized that the illness is recurrent in some 70 % to 80 % of patients (*Zis* and *Goodwin*, 1979). While a subgroup may begin their illness with rapid cycling, the course is often one of longer well intervals between initial episodes with this decreasing as a function of successive recurrences (Fig. 1). The median course of illness in 83 refractory bipolar patients admitted to the tertiary referral center at the National Institute of Mental Health in Bethesda, Maryland, is illustrated in Fig. 2. Examination of individual patterns of progression of episodes revealed that approximately half of the patients showed a tendency for an increased cycle frequency over time, while the other half were represented by patients with rapid cycles occurring from their onset of illness (*Roy-Byrne* et al., 1985).

Given the proclivity of the illness to speed up over time at least in a subgroup of affectively ill patients, we sought to examine models which might help in the conceptualization of this process. Behavioral sensitization to psychomotor stimulants and electrophysiological kindling represent two very different mechanistic based processes which share the common property of showing increasing responsivity to repeated application of the same stimulus over time (*Post* et al., 1984 a; 1986 a). Thus, this proclivity for increased responsivity may be an indirect analogy for the apparent increased vulnerability in patients experiencing repeated occurrences of affective illness. It should be stressed, however, that these models generally do not produce behaviors that are homologous to those observed in affective disorder (except cocaine modelling mania) and constitute only interesting analogies for potential ways of conceptualizing processes which may underlie increased responsivity to the same stimulus over time, rather than being formal animal models for affective illness (Table 1). These caveats are discussed in detail elsewhere (*Post* and *Weiss*, 1989).

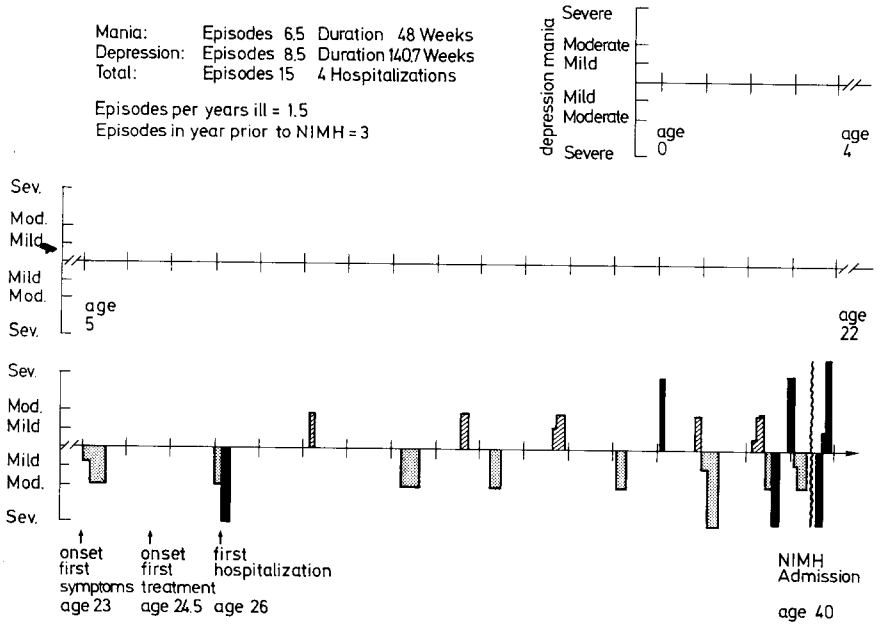

Fig. 2 Median Course of Affective Illness in 82 Bipolar Manic-Depressive Patients

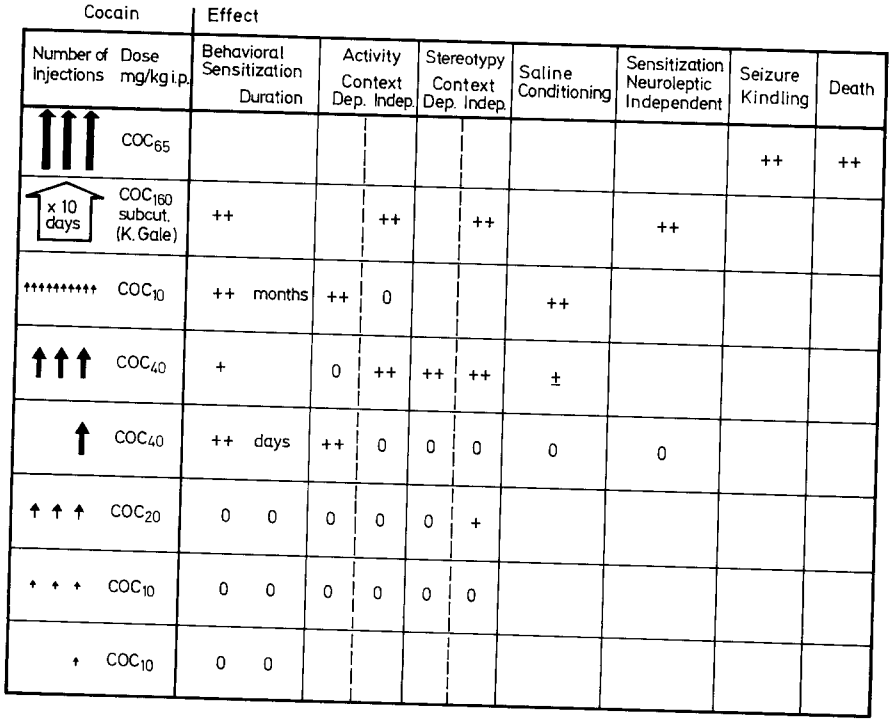

Fig. 3 Effects of dose (size of arrows) and repetition (number of arrows) on magnitude duration, and context-dependency of cocaine-induced behavioral sensitization and kindling

Behavioral Sensitization

Differential Effects of Neuroleptics

In behavioral sensitization to the psychomotor stimulant cocaine, repeated application of the drug results in increasing motor activity and/or stereotypy responses to the same dose (*Post* and *Contel*, 1983; *Kilbey* and *Ellinwood*, 1977). Not only is the amplitude or duration of response enhanced upon repetition, but the rapidity of onset of peak activity or stereotypy is also enhanced, perhaps consistent with observations that onsets of individual affective episodes are more rapid in patients with greater numbers of prior episodes (*Post* et al., 1981 b). With cocaine, an important component of the increased response is conditioned (*Post* et al., 1981 a; *Schiff* et al., 1981). That is, animals treated with cocaine in the context of the test cage show increased hyperactivity compared to the saline pretreated controls, but animals treated with cocaine in a dissimilar environment to the test cage do not show the behavioral sensitization. This conditioned component of behavioral sensitization is observed with repeated administration of low doses of cocaine (10 mg/kg) (*Post* et al., 1981 b) or with a single high dose of cocaine (40 mg/kg) (*Weiss* et al., 1989 a). However, if high doses are given repeatedly, a context-independent component of behavioral sensitization can also be observed (*Weiss* et al., unpublished data, see Fig. 3).

Cocaine-induced behavioral sensitization can be documented in a simple two-day paradigm in which animals receive high doses of cocaine and saline on day 1 and then are tested with a low dose on day 2 (Fig. 4). In this procedure blockade of cocaine-induced hyperactivity on day 1 with neuroleptics blocks the development of sensitization (Weiss et al., 1989 a). However, pretreatment of animals on day 2 with neuroleptics is insufficient to block the expression of behavioral

Tab. 1 Parallels in the Phenomenology of Affective Illness to Kindling and Sensitization

Characteristic of Affective Illness	Characteristic of Kindling	Characteristic of Sensitization
1. Genetic component	X	X
2. Early experience predisposes	X	X
3. Mild alterations emerge as full-blown episodes (threshold effects)	X	X
4. Episodes reach plateau and are similar in content and behavior over repeated recurrences	X	X
5. Onset of maximum disturbance occurs earlier in episode with repetitions	X	X
6. Vulnerable to recurrences and cycles may speed up	X	X
7. Early episodes may be precipitated, later appear spontaneously	X	?
8. Repeated episodes of mania or depression may lead to emergence of opposite phase (conditioned compensatory reactions)	?	X
9. Lithium carbonate effective prophylaxis	–	(X)
10. Carbamazepine effective prophylaxis	(X)	–

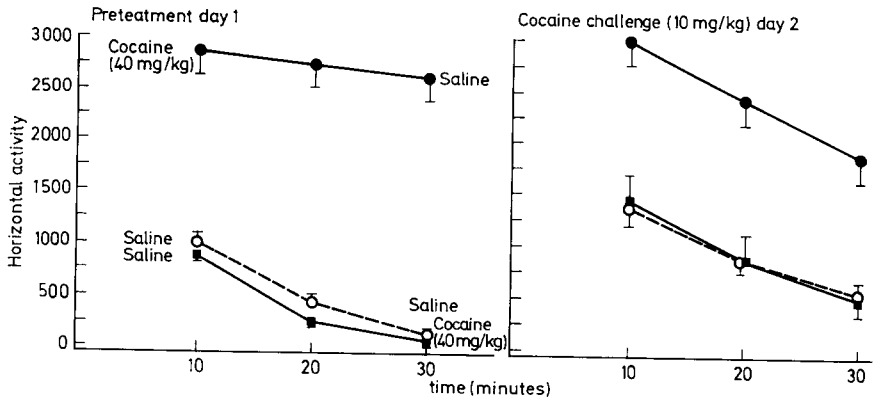

Fig. 4 Cocaine-Induced Behavioral Sensitization Depends on Environmental Context

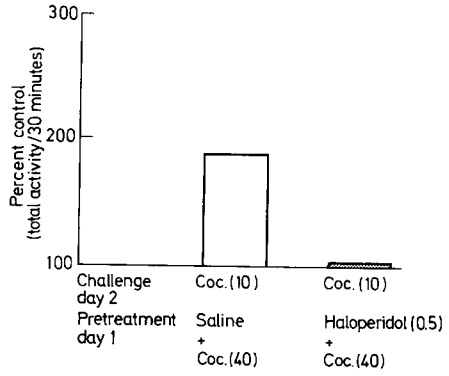

Fig. 5 a

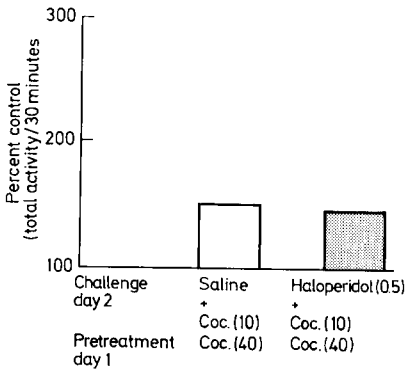

Fig. 5 b

Fig. 5 a Haloperidol Blocks the Development of Cocaine Sensitization

Fig. 5 b Haloperidol does not Block Expression of Cocaine Sensitization

sensitization once the animals have experienced cocaine-induced running on day 1 (Fig. 5). These data, replicated three times in our laboratory, are convergent with previous observations of *Beninger* and *Hahn* (1983), *Beninger* and *Herz* (1986), and *Tadokoro* and *Kuribara* (1986) using different neuroleptics, stimulants, and species, indicating the robustness of the findings regarding the differential impact of neuroleptics depending on the temporal phase. In contrast to the neuroleptics, pretreatment with the benzodiazepine diazepam or the alpha-2 agonist clonidine is able to block both the development and the expression of cocaine-induced behavioral sensitization. These data suggest that dopaminergic mechanisms are critical to the development but not the expression of cocaine-induced behavioral sensitization. Similar pharmacological dysjunctions based on time of intervention have also been observed in other models where the development or initiation of kindling or long-term potentiation is affected by one set of drugs, but completed kindled seizures or the maintenance of long-term potentiation is affected by different agents (*Peterson* and *Albertson*, 1982; *Collingridge* and *Bliss*, 1987). Thus, the animal models illustrate the principle that different phases in the development of a syndrome may be differentially pharmacoresponsive and raise the possibility that a similar process could apply to stages in the evolution of manic-depressive illness (see below and Fig. 8).

To the extent that cocaine administration is a valid model for mania or dysphoric mania (*Post*, 1975; *Post*, 1989), the preclinical findings suggest a potentially useful animal model for neuroleptic refractoriness (*Post* and *Weiss*, 1988). That is, to the extent that conditioned components play a role in the increased behavioral responsivity in successive episodes of affective illness, early treatment of manic and related psychotic syndromes with neuroleptics may be more effective than treatment with these agents once one or more episodes have been experienced. Preliminary data in support of this notion has been garnered by *Wyatt* et al. (1988); in several studies early treatment with neuroleptics in schizophrenic psychotic episodes appears to be more effective than more delayed treatment. While there is little direct experimental evidence for this possibility in the affective disorders, the sensitization model yields a prediction that can be directly formulated and tested in clinical populations.

In many instances there appears to be cross sensitization between behavioral sensitization to psychomotor stimulants and stress. *Antelman* and *Chiodo* (1984), *Antelman* et al. (1980), and *Kalivas* and *Duffy* (1989) have documented that stressed animals may show increased response to psychomotor stimulants and vice versa. These data, taken with the recent observations that cocaine not only potentiates catecholamines but also releases corticotropin releasing hormone (CRH) (*Calogero* et al., 1988; *River* and *Vale*, 1987), further suggest that the drug may be an important analogue for a stressor. Thus, cocaine-induced behavioral sensitization may represent an interesting paradigm for conceptualizing how repeated stressors could come to evoke increasingly robust affective and motor responses over time.

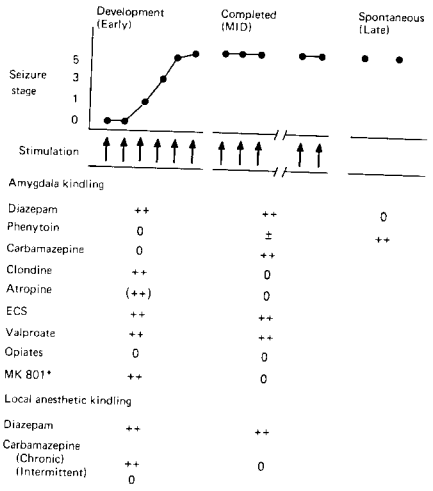

Fig. 6 Pharmacological Responsitivity as a Function of Stage of Kindling

Kindling

A Differential Pharmacology and Anatomy as a Function of Stage of Evolution

Kindling represents another model in which repeated stimulation (in this case electrophysiological stimulation of discrete sites in the brain) evokes increasing responses to repetition of the same stimulus characteristics over time. Repeated and intermittent stimuli are required as continuous stimulation or even stimulation at intervals of once every two or five minutes is ineffective in producing kindled seizures (*Goddard* et al., 1969; *Racine*, 1972, 1978). The repeated, intermittent stimulation is associated with a lowering of the after-discharge threshold, increasing durations of the after-discharge (AD) with increasing spread of the AD and increased complexity of its wave form, finally culminating in the appearance of major motor seizures involving head, trunk, and forepaws with rearing and falling. If these kindled seizures are repeated for a long enough period of time, animals develop spontaneity, i. e. they manifest seizures in the absence of exogenous electrophysical stimulation.

Thus, the kindling process appears to have three separate stages (Fig. 6). There is a phase of kindling *development* associated with changes in after-discharge and associated electrophysiological and biochemical events that eventually culminate in the production of major motor seizures; the stage of *completed* kindled seizures where full-blown seizures are reliably induced following each electrophysiological stimulation; and the late stage of *spontaneity*.

The changes induced in kindling represent permanent changes in synaptic excitability as animals that have been kindled show altered responsivity six months to one year later (*Racine*, 1978). Thus, the model has been used as one for learning and memory as well as epileptogenesis. In this instance we are using the kindling analogy to conceptualize how repeated activation of synaptic pathways may result in increasing responses over time with a permanent change in responsivity. Analogous processes may occur in different biochemical pathways following repeated experiences of affective episodes; that is, episodes may be progressively more easily triggered.

There is considerable evidence that the neuroanatomical and biochemical substrates underlying kindling change as a function of the evolution of different seizure stages. These data are illustrated in Fig. 6. For example, we have found that carbamazepine, one of the most effective drugs in inhibiting completed amygdala-kindled seizures, is without effect on the development of these kindled seizures (*Weiss* and *Post*, 1987). Conversely, in another type of kindling, that induced pharmacologically by repeated injection of local anesthetics, carbamazepine administered in the diet blocks the development of lidocaine- and cocaine-kindled seizures, but is without effect on acute, high-dose or completed local anesthetic-kindled seizures (*Weiss* et al., 1989 b). Thus, this double dissociation illustrates that different phases of kindling are differentially pharmacologically responsive, and that this may vary as a function of type of kindling as well.

Work of *Pinel* (1983) further clarifies this differential pharmacological responsitivity as a function of stage of kindling. He found that diazepam is highly effective in the initial and completed stage of amygdala-kindled seizures, but once animals reached the phase of spontaneity, this drug is without effect. Conversely, phenytoin which is ineffective or weak in the initial stages, is highly effective in preventing spontaneous seizures. Thus, there is strong evidence from these and other studies that different stages of kindled seizure evolution are differentially pharmacologically responsive; this would imply that different biochemical mechanisms underlie different phases of kindling evolution.

Preliminary evidence has been gleaned for differential anatomical substrates also being involved as a function of kindling stage by *Clark* et al. in our laboratory. He observed that amygdala kindled seizures initially involve induction of the proto-oncogene c-fos, as measured by in situ hybridization in the piriform cortex and occipital lobe unilaterally (*Post* et al., 1990). Following repeated after-discharge induction or increase in its duration, cortical c-fos induction became bilateral. Finally, induction of c-fos could be observed unilaterally in the dentate gyrus and then bilaterally with the emergence of stage 3 or stage 4 seizures. These data on the spatio-temporal spread of the kindling process are at least partially paralleled by changes observed electrophysiologically or with 2-deocyglucose to measure regional metabolic activity. It would be of great importance to ascertain the neural substrates involved in spontaneous seizures, as preliminary data from *Pinel* (1981) suggest that these late evolving processes are not associated with after-discharges at the stimulating electrode site as are earlier seizures, and presumedly the AD focus is occurring elsewhere in the brain.

Sensitization and Kindling in Affective Illness

Parallel Mechanisms for Increasing Vulnerability

The stages of kindling evolution and their differential biochemical and anatomical substrates may have important implications for the evolution of analogous processes in different phases of affective illness. Again, we are not suggesting a literal kindling mechanism is occurring in

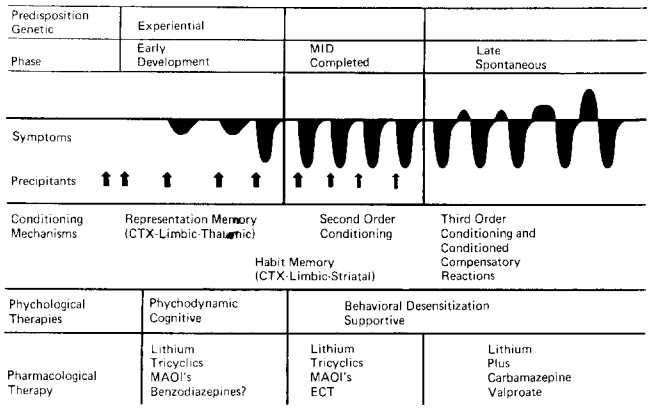

Fig. 7 Sequential Evolution and Sensitization of Affective Illness

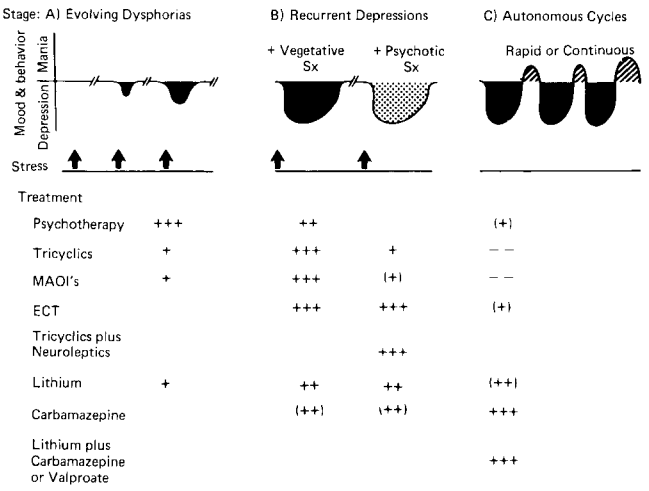

Fig. 8 Psychopharmacotherapy of Affective Illness as a Function of Type and Stage of Development

patients with manic-depressive illness, as they clearly do not show convulsive disturbances (*Post* and *Uhde,* 1985), but that the stages of evolution of affective illness may share processes parallel to those observed in kindling. For example, processes analogous to those occurring in behavioral sensitization and kindling could account for how repeated stressors could come to evoke increasingly severe affective disturbances culminating in full-blown major affective episodes (Fig. 7 and Table 1). With repetition of these episodes the neural substrates involved may progressively become facilitated and vulnerable to re-activation with lesser degrees of stress: Ultimately, with sufficient repetitions, one might begin to experience autonomous episodes of affective illness without exogenous precipitants in a process parallel to that occurring in spontaneity in kindling.

Some evidence bears on this hypothesis derived from repeated separation stresses in the non-human primate. *Young* et al. (1973) and *Mineka* and *Suomi* (1978) have observed that peer separations lead to more severe despair reactions in animals who had previously experienced maternal separations in their youth. There appears to be little evidence that animals show tolerance to repeated peer separations and, recently, *McKinney* (personal communication) has reported that, after multiple peer separations, animals become "depressed" upon the appearance of the handlers (who had previously induced the separations) or spontaneously.

While some patients with high genetic loading may become affectively ill without psychosocial precipitants or exogenous stressors, there may be a subgroup of patients who have both a biological vulnerability and appropriate stressors involved in the induction of initial episodes (*Brown* et al., 1975; *Paykel,* 1979; *Lloyd,* 1980). The kindling and sensitization models would suggest that recurrences of these or related stressors may come to not only evoke increasingly severe affective episodes, but with the repeated occurrence of episodes, the stressors required may become less obvious or more symbolic and then finally not be required at all (Fig. 7). While this formulation remains to be directly tested in affectively ill patients, preliminary data from *Ambelas* et al. (1979) does suggest the possibility that psychosocial stressors are more apparent in initial episodes of affective illness than they are following many recurrences. A variety of data reviewed recently by *Silverstone* and *Romans-Clarkson* (1989) also support the view that psychosocial stressors may be involved in the precipitation of some affective episodes. The current formulation suggests the possibility that not only would there be subgroups of patients who do or do not manifest psychosocial precipitants, but that in some individuals the role of stressors may change over the course of evolution of affective illness, i. e., prominent early in the course and increasingly less obvious with the longitudinal unfolding of the syndrome.

Another prediction of this model which can be directly tested is that pharmacotherapy may differ as a function of course of affective illness as it does, at least with some agents, in the sensitization and kindling models. This hypothetical schema is illustrated in Fig. 8. For example, traditional psychotherapies, as well as cognitive therapy and interpersonal therapy, may be highly effective in the treatment of early episodes of affective illness, but with increasing severity and/or rapid cycling, these techniques alone appear insufficient to control acute episodes or their recurrences. While tricyclic antidepressants and monoamine oxidase inhibitors are highly effective in the treatment of acute or recurrent episodes, in some rapid cycling patients they may precipitate manic episodes or accelerate the frequency of rapid cycling (*Kukopulos,* 1980; *Wehr* and *Goodwin,* 1987; *Wehr* et al., 1988). Considerable evidence documents that prophylactic treatment with lithium carbonate is less effective in rapid cycling compared to non-rapid cycling patients (*Hanus* and *Zapletalek,* 1984; *Bouman* et al., 1986; *Goodnick* et al., 1987; *Abou-Saleh* and *Coppen,* 1986). This may represent a difference in response of subgroups or could be related to the stage of evolution of illness, as rapid cycling is often a relatively late occurring phenomenon in the course of bipolar illness. Many of these relatively lithium refractory patients will respond to carbamazepine and related anticonvulsants (see below). It remains to be documented whether these anticonvulsant agents are equally effective in earlier phases of the illness.

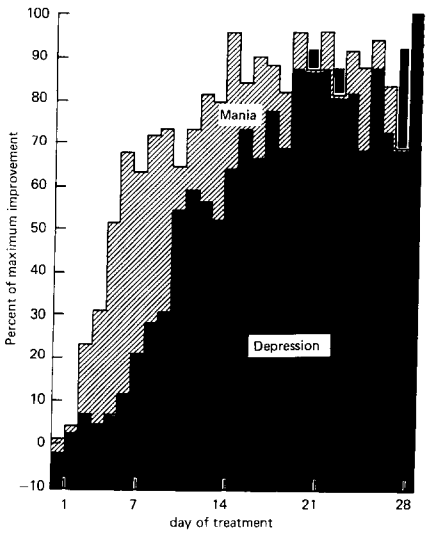

Fig. 9 Rapid Onset in Antimanic Compared to Antidepressant Response to Carbamazepine

Thus, the provisional schema is presented in Fig. 8 in order to raise the possibility for the theoretician and clinician that pharmacotherapy may differ as a function of stage of longitudinal course of illness and to provoke direct testing of this hypothesis; there are clearly other interpretations of the preliminary data that are available, such as the existence of differential subtypes of responsive patients based on genetics or the phenomenology of clinical presentation.

The Anticonvulsant Carbamazepine in Affective Illness

Acute and Prophylactic Efficacy

Several different elements in the kindling model led us to consider the use of carbamazepine in affectively ill patients in the mid 1970s. As noted above, it represented one of the best "limbic" anticonvulsants, although it is clearly effective in other seizure subtypes. Carbamazepine is the most effective anticonvulsant in inhibiting the amygdala-kindled focus compared to that of the cerebral cortex (*Albright* and *Burnham*, 1980). Given the fact that limbic substrates had long been implicated in the modulation of normal and pathological affect, we thought it possible that carbamazepine might help stabilize affective dysregulation if underlying limbic dysfunction was important to the affective illnesses. Since carbamazepine was also able to block the evolution of kindled seizures at least in some models of kindling and in some species (cat, monkey, but not rat), we thought that this agent might also have potential effectiveness in the long-term treatment of the progressive form of the disorder. In addition to these theoretical rationales, empirical data was available from the observations of *Dalby* (1971, 1975) indicating that a substantial percentage of epileptic patients treated with carbamazepine showed improvement in their mood and behavior, at times independent of better seizure control. After deciding to utilize carbamazepine for these purposes, we were also bolstered by the data of *Okuma* et al. (1973) and other Japanese investigators who had performed open clinical trials of carbamazepine in patients with primary affective disorder with some success (*Takezaki* and *Hanaoka*, 1971). *Okuma* et al. have subsequently also followed up on their initial open investigations with double-blind, controlled clinical trials, further supporting the acute and prophylactic efficacy of carbamazepine in patients with primary affective illness (*Okuma* et al., 1979; 1981; 1984).

We initiated double-blind trials of carbamazepine with placebo substitution, generally utilizing a B-A-B design. Initial results, published in 1978, were highly suggestive of the acute antimanic and longer term prophylactic efficacy of the drug (*Ballenger* and *Post*, 1978; 1980). Subsequent work has revealed the acute antimanic efficacy of carbamazepine, with a time course similar to that ovserved with the neuroleptics (*Post* et al., 1987 c). Preliminary analysis of our data indicated that the 12 responders, compared to the seven non-responders, were more severely manic at the outset of their clinical trial, were more rapid cycling in the year prior to NIMH admission, showed a lower incidence of a positive family history of affective illness in first degree relatives, and tended to be more dysphoric. Thus, a series of variables that are often associated with poorer response to lithium, tended to be associated with relatively good acute antimanic responses to carbamazepine. These observations suggesting possible subgroups of responsive patients paralleled those of *Okuma* et al. (1984) and initial observations of *Grof* et al. (personal communication, 1987). As reviewed in Table 2, there are now a total of 14 double-blind, controlled clinical trials of carbamazepine supporting its clinical efficacy in acute mania (*Post* et al., 1989 b).

The acute antidepressant effects of carbamazepine have been less well studied than its acute or prophylactic antimanic effects. We have reported on a double-blind study the first 35 patients, of whom 12 showed at least a moderate to marked degree of improvement (*Post* et al., 1986 b). This series has now been extended to 54 patients with 17 responders (31 %) and is compatible with the study of *Neumann* et al., (1984) on the antidepressant effects of carbamazepine compared to trimipramine. Further systematic clinical trials of carbamazepine in comparison with other antidepressant modalities is required to definitively assess the acute antidepressant efficacy of carbamazepine. Nonetheless, our preliminary data in refractory patients suggest that a subgroup of patients may be acutely responsive during depressive episodes.

We preliminarily explored possible factors associated with improvement during treatment compared to those who did not respond. Those who presented with initially more severe levels of depression in the placebo baseline period and had a history of more discrete episodes and less chronic depression were among those who responded best. Interestingly, those with greater degrees of thyroid suppression, as measured by decreases in T_4 ($r = -.43$, $p < .01$) and free T_4 ($r = -.56$, $p < .001$) were among those who responded best to carbamazepine (*Roy-Byrne* et al., 1984; *Post* et al., 1987 a). This may reflect patients experiencing either an increased drug effect (although blood levels were not significantly different between responders and non-responders) or it may relate to changes in the thyroid axis which are important to the clinical effects of carbamazepine. These data are consistent with those of *Baumgartner* et al. (1988) who reported greater decrements

Tab. 2 Controlled Studies of Carbamazepine in Acute Mania

Study	N	Diagnosis	Design	Dose of Carbamazepine (mg/day) (blood level)	Other Drugs	Duration	Results
Ballenger & Post, 1978, *Post* et al., 1984; 1987	19	Manic-depress. psychosis	Dbl. Blind (B-A-B-A)	600–2000 (7-15.5 µg/ml)	None	11–56 days	12/19 improved – time course similar to neuroleptics; frequent relapses on placebo substitution
Okuma et al., 1979	32 CBZ 28 chlor.	Manic-depress. psychosis ICD-9	Blind vs. chlorpromazine 150–450 mg	300–900 (2.7–11.7 µg/ml) (mean = 7.2 ± 3.4)	Bedtime hypnotics	3–5 wks	21/32 improved on CBZ (marked to moderate) 15/28 improved on chlorpromazine
Klein et al., 1984	11 3	Manic Excited SA	Blind vs Placebo Addition to Haloperidol	600–1600 (6–18 µg/ml)	Haloperidol (15–45 mg/day) all patients	5 weeks	10/14 improved on CBZ + haloperidol (7/13 improved on placebo + halo.)
*Müller & Stoll*a) 1984	6	M–D	Blind vs Placebo	600–1200 mg	Halo. & Hypnotics	3 weeks	?/6 $p < 0.01$ better than placebo
*Müller & Stoll*b) 1984	10	M–D	Blind vs Haloper. (15–50 mg)	600–1200 mg Oxcarbazepine	Halo. & Hypnotics	2 weeks	?/10 OXCBZ = haloperidol
Grossi et al., 1984	18 CBZ 19 chlor.	M–D	Blind vs. chlorpromazine randomized	200–1200 mg 200–500 mg chlorpromazine	?	21 days	10/15 improved on CBZ 13/17 improved on CPZ CBZ = fewer side effects than CPZ
Emrich et al., 1985	7	Manic Psychoses	Dbl. Blind (B-A-B)	1800–2100 Oxcarbazepine	None	Variable	6/7 (> 25% improvement on IMPS)
Lerer et al., 1987	14 CBZ 14 Li	M–D	Blind vs. Li randomized	600–2600 mg (3.3–14 µg/ml)	Chloral hydrate Barbiturates H. S.	28 days	4/14 improved on carbamazepine 11/14 improved on lithium CGI = < .05 (Li) BPRS = N. S.
Brown et al., 1986 *Cookson*, 1987	10 CBZ 15 halop.	Manic	Blind vs. haloperidol 20–80 mg/day	400–1600 mg	Chlorpromazine to 3 pts CBZ to 5 pts halop.	42 days	5/8 marked improvement CBZ 2/9 marked improv. haloper. and both switch into depression CBZ better efficacy & accept
Lenzi et al., 1986	11 CBZ 11 Li	M–D & SA	Blind vs. Lithium 900 mg	400–1600 mg (7–12 µg/ml) (.6–1.2 mEg/1)	Chlor. all pts.	19 days	Equal efficacy in CBZ & Li groups. Less CPZ required in carbamazepine group acutely. CBZ better on paranoia; less EPS
Desai et al., 1987	5	Manic	Blind vs placebo addition to Li	400 mg fixed dose	?	4 weeks	CBZ + Li ($p < .05$) better on BRMS scores than Li alone by 2nd week
Okuma et al. 1988	50 CBZ 51 Li	M–D	Blind vs.Li	400–1200 mg	Neuroleptics	4 weeks	31/50 improved on carbamazepine 30/51 improved on lithium onset earlier on CBZ
Okuma et al. 1988	103 CBZ 98 Placebo	SA S. Atypical P	Blind vs. Placebo		Neuroleptics		50 % improved on CBZ 30 % improved on placebo
Small et al. 1989	43 Total	M–D	Blind vs. Li			6–8 weeks	CBZ significantly better than Li in 2nd & 3rd weeks of treatment
14 studies in 299 patients							99/159 (62 %) improved on CBZ

Abbreviations: CBZ = carbamazepine; CPZ = chlorpromazine; Li = lithium; IMPS = Inpatient Multidimension Rating Scale; BRMS = Bech-Raefelson Mania Scale; CGI = Clinical Global Impressions; BPRS = Brief Psychiatric Rating Scale; EPS = Extrapyramidal Side Effects.

in thyroid indices associated with better response to maprotiline and chlorimipramine.

Importantly, we found no association between EEG abnormalities (even within the mild and normal range) or degree of paroxysmal psychosensory experiences (similar to those reported by patients with complex partial seizures) and degree of acute antidepressant response to carbamazepine (*Post* et al., 1989 b). Thus, although we postulated carbamazepine may be exhibiting its psychotropic effects through stabilization of limbic system excitability, to date we have no evidence that our patients are either experiencing overt or covert seizure disorders or that indirect measures of limbic system dysfunction are associated with degree of psy-

Tab. 3 Controlled and Quasi-Controlled* Studies of Carbamazepine Prophylaxis in Manic-Depressive Illness

Study	N	Diagnosis	Design	Dose of Carbamazepine (mg/day) (blood level)	Other Drugs	Duration	Results
Ballenger & Post, 1978 *Post* et al., 1983	7	6 M–D 1 conf. psychosis	4 Blind 3 open	800–2000 mg (11.3 µg/ml) (7.5–15.5 µg/ml)	None for 3 patients Li in 3 Neurolep. in 1	6–51 mos.	6/7 improved, esp. lithium non-respective cyclers
Okuma et al., 1981	12 CBZ 10 placebo	M–D	Carba. vs. placebo Blind Randomized	400–600 mg (5.6 ± 2.0 µg/ml)	Acute treatments added during episode breakthroughs	12 mos. either Rx	6/10 improved on CBZ; 2/9 improved on placebo ($p < .10$ diff.)
Placidi et al., 1986	CBZ: 20 9 Li: 27	M–D SA M–D + SA	Carba. vs. Lithium Blind Randomized	400–1600 mg (7–12 µg/ml)	Acute treatments added during episode breakthroughs	36 mos	21/29 marked to moderate improvement on CBZ 20/27 on Li improved by relapse criteria
Kishimoto & Okuma, 1985	18	BPI & II	Open crossover A–B or B–A vs. Lithium (400–800 mg)	200–600 mg		> 1 yr. each x = 52.4 mos. CBZ x = 42.2 mos. Li	Significantly fewer hospitalizations on CBZ CBZ effective in Li non responders
Watkins et al., 1987	19 CBZ Li	7 UP 12 BP	Carba. vs. Lithium D-blind Randomized	(5–12 µg/ml)	Antidepress. as needed		16/19 improved on carbamazepine 15/18 improved on lithium $p < .001$ increases in mos. of remission both drugs; Li > CBZ
Bellaire et al., 1988	50 CBZ	18 UP 24 BP 8 SA	Carba. vs. Lithium Open Randomized	600–800 mg (.2–12.5 µg/ml)		24 mos.	Global efficacy and tolerance n. s. favor CBZ
Lusznat et al., 1988	20 CBZ 20 Li	M–D	Carba. vs. Lithium Blind, Randomized	(6–12 µg/ml)	Neuroleptics, Antidepressants as needed	12 mos.	9/16 Satisfactory on CBZ 5/17 Satisfactory on Li. CBZ n. s., better than Li on readmission, depression side effects
					Controlled Studies		58/ 81 (72 %) response to carbamazepine
					Uncontrolled Studies		286/445 (64 %) response to carbamazepine
					Total		344/526 (65 %) response

* Blinded; Crossover; or Randomized

chotropic response to carbamazepine (*Post* and *Uhde*, 1986). In preliminary attempts to directly test the limbic dysfunction hypothesis, we administered acute doses of procaine to patients with affective illness and borderline personality disorder as well as normal controls (*Kellner* et al., 1987). Procaine administration was associated with evidence of limbic activation, including the emergence of prominent psychosensory symptoms in all sensory modalities, a range of affective changes, increased activity in fast frequencies over the temporal cortex, and increases in secretion of ACTH and cortisol and prolactin, but not growth hormone. However, in the borderline personality patients there was evidence of association of procaine-induced EEG changes and degree of response to carbamazepine. It remains to be further studied whether any element of the procaine activation test is associated with degree of the psychotropic response in patients with manic-depressive illness.

Seven controlled or quasi-controlled studies (double-blind, randomized, or crossed-over) have been conducted of carbamazepine prophylaxis revealing a 72 % response rate (Table 3). These data parallel a much more extensive body of uncontrolled studies indicating 286 or 445 or 64 % of patients showed a moderate to marked response. Taken together, 344 of 526 or 65 % of the patients reported in the literature have shown a moderate to marked improvement during carbamazepine prophylaxis. Particularly in the uncontrolled studies, carbamazepine has often been added to previously ineffective regimens including lithium carbonate. The adequacy of carbamazepine alone in comparison to lithium has been reported in more recent studies (*Bellaire* et al., 1988; *Lusznat* et al., 1988; *Watkins* et al., 1987; *Placidi* et al., 1986), but still requires further clarification. Moreover, the issue of whether there are differential subgroups of responders to one drug compared to the other also requires further study. Obviously, it would be of great help to have discrete clinical or biological markers of which patient might respond to which drug or of which patients appear to require the combination.

Our follow-up studies of the long-term effectiveness of carbamazepine in previous lithium non-responders show a reduction in frequency, duration, and severity of both

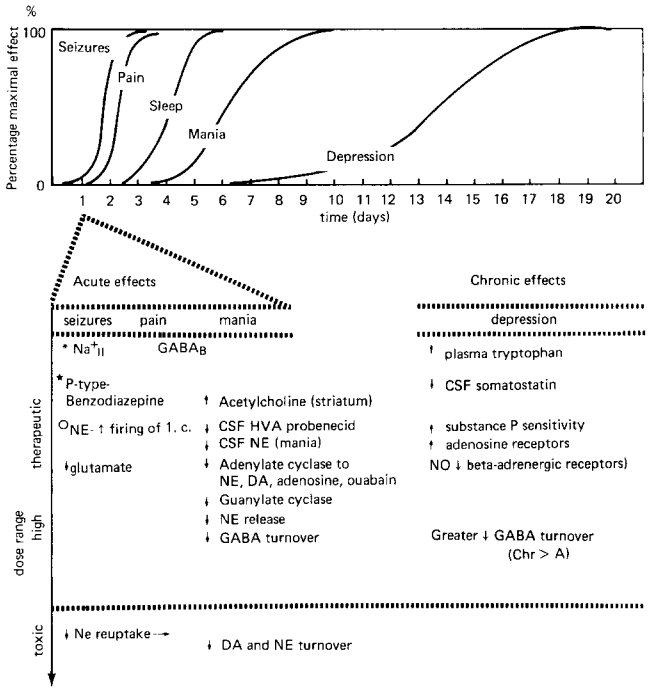

Fig. 10 Time Course of Clinical and Biochemical Effects of Carbamazepine

manic and depressive episodes (*Post* et al., 1983; 1990). Of the 24 patients followed for an average of four years, half appeared to show a pattern of sustained improvement, while the other half showed some evidence of loss of efficacy in the second and third year of treatment, perhaps consistent with the development of tolerance, although other explanations (including pharmacokinetic ones) remain to be explored. In the amygdala kindling model, we have observed the development of tolerance to the anticonvulsant effects of carbamazepine administered on a once-daily basis immediately prior to amygdala kindled seizures, but not in animals administered the drug on a once-daily basis immediately after the seizure has occurred (*Weiss* and *Post*, 1989). These data suggest that tolerance development is contingent on the pairing of drug with the seizure state. Moreover, the tolerance could be reversed by a period of induction of kindled seizures without drug or with drug administered after the seizures have occurred. Merely waiting an extended period of time (up to three weeks) does not reverse the tolerance. Thus, this type of tolerance observed to the anticonvulsant effects of carbamazepine appears to be contingent, and based on conditioning variables related to the pairing of drug and seizure state and reversed by altering these temporal contingencies. It is possible that a similar phenomenon could be occurring in the subgroup of patients demonstrating apparent tolerance to the antinociceptive (*Fromm* et al., 1984; *Fromm* and *Terrence*, 1987) or psychotropic effects of carbamazepine in manic-depressive illness and that a period of drug discontinuation may be associated with renewed efficacy of carbamazepine. Again, this preclinical model of contingent tolerance provides a directly testable hypothesis which could be of clinical import in the subgroup of patients who become refractory to the therapeutic effects of carbamazepine in neuropsychiatric syndromes including seizure disorders, paroxysmal pain syndromes, as well as manic-depressive illness.

Biochemical Substrates of Carbamazepine's Action

Given the strong evidence for carbamazepine exerting acute antimanic and prophylactic effects in patients with manic-depressive illness, the possible biochemical substrates for this effect deserve critical evaluation. Although the mechanisms of antimanic and antidepressant action of traditional psychotropic drugs have not been definitively delineated after decades of intensive study, the unique spectrum of clinical efficacy of carbamazepine provides additional leverage points in assessing its possible mechanisms of action (*Post*, 1987; 1988; *Waldmeir*, 1987). While the therapeutic efficacy of carbamazepine in most seizure syndromes and in trigeminal neuralgia tends to be very rapid in onset, acute antimanic efficacy often requires several weeks to become maximal and acute antidepressant efficacy some four to six weeks for maximal effect (Fig. 9) (*Post* et al., 1987 c). Thus, effects of carbamazepine that are immediately apparent acutely might be more likely related to anticonvulsant and antinociceptive effects, while those requiring time and chronic administration may be more closely related to psychotropic effects, particularly the antidepressant effects of carbamazepine. This is schematically illustrated in Fig. 10 with a variety of the neurotransmitter candidates that might be considered in this time frame analysis (*Post*, 1987; 1988).

Considerable evidence suggests that peripheral-type benzodiazepine receptors may be associated with the acute anticonvulsant effects of carbamazepine on amygdala-kindled seizures (*Weiss* et al., 1985; 1986). Carbamazepine binds more potently to peripheral-type and central-type benzodiazepine receptors, and its anticonvulsant effects are reversed by ligands active at the peripheral-type receptor (such as RO-5-4864) and not the classical antagonist for the central-type receptor (RO-15-1788). In contrast, the anticonvulsant effects of diazepam are reversed by RO-15-1788 and not by RO-5-4864. A variety of other controlled studies suggest that the differential reversal by RO-5-4864 is not an artifact of weaker anticonvulsant effect of carbamazepine or to the nonspecific proconvulsant effects of RO-5-4864, since the beta-carboline BCCM (which is also proconvulsant) reverses the anticonvulsant effects of diazepam but not that of carbamazepine (*Weiss* et al., 1985, 1986). Moreover, in the contingent tolerance paradigm we have observed cross tolerance between carbamazepine and PK 11195 (a ligand selectively active at peripheral-type benzodiazepine receptors) but not to diazepam which exerts its anticonvulsant effect through central-type receptors (*Weiss* and *Post*, unpublished observations, 1989).

Noradrenergic alpha-2 mechanisms also appear to be important to carbamazepine's acute anticonvulsant effects on amygdala-kindled seizures, as they are reversed by the alpha-2 antagonist yohimbine (*Weiss* et al., unpublished data). A variety of other data implicate carbamazepine's effects on type-2 sodium channels as potentially important to its acute anticonvulsant effects (*Willow* et al., 1984; *MacDonald* et al., 1985). These systems involved acutely are likely to be related to acute anticonvulsant effects, but also remain possible candidates for the psychotropic effects of carbamazepine, but

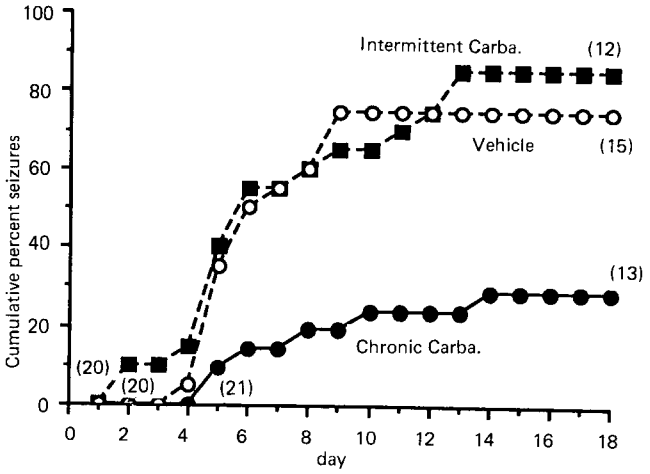

Fig. 11 Pretreatment with Chronic Carbamazepine in Diet (not Repeated Injection) is Required to Block Lidocaine-Kindled Seizures

a further mechanistic explanation (such as an adaptive change being required in a given system) would be required to explain the observed lag in onset of clinical psychotropic efficacy. This formulation might parallel that observed with tricyclic antidepressants where acute effects on amine reuptake are immediately apparent, but it is thought that the secondary consequences of this effect, i. e., downregulation of beta receptors or the associated second messenger system, is likely temporally associated with the ultimate antidepressant effects.

The antinociceptive effects of carbamazepine are likely related to $GABA_B$ mechanisms (*Terrence* et al., 1983; *Fromm* and *Terrence,* 1987). Both carbamazepine and L-baclofen share antinociceptive effects in paroxysmal pain syndromes such as trigeminal neuralgia and in the appropriate feline model system the electrophysiological effects of both of these compounds are reversed by the D-isomer of baclofen. However, we have not observed substantial anticonvulsant effects of L-baclofen on amygdala-kindled seizures and the anticonvulsant effects of carbamazepine are not reversed by the D-isomer as are the antinociceptive effects in the model of *Terrence* and *Fromm.* Thus, these preclinical data suggesting the relationship of carbamazepine's $GABA_B$ effects to its antinociceptive but not anticonvulsant efficacy leave open the question of whether $GABA_B$ mechanisms are related to its psychotropic efficacy in patients with manic-depressive illness.

In order to further explore this possibility, especially given the $GABA_B$ hypothesis of *Lloyd* et al. (1986), we initiated a double-blind clinical trial of L-baclofen in patients with acute depression (studied in collaboration with *Joffe, Kramlinger, Altshuler,* and *Ketter*). Initial data in the first five patients studied revealed no antidepressant effects of L-baclofen, but rather several patients who showed clinical exacerbation during blind administration of the compound and clinical improvement during withdrawal. Moreover, one rapid cycling patient showed an increased frequency and amplitude of ultra rapid cycling while treated with baclofen and returned toward baseline cycling following discontinuation. Taken together these data suggest that the psychotropic effects of carbamazepine are not likely mediated through a $GABA_B$ mechanism. Further exploration of GABA mechanisms is warranted in light of the promising effects of valproate in refractory bipolar patients (*Emrich* et al., 1980) and the emerging evidence that responses to one anticonvulsant (such as carbamazepine) may not be predictive of response to a different one (such as valproate) with a potentially different mechanism of action.

A variety of potential neurotransmitter/neuromodular candidates that could mediate carbamazepine's antimanic efficacy remain to be explored (*Post,* 1987; 1988). However, essentially every neurochemical system that has been implicated in manic syndromes is affected by carbamazepine, and elucidating which of these is critical to the antimanic effects of the drug may not be any easier a task than it continues to be for lithium carbonate. However, in considering antimanic and antidepressant effects one can focus on effects of carbamazepine which take time to develop (require chronic administration) as more likely candidates for the psychotropic effects of carbamazepine than biochemical changes which occur acutely. For example, carbamazepine does appear to upregulate adenosine receptors upon chronic administration, a finding similar to that of the adenosine antagonist caffeine (*Marangos* et al., 1985, 1987; *Daval* et al., 1989). In contrast to many classical antidepressants, carbamazepine does not appear to downregulate beta receptors. Changes in substance P levels and sensitivity are also induced by chronic carbamazepine in preclinical studies (*Mitsushio* et al., 1988; *Jones* et al., 1985) In clinical studies, chronic administration of the drug is associated with increases in plasma tryptophan (*Pratt* et al., 1984) and urinary free cortisol (*Rubinow* et al., 1986) and decreases in somatostatin levels in cerebrospinal fluid (*Rubinow* et al., 1985), as well as reductions in plasma thyroid indices (*Roy-Byrne,* 1984) and serum sodium and calcium (*Joffe* et al., 1986) associated with alterations in vasopressin responsivity (*Gold* et al., 1983). Clearly these and a variety of other systems require careful study as possible mediators of the antidepressant effects of carbamazepine. Since no well-validated animal model of depression exists which might be used to discriminate among these variety of potential candidate systems, the task of linking specific neurotransmitter mechanisms to the psychotropic effects of carbamazepine is likely to remain a long and tedious task, much akin to that observed with lithium carbonate where no specific mechanism has yet been documented.

However, recently Dr. Weiss in our laboratory has developed a seizure model, local anesthetic kindling, which requires chronic carbamazepine administration in order to demonstrate anticonvulsant efficacy. Thus, in contrast to the effects of carbamazepine on amygdala-kindled seizures which are apparent after a single acute administration, effects of the drug which require chronic administration may be more closely linked to psychotropic efficacy. Chronic administration of carbamazepine in the diet is apparently required to demonstrate the anti-kindling effect of carbamazepine against local anesthetic seizures kindled either with lidocaine (Fig. 11) or cocaine (*Weiss* et al., 1989 b), although recent data suggest that short periods (2 hours) of dietary administration may also be effective. Repeated, intermittent administration of carbamazepine (15 mg/kg, i. p.) is not only ineffective, but when high doses of carbamazepine are utilized (50 mg/kg i. p. administered one hour prior to each cocaine-kindled seizure), exacerbation rather than protection

is observed. In this fashion one might use a seizure model which appears to require chronic administration of the drug in order to narrow the range of possible candidate mechanisms for psychotropic effects.

In this regard we have observed that the chronic effects of carbamazepine on local anesthetic seizures do not appear to depend on alpha-2 mechanisms as do the acute anticonvulsant effects on amygdala kindled seizures. Preliminary studies suggest the possibility that effects of carbamazepine on corticotropin releasing hormone (CRH) may be important to efficacy in this model, as the anticonvulsant effects of carbamazepine on cocaine-kindled seizures are reversed by i. c. v. administration of CRH (*Weiss* et al., unpublished data). However, careful delineation of the dose-response issues involved in this study remain to be conducted, as it also appears that CRH increases seizure susceptibility to cocaine in its own right. Nonetheless, this series of studies provides an example of the potential utility of using a seizure model requiring chronic carbamazepine in order to elucidate potential candidate systems involved in carbamazepine's psychotropic effects which also require chronic administration. Once the candidates can be identified in this model system, appropriate clinical studies could then be conducted to further validate their involvement in the psychotropic effects of this compound in man.

Conclusions

In this fashion it is hoped that not only will carbamazepine prove to be a clinically useful alternative treatment for lithium refractory bipolar patients, but will help in the identification of mechanisms critical to its animanic and antidepressant effects. This, in turn, may lead to a new generation of more specifically targeted biochemical treatments with fewer side effects.

We have used temporal factors in a variety of different ways in the studies summarized in this manuscript. Temporal factors have been emphasized in the longitudinal course of manic-depressive illness with the potential differential pharmacotherapy as a function of stage of evolution of illness. Time course of clinical efficacy of carbamazepine has been used to attempt to elucidate possible mechanisms of action. The temporal sequence of drug administration and seizure induction has been used to explore the phenomenon of contingent tolerance to the anticonvulsant effects of carbamazepine and its reversal by administering the drug after rather than before a seizure is induced. The temporal patterning of drug administration also appears important in the model of blockade of local anesthetic kindling as chronic oral administration appears effective while repeated, intermittent i. p. administration is ineffective.

It is hoped that careful consideration and delineation of the temporal factors involved may lead to a better understanding of the evolution of affective syndromes, their amelioration with appropriate pharmacotherapy, and an understanding of the mechanisms involved in these therapeutic effects. As is obvious from this report, the work in our laboratory is heavily dependent on an active interplay between preclinical and clinical studies. Without appropriate animal studies particularly involving the anticonvulsant effects of carbamazepine on amygdala-kindled seizures, we may not have chosen this anticonvulsant to explore clinically. We hope in this era of constricting research resources and attacks on use of animals for biobehavioral research that appropriate preclinical studies will continue to be supported and seen as a critical component to basic and clinical science efforts directed toward discovering new treatments and bettering the lives of patients with recurrent affective disorders.

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R. M. Post, M. D.

Biological Psychiatry Branch
National Institute of Mental Health
Building 10, Room 3N212
9000 Rockville Pike
Bethesda, Maryland 20892
USA