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Antidepressant Withdrawal-Induced Activation (Hypomania and Mania): Mechanism and Theoretical Significance

STEVEN C. DILSAVER[1] and JOHN F. GREDEN[2]

[1]*Department of Psychiatry, University of Michigan Hospitals and* [2]*Department of Psychiatry, University of Michigan, Ann Arbor, MI 48109 (U.S.A.)*

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CONTENTS

1. INTRODUCTION

Characteristic clinical syndromes often follow abrupt or gradual discontinuation of non-monoamine oxidase inhibitor antidepressants. Dilsaver et al.[44,48] have described 4 distinct operational clinical profiles. These include: (1) gastrointestinal and general somatic distress; (2) sleep disturbance; (3) movement disorder; and (4) behavioral activation on a continuum to frank mania. Withdrawal induced cholinergic overdrive has been implicated in the etiology of these syndromes[44,45]. The first 3 of these profiles appear to

Correspondence: S. C. Dilsaver, Department of Psychiatry, University of Michigan Hospitals, Ann Arbor, MI 48109, U.S.A.

be most compatible with the 'cholinergic overdrive' hypothesis. Indeed, the neuropharmacological, physiological, and anatomical evidence supporting the hypothesis that these antidepressant withdrawal syndromes are precipitated by central and/or peripheral cholinergic overdrive is abundant[44]. The observation that centrally active anticholinergic drugs are useful in the treatment of antidepressant withdrawal symptoms further supports this[45]. It is, however, more difficult to explain how antidepressant withdrawal may precipitate hypomania or frank mania. Since January, 1981, there have been 10 reported cases of tricyclic antidepressant withdrawal associated with hypomania or mania[41,48,137] and an 11th case of near hypomania developing in a severely depressed woman withdrawn from imipramine[44]. In two instances a tricyclic was restarted after the hypomanic or manic state was crystalized and in both there was prompt and complete resolution[37]. This suggests that these hypomanic and manic syndromes are causally related to tricyclic withdrawal. In this article we propose a testable model of antidepressant withdrawal induced activation which incorporates the adrenergic-cholinergic hypothesis of affective disorders[90]. It differs from previous explanations of affective disturbance in that it emphasizes both dysfunction of homeostatic mechanisms essential to the maintenance of balance between neurotransmitter systems and cholinergic–monoaminergic imbalance, rather than simple under- or over-function of these neurotransmitter systems[21,22,37,90,170,187]. This model may also be of heuristic value in the study of affective disorders in general but may be particularly relevant to understanding the pathophysiology of rapidly-cycling bipolar illness.

2. BASIC CONCEPTS AND OBSERVATIONS

2.1 *The meaning of 'activation'*

'Activation' has traditionally referred to both electroencephalographic (EEG) and behavioral parameters. Not so long ago, electrocortical desynchronization was inextricably conceptually associated with behavioral (especially psychomotor) arousal[81,116–118]. A corollary of the unitary doctrine, that is, the teaching that electrocortical desynchronization and behavioral activation are identical events, was that the reticular activating system (RAS) was regarded as the sole unit mediating behavioral arousal. Favoring the unitary doctrine were the observations that simultaneous EEG and behavioral arousal could be produced by direct electrical stimulation of the midbrain reticular substance[116,117,134], arousal produced by peripheral stimulation was blocked by deafferentation of the RAS[179], and massive destruction of the RAS prohibited both EEG and behavioral arousal[123]. The significance attached to EEG desynchronization was manifest in the use of the term 'paradoxical sleep' for rapid-eye-movement (REM) sleep in the older sleep literature. Early investigators regarded REM sleep as 'paradoxical' because there is diffuse cortical desynchronization, a correlate of wakefulness, during this sleep stage.

2.2. *Anatomical bases of electroencephalographic (EEG) and behavioral activation*

More than 40 years ago, bilateral lesioning of the posterior hypothalamus was shown to produce coma[150]. Investigators later found that lesioning of the brainstem reticular formation blocked the EEG arousal response but did not prevent behavioral activation when the posterior hypothalamus was stimulated[60]. Studies also showed that though bilateral hypothalamic lesions produce irreversible coma[81,150] that the EEG can show a pattern suggesting full behavioral arousal[60]. In summary, neurophysiological and anatomical studies strongly suggested that the hypothalamus (and associated limbic structures) and the RAS subserve two different functions associated with 'arousal'; one system seemed to be intricately involved in producing the EEG correlate of behavioral arousal and the other appears to be involved in producing behavioral arousal itself. However, in the intact animal, EEG and behavioral arousal are not observed separately; hence, for years neurophysiologists viewed behavioral activation and its EEG correlate as being inextricably linked and regarded the posterior hypothalamus, apart from it being in electrical connection with the RAS, as being non-functional in affecting arousal. Later, we will see that these anatomical considerations are relevant to understanding behavioral activation occurring when antidepressants are withdrawn.

2.3. *The EEG arousal response*

Other observations useful in developing a model of antidepressant withdrawal induced activation are those of Rinaldi and Himwich[154,155]. They did a series of important experiments showing the following: (1) acetylcholine injection into the carotid artery produces EEG activation in an anesthetized animal; (2) this activation does not occur unless the hemisphere is in anatomical continuity with the RAS; and (3) atropine blocks the cortical response to the injection of acetylcholine. These data suggest that the injected acetylcholine activates the RAS which in turn activates the cortex.

Other investigators have further emphasized the role of the RAS and cholinergic systems in affecting electrocortical arousal. First, stimulation of the RAS produces desynchronization of the electrocorticogram accompanied by the release of acetylcholine at the cortex[108,180,181]. Second, consistent with the work of Rinaldi and Himwich[154,155], they showed that the injection of acetylcholine or of an acetylcholinesterase inhibitor into the systemic circulation produces EEG arousal[15,16,19,20,79,129,130,186]. Third, in contrast, to the effects of cholinergic activating agents, the administration of high doses of atropine and other anticholinergic agents to man and animals is associated with high voltage slow-wave patterns characteristic of non-rapid eye movement (NREM) sleep[15,17,18,41,60,118–121,128–131,139,140,180,194,202–204]. Fourth, atropine blocks the electrocortical arousal produced by direct electrical stimulation of the RAS even though acetylcholine accumulates at the cortex[108,180]. Last, the cortical desynchronization of REM sleep is also cholinergically mediated[72,80]. REM sleep is also accompanied by an increase in acetylcholine release at the cortex[99] and atropine and related compounds suppress REM sleep[169,185]. Thus, EEG arousal is both temporally and causally related to acetylcholine release at the cortex in both the waking and sleeping states. Fig. 2 schematizes the main points of this section.

In summary neuropharmacological data is consistent with the notion that cortical desynchronization is always cholinergically mediated. As will become clear, any theory which attempts to comprehensively explain the behavioral activation (hypomania and mania) associated with antidepressant withdrawal must consider the dissociations and relationships between behavioral and EEG activation as well as the role of cholinergic influences in affecting each.

2.4 *Activation of the EEG in sleep: a model linking cholinergic and adrenergic systems*

Activation of the EEG during sleep involves an interaction between cells of the pontine gigantocellular tegmental field (FTG) and locus coeruleus (LC)[83–86,125]. Hobson et al.[85] have proposed a model of reciprocal interaction between cholinergic FTG and adrenergic LC cell populations. Their model provides a paradigm after which a model of antidepressant withdrawal induced activation is to be constructed. According to this paradigm, FTG cells are said to be 'excitatory' because their activity is associated with desynchronization of the EEG. Conversely, the LC cell population is said to be inhibitory because crescendoing of its activity is associated with a decrease in the EEG frequency and synchronization of cortical activity. Experimental data suggest that FTG activity is subject to both auto-regulation and regulation by the LC population. The model includes a precise mathematical description of the FTG-LC relationship. It is suggested that the neural mechanisms regulating the onset of REM and NREM sleep produce what is mathematically described as reciprocal interaction between cells in the FTG and LC regions and that the crescendoing of FTG activity prior to the onset of REM sleep is logarithmic. This model has much support. First, the temporal organization of FTG discharges with respect to the sleep–waking cycle is indeed reciprocal to LC discharges. Second, each episode of desynchronized sleep is temporally correlated with the peak of FTG discharge activity. Third, NREM sleep episodes are associated with diminution of FTG activity and a logarithmic crescendoing of LC cell firing[85]. Fourth, histochemical and neurophysiological studies suggested that FTG cells use acetylcholine as a neurotransmitter and are auto-stimulated by synaptically-released acetylcholine[142]. Fifth, functional connections extend from the LC to FTG cells and from LC to LC cells. Finally, norepinephrine varicosities are present in both the FTG and LC[60,84,85]. Fig. 1 schematizes the Hobson–McCarley model.

What would happen if there were excessive cholin-

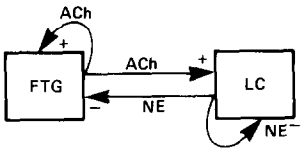

Fig. 1. FTG, gigantocellular tegmental field; LC, locus coeruleus; ACh, acetylcholine; NE, norepinephrine, +, excitatory neurotransmission; —, inhibitory neurotransmission.

ergic activity? Increased cholinergic outflow via the FTG would, according to the model, lead to an activation of LC cells. Simultaneously there would be a crescendoing of FTG activity. The excitation of LC cells by FTG cholinergic transmission would increase the inhibitory norepinephrine transmission to the FTG population but the LC cell population would also be subject to concurrent auto-inhibition by norepinephrine. According to the model, the net result of these factors would be a 'turning off' of the LC cell population. The point at which this would happen is a hypothetically-quantifiable index of aggregate FTG activity. In this way, cholinergic overdrive is expected to produce disturbances of sleep staging. The relationship between the FTG and LC cell populations, provided by the model of Hobson and colleagues, provides us with a case example to be used in the development of a theory.

2.5. *An important paradox: 'excessive' stimulation of the ascending activating system produces sleep*

Electrical stimulation of the ascending activating system by implanted electrodes produces release of acetylcholine at the cortex[8,108,180,181], and generally behavioral arousal[116,117,134]. But Parmeggiani[143,144] showed that the feline response to electrical stimulation of the RAS is paradoxical. At relatively low intensity, electrical stimulation produced behavioral and EEG activation. However, high intensity or 'excessive' electrical stimulation of the RAS surprisingly induced all of the rituals preceding normal sleep and then actual sleep. The model of electrocortical and behavioral activation to be developed will account for these observations.

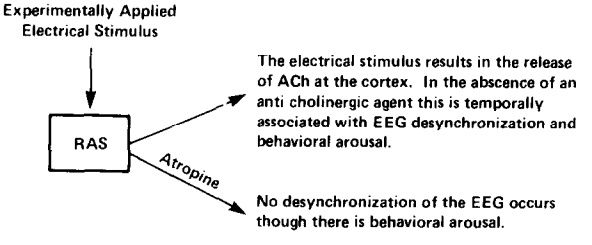

Fig. 2. RAS, recticular activating system.

2.6. *Different mechanisms affect EEG and behavioral activation*

Fig. 3 schematizes the hypothetical relationship between the RAS and a behavioral 'activating' system (System 'A'). These statements are offered as hypotheses or comments on previous experimental observations: (1) the behavioral 'activating' system (System 'A') may, depending on the intensity of its output, exert either an inhibitory or activating effect on the RAS. (2) the RAS also may either directly activate or indirectly inhibit System 'A' because: (3) system 'A' may — comparable to other neurophysiological functional units, such as the FTG — be self-inhibitory.

Observations show that activation of the RAS can produce, at least secondarily, behavioral activation. This is demonstrated by Parmeggiani's[143,144] finding that relatively low intensity electrical stimulation of the RAS is associated not only with EEG activation

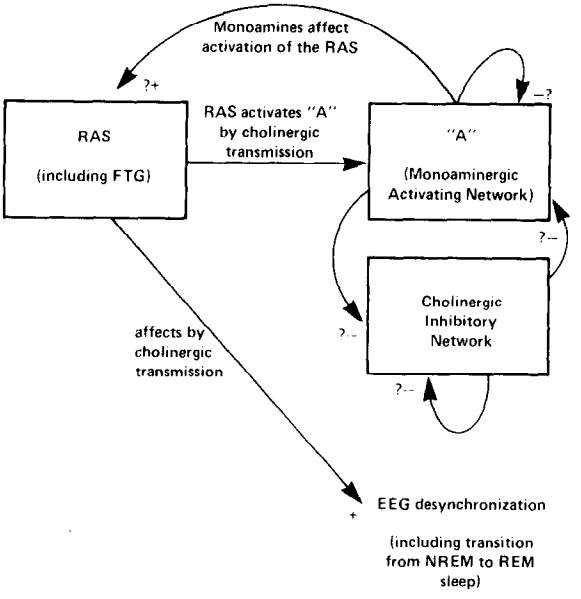

Fig. 3. ? denotes hypothesized pathways. For other symbols see legends to Figs. 1 and 2.

but with behavioral arousal as well. Parmeggiani's finding that behavioral inhibition follows high intensity stimulation of the RAS makes sense if we hypothesize that System 'A' is self-regulatory; hence at a critical point it is auto-inhibited and behavioral inhibition results. The existence of this hypothesized self-inhibiting 'activating' system is supported by the fact that the RAS can be electrically driven, with all the usual biochemical changes associated with behavioral arousal and desynchronization of the electrocorticogram occurring, but with sleep resulting. The factor accounting for this is likely not inhibition of the RAS by itself or by another system (since the corticogram remains desynchronized), but direct or indirect inhibition, due to RAS overstimulation, of a collateral system directly involved in affecting behavioral activation.

2.7. *The behavioral inhibitory effects of acetylcholinesterases and cholinomimetics on behavior*

Cholinergic excess can produce psychomotor retardation, anergy, and other signs and symptoms of behavioral inhibition[14,25,55,72,78,90–98,132,158–160,164]. It can also inhibit methylphenidate induced stereotypy, a phenomenon due to drug induced monoaminergic overactivity[91]. Behavioral inhibition produced by infusion of anticholinesterases and cholinomimetics, as will become increasingly clear, appears to be the consequence of inhibition (or antagonism) of a monoaminergic behavioral 'activating' system by excessive cholinergic transmission. Likewise, the suppression of manic symptomatology by physostigmine may be due to cholinergic inhibition of a limbic activating system[93,132]. The hypothesis that anticholinesterases and cholinomimetics inhibit a limbic 'activating' system accords with the observation that they produce an EEG picture fully consistent with behavioral activation even though their immediate effect is also behavioral inhibition[79].

Supposing System 'A' exists, we propose that those neurotransmitters involved in its inhibition (e.g. acetylcholine) are also indirectly involved in normal behavioral activation (just as those transmitters involved in the onset of REM sleep are indirectly involved in the onset of NREM sleep). This hypothesis involves the prediction that there is interaction between the neurotransmitter systems governing behavioral arousal akin to that postulated to exist between the FTG and the LC. We will also present evidence supporting the notion that a state characterized by chronic 'tonic', or excessive inhibition of System 'A' contains the seeds of its own abolition and can predispose the organism to rebound behavioral hyperactivity.

2.8. *Paradoxical or 'rebound' behavioral activation after physostigmine infusion in manic patients and animals*

The reversible anticholinesterase, physostigmine, produces a syndrome in manic patients with similarities to retarded depression[93,173]. Two to three hours following a post-infusion period of retardation and dysphoria subjects may display 'rebound' mania. The rebounding is characterized by an intensification of manic signs and symptoms as assessed by the use of standard rating scales and operationally defined measures of global clinical judgment. In the rat, as it also appears to be in man, adrenergic mediated arousal is antagonized by a cholinergic system[24,61,62]. Pilocarpine or physostigmine infusion also produces a biphasic response in this animal; that is, an initial period of motor inhibition is followed by marked motoric hyperactivity[62].

2.9. *Another observation to be explained by the theory: physostigmine and amphetamine given alone antagonize barbiturate induced sleep but given together antagonize one another*

There is more evidence, consistent with the theory being developed, that cholinergic systems are secondarily involved in affecting behavioral activation. Pentobarbitol induced sleep is antagonized by both physostigmine and amphetamine[6]. A sympathomimetic would be expected to antagonize barbiturate induced sleep, but it is not obvious that physostigmine would do this. After all, physostigmine is a drug associated with behavioral inhibition. The data are made more perplexing by the fact that simultaneous administration of physostigmine and amphetamine are not as effective in producing arousal as is amphetamine given alone; that is, these drugs are antagonistic. These conflicting observations can be accounted for and explained by a model which incorporates the

theme that cholinergic mechanisms are directly involved in affecting behavioral inhibition and indirectly involved in affecting behavioral arousal via the activation of a collateral monoaminergic system upon which amphetamine acts directly. In this scheme unopposed cholinergic tone is thought to directly inhibit and indirectly activate a monoaminergic activating system (System 'A') that is auto-inhibited by monoamines. Since the activating system is indirectly activated by physostigmine (by virtue of its activating effects on the RAS which can directly activate the monoaminergic activating system, and auto-inhibition of the cholinergic inhibitory system) and since amphetamine would tend to increase its auto-inhibitory input, the combination of physostigmine and amphetamine might be predicted to produce less activation than either drug given alone.

2.10. *Evidence that cholinergic systems can mobilize an activating system*

Flicker and Geyer[65] have shown that carbachol, iontophoretically infused into the dentate gyrus of the rat, produces profound hyperactivity after a latency of 10–40 min. This time lag is a function of dose and dramatically contrasts with the more immediate effects of iontophoretically applied norepinephrine, dopamine, and dopamine agonists and potentiating agents to the same and other limbic regions[2,38,50,64–67,88,103,147]. The lag does not appear to be due to the diffusion of carbachol to other areas where it directly produces motoric hyperactivity[65]. Rather, this latency seems most consistent with the hypothesis that the drug's activation of the animal is indirect and that cholinergic stimulation activates dopaminergic and/or other monoaminergic pathways which directly induce motoric hyperactivity.

2.11. *Cholinergic–monoaminergic interaction*

Studies of complex central and peripheral cholinergic–monoaminergic interactions suggest that the relationship between cholinergic and monoaminergic systems is maintained in proper balance by sophisticated homeostatic mechanisms. For example, a noradrenergic system produces arousal in rats[24,61]. This system is inhibited by a cholinergic system[61]. The behavioral state of the animal is contigent on the noradrenergic–cholinergic balance which is, in turn, according to the evidence to be presented below, subject to autoregulation.

Kazic[109] reported that physostigmine produced a significant drop in hypothalamic and brainstem norepinephrine levels within 15 min of infusion. Within this time period, there was also an increased synthesis and turnover of [^{14}C]tyrosine, the norepinephrine precursor. Furthermore, 7 days of physostigmine treatment induced a significant increase of tyrosine hydroxylase (the enzyme governing the rate limiting step in catecholamine synthesis) activity in the hypothalamus and brainstem.

In the peripheral nervous system, increased preganglionic cholinergic activity increased the synthesis of tyrosine hydroxylase in noradrenergic adrenergic neurons and cholinergic hyperfunction lasting only 60 min was sufficient to produce a measurable increase in tyrosine hydroxylase levels 48 h later[183]. Since tyrosine hydroxylase governs the rate limiting step in the synthesis of norepinephrine, one might hypothesize that prolonged cholinergic hyperfunction could predispose an organism to developing a hypernoradrenergic state should there be a subsequent diminution in cholinergic tone.

In the peripheral nervous system acetylcholine decreased norepinephrine release by adrenergic neurons[135]. In the rat, muscarinic stimulation produced decreased norepinephrine release in the hypothalamus whereas nicotinic stimulation increased its release[200]. Unless calcium is related or a muscarinic antagonist is administered the net effect of acetylcholine was to decrease norepinephrine release.

One may postulate that hypercholinergic states produce chemical denervation of post-synaptic noradrenergic and dopaminergic receptors. The result of this denervation could be 'compensatory' or 'restorative' receptor supersensitivity. Thus cholinergic excess may, in this way, entail the possibility of monoaminergic rebound. Chemical denervation can indeed produce receptor supersensitivity and up-regulation. Rehavi and associates[152] have shown that treatment with amitriptyline, a tricyclic antidepressant with antimuscarinic properties, produces an increased number of muscarinic binding sites in the rat brain. Treatment with belladonna alkaloids also produces muscarinic receptor up-regulation[10]. Up-regulation[23,33,82] and biochemical and behavioral super-

sensitivity[33,201] of dopaminergic systems, in response to dopamine receptor blockade by antipsychotic drugs, provides another excellent example of the effects of chemically induced denervation. The practical significance of chemical denervation is highlighted by the strong body of evidence supporting the thesis that antipsychotic induced tardive dyskinesia is the consequence of nigrostriatal dopaminergic supersensitivity resulting from chronic dopamine receptor blockade[182]. There are many reports that this movement disorder responds to cholinergic agents[58,101,199]. If tardive dyskinesia is indeed due to dopaminergic supersensitivity, cholinergic drugs likely have their favorable effects through affecting a functional decrease in dopaminergic tone. This would evidence the capacity of a cholinergic system to partially 'denervate' a monoaminergic system. But, if dopaminergic systems respond to denervation by up-regulation and by becoming supersensitive one might expect that the partial denervation produced by a cholinergic overdrive state, such as that occurring when tricyclics are withdrawn, may in its own right affect some degree of dopamine receptor up-regulation and supersensitivity.

Cholinergic[3] and dopaminergic agonists[7] can also increase the turnover of dopamine and acetylcholine, respectively. This implies increased rates of neurotransmitter synthesis. This phenomenon is best described in the striatum[3] where cholinergic and dopaminergic systems act antagonistically. The physiology of dopaminergic and cholinergic balance in the limbic system is not as well worked out. There is, however, evidence that mesolimbic dopaminergic and cholinergic systems also exert antagonistic influences[53,69]. Further, one might expect that if cholinergic hyperfunction leads to increased synthesis of tyrosine hydroxylase in noradrenergic neurons that it might do the same in mesolimbic dopaminergic neurons where it is the enzyme governing the rate limiting step in the synthesis of dopamine. Hence, a cholinergic overdrive state might result in increased dopamine synthesis and intraneuronal dopamine stores, and thus an increase in the amount of this neurotransmitter available for release.

3. THE CHOLINERGIC–MONOAMINERGIC INTERACTION THEORY

3.1 *System 'A' theory*

Fig. 3 schematically portrays the functional entities posited by a theory of activation (System 'A' theory). The theory is sufficiently encompassing to explain the relationships between the RAS, the FTG, and behavioral activating and inhibiting systems. Fig. 3 does not imply the anatomical localization of system 'A', however, the neurophysiologic and iontophoretic studies cited above suggest that it is a limbic activating system.

Activating input from 'A' to the RAS is postulated to occur, on the grounds that chemicals acting directly on the limbic system produce electrocortical desynchronization and behavioral arousal simultaneously[118]. 'A' is hypothesized to be inhibited by monoamines; this is consistent with the ability of psychostimulants to produce paradoxical inhibition[87,151,195] and with the observation that excessive electrical stimulation of the feline RAS produces sleep, despite an EEG profile suggesting marked behavioral arousal. Fig. 3 depicts 'A' as being directly inhibited by acetylcholine; this is consistent with the known effects of anticholinesterases and cholinomimetics. However, excessive tonic cholinergic inhibition of System A is predicted to produce restorative monoaminergic changes predisposing the organism to rebound behavioral arousal should cholinergic tone lessen; this is consistent with the fact that the behavioral inhibition affected by pharmacologically induced cholinergic overdrive is followed by rebound increases in activity level. Monoaminergic outflow from 'A' is shown as inhibiting the cholinergic system with which it is supposed to be in functional relationship as this postulation provides the most parsimonious means of maintaining balance between the cholinergic and monoaminergic systems given the many data cited above.

The model set forth is consistent with the fact that catecholamine antagonists and depleting agents produce profound behavioral inhibition[21,22,37,90,170,187] The model also accords with the observation that bupropion, a dopamine reuptake inhibitor without known anticholinergic, noradrenergic, or serotonergic effects is an effective antidepressant. Buproprion's only known important property is inhibition of dopamine reuptake. It is supposedly an activating compound and in a recently completed study of de-

pressed patients was found to be of greatest value in the treatment of patients with psychomotor retardation[57,59]. Given the model proposed one would predict that bupropion affects the activating system we call 'A' directly and indirectly acts to inhibit the cholinergic inhibitory system and affect mood. This draws attention to the point that System 'A' is a behavioral activating unit and change in its activity has no intrinsic implications for change in mood. Nevertheless, drugs producing activation, such as amphetamine, caffeine, *and anticholinergic agents*[13,100,107,127,165] generally produce favorable alterations in mood. Likewise states characterized by diminished motor activity are often associated with dysphoria. Conversely, states characterized by motor hyperactivity are often associated with euphoria, for example, hypomania and mania. However, whether 'A' regulates mood directly or indirectly is an open question. Indirect regulation of mood could occur through 'A's' inhibitory influences on the cholinergic systems. This accords with the observations that cholinergic hyperactivity is associated with both decreased motor activity and depressed mood[14,25,56,73,79,90–93,96–98,132,157,158,160].

3.2. *Other factors favoring 'A' theory*

Several other factors favor the model set forth. These are (1) the evidence that all effective treatments for depression and mania act on cholinergic systems, block or potentiate the action of monoamines, or simultaneously act on both cholinergic and monoaminergic systems. Lithium is the most instructive example. Janowsky et al.[94,95,97] have shown that lithium antagonizes physostigmine mediated inhibition. In laboratory animals, lithium interferes with acetylcholine release and synthesis[12,193,196] and it is associated with increased erythrocyte choline uptake[102]. Extended treatment with lithium has been shown to inhibit the increase in the number of extrajunctional acetylcholine receptors that occur in denervated skeletal muscle[145]. Tollefson and Senogles[184] recently reported that lithium treatment, with plasma levels titrated to within the therapeutic range, produced down-regulation of QNB binding sites ($P < 0.1$) in the human caudate nucleus and an increase in K_d ($P < 0.05$). They suggested that lithium's effect is due to its action at antagonist sites of the muscarinic receptor and hypothesized that lithium consequently has a cholinomimetic effect. However, this would accord with lithium's antimanic properties, but conflicts with its antidepressant effects. Given data suggesting that central muscarinic cholinoceptor supersensitivity and cholinergic hyperfunction characterize the depressed state[44], one would suspect that even if lithium has a cholinomimetic effect that this is not the primary basis for its efficacy in the treatment of affective disorders. The hypothesis that cholinomimetic properties lithium might have accounts for its therapeutic efficacy also clashes with the observations that lithium treatment attenuates physostigmine induced inhibition. Two alternative hypotheses may be offered. Alternative hypothesis I is bases on the assumption that lithium binds to and blocks antagonist sites and thereby exerts a cholinomimetic effect transiently, but that by virtue of this effect affects down-regulation and/or subsensitivity of muscarinic agonist sites. This is a well documented effect of drugs with direct or indirect cholinomimetic properties[39,54,71,122,141,146,166–168,171,172,175]. Further, unless lithium were to exert an antagonist effect at antagonist muscarinic binding sites (which is contrary to the Tollefson–Senogles hypothesis — such an effect of lithium would give it anticholinergic properties), its binding might be expected to produce antagonist site up-regulation and/or supersensitivity; this could result in relative underactivity of the cholinergic system and would accord with observations that lithium interferes with acetylcholine release and decreases physostigmine mediated inhibition. Another alternative hypothesis is that there is really no fundamental difference between the antagonist sites and agonist sites; the two sites represent different states of the same receptor complex. Hence the decrease in QNB binding observed by Tollefson and Senogles would, de facto, represent down-regulation of agonist sites. This interpretation accords with the view of Ehlert et al.[56] who, in a recent review, concluded that the experimental data suggests that muscarinic agonists and antagonists bind to the same sites. We hypothesize that lithium-induced changes in cholinergic physiology render cholinergic systems less apt to be perturbed by the vicissitudes of monoaminergic function. Lithium induced down-regulation of muscarinic receptors might rectify what may turn out to be etiologically the most significant neurobiological defect in affectively

disturbed patients: the propensity to develop muscarinic receptor supersensitivity. This could, for example, diminish the chance that monoaminergic hyperfunction would precipitate a hypercholinergic state. Lithium may also attenuate the cholinergic influence on 'A' and decrease the likelihood of cholinergic excess precipitating restorative monoaminergic hyperfunction. Lithium's antidepressant, antimanic and anticycling efficacy could be accounted for by this theory of its action.

Experimentally induced seizures have recently been shown to down-regulate muscarinic cholinergic receptors[42,43]. Electroconvulsive therapy, like lithium, interferes with cholinergic systems[1,63,115,121] and simultaneously acts on monoaminergic networks in complex ways[5,9,31,74]; it may similarly restore cholinergic–monoaminergic balance by virtue of its capacity to act on both systems. In contrast to lithium and electroconvulsive therapy, treatments which further disturb the cholinergic–monoaminergic balance might be expected to precipitate an increased frequency and severity of mood oscillations. Tricyclic antidepressants are examples of such drugs[197]. Tricyclics up-regulate muscarinic receptors[152] and appear to produce muscarinic system supersensitivity[44,45,46,48]. For example, in man, 21 days of treatment with desipramine is associated with a marked enhancement of the miotic response to the cholinomimetic pilocarpine; this was interpreted by Dilsaver and Greden[46] as providing evidence of tricyclic induced cholinoceptor supersensitivity. We suspect that these effects of the tricyclics on cholinergic systems may have something to do with their capacity to induce rapid cycling in bipolar patients[197].

3.3. *Antidepressant withdrawal induced activation: The role of cholinergic-monoaminergic interaction*

It is clear that hypomania or mania may follow the discontinuation of antidepressants with anticholinergic properties. However, the discontinuation of anticholinergic drugs other than antidepressants is not followed by the degree of behavioral activation observed with the withdrawal of tricyclics. This suggests that in addition to withdrawal induced cholinergic overdrive other effects of tricyclic antidepressants are pertinent. One might expect antidepressant induced priming of monoaminergic networks[11,28,30,40,70,114] may be necessary for withdrawal induced cholinergic overdrive to precipitate marked behavioral activation. This hypothesis is easily tested. As mentioned previously. Fibiger et al.[62] have shown that muscarinic agonists produce a biphasic response in animals; initial behavioral inhibition followed by rebound hyperactivity. Fibiger's experiment might be repeated using 3 sets of animals. One set could be chronically treated with a monoamine oxidase inhibitor, a class of drugs which primes monoaminergic systems in ways similar to the tricyclics[34,174]. The second and third groups, respectively, could be treated with a tricyclic antidepressant and placebo. We predict that the first two groups would show, as a result of priming of monoaminergic systems, greater rebound motor activity after cholinomimetic or anticholinesterase administration than the placebo group, and that the second will also show a greater reduction in motor activity during the inhibition phase owing to tricyclic induced muscarinic receptor supersensitivity, as well as a more marked or dramatic period of excitation.

3.4. *Rapidly-cycling manic depressive patients: The role of cholinergic-monoaminergic interaction*

Post and colleagues[148] have reported that the switch from depression to mania in a rapidly-cycling manic depressive patient is preceded by slow changes in behavior and in biochemistry suggesting active preparatory alterations are occurring in neurotransmitter systems over the course of an episode and that necessary compensatory or preparatory alterations occur, 'priming the patient for the next mood phase'. The authors observed that the switch from depression into mania is preceded by significantly increased urinary norepinephrine excretion. It is conjectured that 'critical loci in the central nervous system involved in the regulation of mood may . . . undergo cyclic oscillations based on alterations in neurotransmitter function and receptor sensitivity acting reciprocally . . . a functional unit, such as the limbic system . . . could be activated in a facilitory or inhibitory manner in mania or depression . . . small changes in neurotransmitter systems such as those reflected by the alteration in urinary concentration of norepinephrine . . . may be amplified by altered receptor sensitivity such that critical pathways are rapidly acti-

vated'. The authors' observations of changes in biochemistry, suggestive of preparatory alterations in neurotransmitter function, preceding switches in the rapidly-cycling patient accord with the hypothesis that antidepressant withdrawal induced cholinergic overdrive and treatment induced priming of requisite neurotransmitter systems are essential to the production of tricyclic withdrawal associated hypomania.

Post et al.[148] noted that depressive swings, in their rapidly-cycling manic-depressive patient, were predicted by a decrease in urinary 3-methoxy-4-hydroxy-penylglycolic acid and norepinephrine excretion. According to the theory developed in this paper, the depressed phase would be characterized by cholinergic overactivity and monoaminergic underactivity, which would, in turn, trigger the next episode of hypomania or mania by functionally denervating and hence indirectly priming monoaminergic systems. The transition from a state of relative denervation of monoaminergic systems and cholinergic hyperfunction to a state of monoaminergic hyperfunction and relative denervation of cholinergic systems would occur over time, with 'preparatory' changes for the switch in neurotransmitter systems occurring progressively. The switch itself may be abrupt and dramatic but many of the processes underlying it would reasonably be regarded as occurring gradually. We will focus on the relationship between these gradual changes and the neurobiological events occurring at the time of the switch below.

Further, evidence for our theory is provided by the observation that escape from dexamethasone suppression, a marker of the depressed state[27] can be induced by physostigmine infusion (increased cholinergic activity)[26,49]. Evidence that the swing from depression into hypomania or mania involved priming of monoaminergic systems and a diminution of cholinergic tone is provided by the observations of increased urinary norepinephrine excretion prior to the switch[148] and by the tendency for the dexamethasone suppression test to revert to normality just prior to switches in rapidly-cycling bipolar patients[77], as well as in other depressed patients with positive dexamethasone suppression tests[78].

The sequence of events accounting for the transition from mania to depression in a rapidly-cycling patient would include the following: (1) monoamines acting in an inhibitory fashion on the cholinergic inhibitory system thus producing presynaptic muscarinic autoreceptor[56] subsensitivity and postsynaptic receptor supersensitivity and on the monoaminergic activating system to produce presynaptic autoreceptor supersensitivity and postsynaptic receptor subsensitivity; (2) the induction of postsynaptic cholinergic receptor up-regulation and supersensitivity within the monoaminergic activation system secondary to tonic inhibition of cholinergic function by monoamine excess; (3) as receptor changes 1–2 occur, gradual reduction in monoaminergic activity is expected to occur (as evidenced by decreased urinary norepinephrine and 3-methoxy-4-hydroxypenylglycolic acid levels in the rapidly-cycling patient of Post et al.[148] just prior to switches) followed by a rapid switch to a state of cholinergic excess.

The transition from depression to mania would involve: (1) induction of the synthesis of enzymes involved in monoamine generation, such as tyrosine hydroxylase; (2) changes in the sensitivity of monoamine receptors consistent with the eventual development of a hypermonoaminergic state (such as presynaptic autoreceptor subsensitivity and postsynaptic receptor supersensitivity); (3) up-regulation and supersensitivity of the postsynaptic monoaminergic receptors in the cholinergic inhibitory systems and down-regulation of postsynaptic cholinergic receptors in the monoamine activating system; (4) as steps 1–3 occur a gradual increase in monoamine activity might well occur (as suggested by the observation of Post and colleagues that the switch from depression to hypomania or mania is preceded by an increased excretion of urinary norepinephrine) followed by a rapid transition to a state of monoaminergic overdrive.

Switches occur rapidly though they are preceded by gradual changes in the pertinent neurotransmitter systems. This would occur if inhibition of the cholinergic system by the monoaminergic activating system and vice versa is logarithmically (rather than linearly) related to input.

3.5. *Theory of antidepressant withdrawal induced activation summarized*

A theory of the neurochemical basis of antidepressant withdrawal induced activation can now be summarized. Antidepressant treatment primes a mono-

aminergic activating system by producing changes in receptor sensitivity, consistent with the development of a manic state. Examples of such changes might be subsensitivity of presynaptic dopamine and noradrenergic autoreceptors[11,28,30,32,40,70,114]. Because of their antimuscarinic properties, tricyclic antidepressants produce cholinergic receptor supersensitivity in both the cholinergic inhibitory system and in the monoaminergic activating system[152]. Antidepressant withdrawal then precipitates cholinergic overdrive[44–46,48] which in turn activates monoamine synthetic pathways and partially denervates a monoamine activating system. After a period, the cholinergic overdrive state remits through agonist-induced down-regulation of postsynaptic and up-regulation of presynaptic cholinergic receptors, and/or a gradual increase in monoamine function. However, after the cholinergic overdrive state abates, in some patients, the monoaminergic system has failed to sufficiently down-regulate in parallel, resulting in a state of relative monoaminergic excess and associated hypomania or mania.

This account of tricyclic antidepressant withdrawal-induced activation is consistent with the time course of its development and treatment response. Gastrointestinal symptoms, sleep disturbance and movement disorder often develop within 24–48 h of the first missed dose of antidepressant medication[44,45], whereas behavioral activation, with the exception of two cases recently reported by Nelson et al.[137] occurs several days to a week after the last dose[44,45,131]. Thus, the time course of antidepressant withdrawal-induced activation is generally consistent with the hypothesis that withdrawal produces cholinergic hyperfunction which has a role in indirectly activating the organism and which remits, at least somewhat, prior to the development of hypomania or mania. Nelson and colleagues[137] successfully treated two individuals with tricyclic withdrawal induced hypomania with desipramine. These patients had developed hypomania within 36 h of their last dose of desipramine. Tapering of the tricyclic preceded complete cessation of antidepressant treatment in one patient, thus making it difficult to interpret the meaning of the observation that this patient became hypomanic within a considerably shorter period of time after receiving the last dose than did the patients reported on by Mirin et al.[131] and Dilsaver et al.[44] In any event, the responsiveness of Nelson's et al.[137] patients to desipramine is noteworthy and accords with the hypothesis that cholinergic overdrive is a significant factor in the etiology of tricyclic withdrawal associated activation. It also suggests that hypomania and mania developing after tricylic withdrawal is probably not due to a chance switch in a bipolar or latently bipolar patient. It would be of interest to know what effects a tertiary belladonna alkaloid might have on this syndrome.

3.6. *Miscellaneous evidence*

The theory of antidepressant withdrawal induced activation and of rapidly cycling manic-depressive illness developed will now be referred to as the 'Cholinergic–Monoaminergic Interaction Theory'. Other data also support this theory. Charney et al.[29] have recently shown that tricyclic antidepressant withdrawal increases the turnover of central norepinephrine as inferred by withdrawal induced increases in urinary 3-methoxy-4-hydroxy-phenylglycolic acid excretion.

Several investigators have reported findings showing that cholinergic systems behave in ways the 'Cholinergic–Monoaminergic Interaction Theory' predicts they would. Cholinergic overdrive and underactivity, respectively, affect decreases (down-regulation)[39,53,71,122,141,146,166–168,171,172,175] and increases (up-regulation)[10,152] in muscarinic binding sites in several tissues. There is also evidence that monoaminergic activity may mediate muscarinic binding; Ehlert et al. demonstrated dopaminergic regulation of muscarinic receptor binding in the corpus striatum[54].

Cholinoreceptor supersensitivity is held, by the Cholinergic–Monoaminergic Interaction Theory, to characterize the depressive phase of a rapidly-cycling manic-depressive course. It further suggests that cholinergic–monoaminergic balance may be subject to marked fluctuations due to the propensity for muscarinic receptors to become inordinately supersensitive during both periods of euthymia and mania. This instability is, if the theory is taken to its extreme, the hallmark of manic-depressive illness, rapidly-cycling or otherwise. For the sake of parsimony, one could postulate that affective disorders are in general due to a derangement of the homeostatic mechanisms which normaly keep cholinergic and monoaminergic

systems in proper balance. There is evidence for this. Risch et al.[156-161] have shown that affective disorder patients show a behavioral and neuroendocrine hyperresponsiveness to physostigmine compared to normals and patients with other psychiatric illness. Physostigmine affects release of β-endorphin in normal man[49,157]. Risch et al.[159,161] also report that depressed patients, compared to normal controls and other psychiatric patients, have significantly greater increases in plasma β-endorphin concentration in resonse to physostigmine. Gillin et al.[76] reported that scopolamine given to normal subjects for 3 consecutive days is associated with shortening of REM latency (a marker of the depressed state) after withdrawal. Sitaram et al.[175,177] have shown that the muscarinic agonist, arecoline, infused intravenously, more dramatically shortens REM latency in euthymic affective disorder patients than in normal controls. All these data provide support for the notion that the depressed state (in both bipolar and unipolar individuals) is associated with cholinoceptor supersensitivity and cholinergic hyperfunction and that vulnerability to relapse during euthymic periods may be at least partially related to this factor. This is consistent with the recent discovery that fibroblasts isolated from affectively ill patients and their relatives demonstrated increased muscarinic binding sites relative to other psychiatric patients and normal control subjects[73].

The Cholinergic–Monoaminergic Interaction Theory requires that 'compensatory' or 'restorative' up- and down-regulation of neurotransmitter systems occur within short frames of time. Indeed, statistically significant changes in adrenergic[103,205], dopaminergic[136,205] and cholinergic receptor binding[106,205] occur over the course of the usual day. The changes in receptor function and binding caused by the hypercholinergic and monoaminergic states which the Cholinergic–Monoaminergic Interaction Theory posits to affect switches in rapidly-cycling bipolar patients would be tantamount to alteration of cholinergic and monoaminergic receptor function and number by means of endogenously occurring drug effects. These carcadian adrenergic, dopaminergic and cholinergic rhythms are, in fact, subject to drug effects[105,106,136,205].

Any drug which sensitizes or renders cholinergic or monoaminergic systems more perturbable may produce increased vulnerability to the development of depressive or manic episodes or of a rapidly-cycling bipolar course. We have already discussed tricyclic antidepressant induced rapid-cycling. Marijuana has cholinergic effects, producing tachycardia, dry mouth, suppression of REM sleep, a trend toward slowing of the electrocorticogram, and short-term memory deficits as well as other effects characteristic of the belladonna alkaloids[51,89]. Kumbarachi and Nastok[111] found that Δ^9-tetrahydrocannabinol (THC) caused a decrease in quantal acetylcholine release at neuromuscular junctions and if drug application was protracted complete blockade of acetylcholine release ensued. Yoshimura et al.[206] observed an increase of striatal and amygdala acetylcholine content in response to treatment with Δ^9-THC and concluded that this is consistent with a drug induced decrease in quantal acetylcholine release in these structures. Layman and Milton[113] demonstrated that cannabinoids do in fact reduce acetylcholine release at muscarinic junctions. Drugs significantly interfering with acetylcholine release would chemically denervate postsynaptic neurons and would be expected to thereby produce postsynaptic cholinoceptor upregulation and supersensitivity[174]. In vivo studies in man and animals and clinical observations are consistent with the hypothesis that cannabinoids render central cholinergic systems supersensitive. El-Yousef et al.[55] found that chronically intoxicated marijuana users develop an unusually profound depression with physostigmine infusion. Rosenblatt et al.[162] reported that Δ^9THC potentiates the toxicity of physostigmine in rats. We successfully treated a chronic marijuana abuser, without a personal or family history of depression, with high dose atropine (up to 7.2 mg in 24 h) when she developed a profound depressive syndrome and 'anticholinesterase-like' symptomatology, after psychotropics with anticholinergic properties (thiothixene and benzotropine) were stopped[47]. Withdrawal induced cholinergic overdrive was concluded to be etiologic. Marijuana use (as opposed to withdrawal) has also been implicated in the genesis of hypomania and of 'hypomania-like' syndromes[113,163]; this is consistent with the idea that the manic state is one of cholinergic hypofunction. These reports of affective disturbance in heavy marijuana users, and of their vulnerability to developing affective symptomatology with pharma-

cologic provocation (drug withdrawal or physostigmine infusion), lend further support to the hypothesis that cholinergic supersensitivity characterizes the depressed state, and that it predisposes one to or is a possible 'risk factor' for developing significant depression

3.7. *Testing the Cholinergic-Monoaminergic Interaction Theory*

The Cholinergic-Monoaminergic Interaction Theory may be amenable to testing by application of positron emission tomographic (PET) strategies. Receptor radioligands appropriate for PET studies, are now available for investigation of some neurotransmitter systems[35,36,124]. When radioligands for muscarinic and monoaminergic receptors useful in PET studies are developed, and the level of PET resolution within the limbic system is improved, the elements of the theory may be tested in vivo. One would predict that the depressive phase of rapidly-cycling manic-depressive illness would be characterized by increased muscarinic binding and decreased monoaminergic binding in limbic areas. The converse would be true in the hypomanic or manic phase.

Physostigmine and cholinomimetic administration provides a pharmacologic model for depression[14,25,55,73,76–79,90–98,132,156–161,173,176–178]. As mentioned previously, Shopsin et al.[173] and Fibiger et al.[62], respectively, have shown that physostigmine can produce a biphasic response in man and animals. It may be possible to test the Cholinergic-Monoaminergic Interaction Theory by combining the PET and the physostigmine strategies. The rebound phase would, according to the theory, be marked by decreased muscarinic and increased monoaminergic binding of the appropriate radioligands.

A few simple naturalistic and laboratory experiments would also be of value in testing hypotheses raised in this paper. If drug induced cholinoceptor supersensitivity is of etiological significance in affecting tricyclic induced rapid cycling one would predict that trazodone and bupropion would be less apt to produce this effect. Laboratory animals treated with a highly potent antimuscarinic antidepressant, such as amitriptyline, would be predicted to show exaggerated inhibition of behavior post-pilocarpine or physostigmine infusion, followed by a period of exaggerated hyperactivity relative to control animals. The concomitant use of high dose amitriptyline and of a monoamine oxidase inhibitor conceivably may so disturb homeostatic mechanisms essential to preservation of cholinergic–monoaminergic balance that 'rapid-cycling,' periods of marked behavioral inhibition oscillating with epochs of hyperactivity, might be induced. This would provide an important animal model of a psychiatric disorder.

3.8. *Why is EEG arousal tied to behavioral arousal if they can be dissociated?*

Why would cortical activation be so closely linked to behavioral arousal if the two can be so easily disjoined? This is a question of considerable intrigue. Perhaps a teleological explanation is called for. The traditional teleological explanation has been that cortical desynchronization is a prerequisite for effective learning and information processing. However, this explanation follows on the hypothesis of Lindsley[116–118] and others that both wakefulness and low voltage fast EEG activity depend on a 'tonic' facilitory effect of the RAS. It was assumed that behavioral alertness and desynchronization of the EEG are one and the same phenomenon. An alternative teleological explanation is that desynchrony of the cortex decreases the probability of neuronal recruitment; something which would tend to be seizurogenic. If the biochemical changes producing behavioral arousal promote neuronal recruitment, a mechanism operating in parallel making recruitment unlikely, would be of adaptive value. Indeed, desynchrony of the cortex appears to raise the seizure threshold[138]. One could challenge the notion that the cholinergic electrocortical and monoaminergic behavioral activating units act in concert, for the reason proposed, on the grounds that physostigmine induced cholinergic crisis precipitates seizures. However, *at toxic doses*, physostigmine (and by implication acetylcholine) produces epileptogenic hypersynchrony of subthalamic nuclei which may override the propensity of these loci to affect desynchronization of the cortex; this is because hypersynchrony of these nuclei can lead to recruitment of cortical neurons[4]. Importantly, anticholinergic agents, as the hypothesis under discussion would suggest, lower the seizure thre-

shold[189–192]. The relationships between monoaminergic activity and seizure threshold, when the cortex is subject to desynchronization and when desynchronization is prevented neuropharmacologically, is subject to investigation. This teleological explanation is therefore as testable as any such explanation can be.

There is some prima facie evidence against the hypothesis that the neurochemical basis of behavioral activation predisposes individuals to seizures. Amphetamine can actually be used as a prophylaxis against petit mal seizures[198]; however, in the normal course of events amphetaine activates the RAS[118]. Unless the RAS is ablated, psychostimulants actually induce desynchronization of the electrocorticogram by virtue of their direct and indirect actions on the RAS. In order to test whether stimulants intrinsically predispose the organism to seizures one would have to use a belladonna alkaloid or other agent producing behavioral-EEG dissociation and study the effects of monoaminergic agents on seizure threshold during a state of forced EEG quiescence. Of note, overdose with psychostimulants, in marked contrast to the effects of toxic doses of central nervous system depressants, is associated with convulsions[110]. L-Dopa[126,188], bromocriptine[188], amphetamine[153] and cocaine[89], methylxanthines[149] and methylphenidate[68] are examples of seizurogenic stimulants. Thus, there is reason to believe that the biochemical basis of behavioral arousal may be seizurogenic and that cholinergic influences provide a measure of protection against the development of convulsions.

4. SUMMARY

Electrocortical and behavioral arousal are separate phenomena subserved by different neural substrata operating in parallel. A comprehensive theory of 'activation' must take into account the relationships between the electrical and behavioral activating systems. In pathological or experimentally induced states paradoxes, resolvable by a theory positing functional interaction between these systems, arise.

EEG arousal is directly mediated, in both the waking and sleeping state, by cholinergic mechanisms. Antidepressant withdrawal precipitates cholinergic overdrive; this would account for the apparent disturbances of REM sleep occurring when antidepressants are stopped. Generally, cholinergic overdrive would produce behavioral inhibition but in particular instances it triggers marked psychomotor arousal by mobilizing a 'limbic activating system'.

The existence of a monoaminergic 'limbic activating system', system 'A', with the properties attributed to it in this paper, is supported by both clinical and laboratory observations. System 'A' theory provides a parsimonious means of adequately explaining many phenomena. This theory also has in its favor explanatory power and scope. The Cholinergic-Monoaminergic Interaction Theory of antidepressant withdrawal induced activation and of rapidly-cycling manic-depressive illness maintains that system 'A' and a cholinergic inhibitory system interact dynamically, and that excessive monoaminergic function can precipitate excessive cholinergic function and a dearth of monoaminergic function (due to autoregulation) and hence depression. Likewise, excessive cholinergic function is posited to activate monoaminergic systems and hence to secondarily cause behavioral activation. Rapidly-cycling manic-depressive patients, according to the model, develop alternating cholinergic and monoaminergic overdrive states because the homeostatic mechanisms which should serve to maintain, within normal limits, the composite of cholinergic inhibitory and monoaminergic activating influences are defective. Consequently, rather than reaching a reasonable balance compatible with adaptive function there is oscillation between extremes. Each oscillatory movement is actually a move towards the 'golden mean' and is induced by deviation from this ideal but the defective homeostatic mechanisms promote 'perpetual' overshooting. Lithium and ECT may be useful in the treatment of rapidly-cycling patients as both treatments may down-regulate muscarinic receptors, and otherwise modify cholinergic and monoaminergic systems in ways promoting homeostasis. In contrast, tricyclics, drugs which up-regulate muscarinic receptors or otherwise render cholinergic systems supersensitive, can precipitate rapid-cycling.

Tricyclic withdrawal may produce hypomania or mania by cholinergic mobilization of properly primed monoaminergic pathways. The model set forth, the Cholinergic-Monoaminergic Interaction Theory, incorporates the cholinergic-adrenergic and catecholamine hypotheses of affective disorders. It is not, how-

ever, a hypothesis or set of unrelated hypotheses but an actual theory to be evaluated on the basis of its explanatory power and scope, parsimony and utility in generating testable questions for investigation by clinicians and basic scientists. This theory suggests new ways of studying the pathophysiology of affective disorders using pharmacological probes, neurophysiological techniques, and PET strategies. Thus the Cholinergic-Monoaminergic Interaction Theory not only explains a plethora of observations, some of which are otherwise paradoxical, but also has heuristic value to be capitalized on in the study of affective disorders.

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