Animal Models
for the Symptoms of Mania

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1. Introduction and Working Hypothesis

Methods for modeling a human illness must have relevance to the clinical description of the abnormal condition, and they should be capable of generating an experimental condition that responds to the treatments commonly used with that disorder. In the case of mania, there are some immediate problems with definition of the syndrome. The following discussion is based on the American Psychiatric Association's DSM-III (1980) classifications of mania and depression. However, it is suggested that this classification may be deficient in some important respects (Lyon, 1990), and any critique of neuromethods for inducing an animal state resembling mania must take these shortcomings into account.

Mania is typically held to be a separate disorder from schizophrenia, even though some symptoms overlap in practice, and it is usually classified as one pole of a manic-depressive continuum, with some patients, however, having essentially only a depressive set of symptoms. It is noticeable in DSM-III (1980) that only mania is strongly associated with hyperactivity, and also with highly repetitive, or constantly switching, response patterns. However, as noted in Chapter 2 by Lyon, on animal models of schizophrenia, these symptomatic features are probably also a major factor in producing the seemingly different syndrome of schizophrenia.
It is probably more than coincidental that neuroleptics are used in conjunction with lithium in the early treatment of hypermanic patients. The neuroleptics are said to have a more immediate calming effect, whereas the lithium seems to exert its effect somewhat later, in damping the otherwise dangerously strong swings in mood. Since neuroleptic drugs principally act to block dopaminergic (DA) activity, this suggests that an overly active DA system is one of the typical signs of mania (though not of depression).

In agreement with this, neuroleptics usually do not have any beneficial effect on purely depressive symptoms, and may make them worse. This suggests that the initial feature that dominates in the manic phase is overstimulation of DA systems, with stimulation of the nigrostriatal DA system affecting mainly the response choice, which indirectly also affects the incidence of "switching" and/or repetition of responses (Lyon and Robbins, 1975). The mesolimbic DA system has a greater effect on the rate of responding and, directly or indirectly, on the autonomic excitation (emotional tone) accompanying the behavior (Iversen, 1977; Stevens, 1975).

The above actions on DA systems must be considered against the background of circadian rhythms and environmental stimuli affecting the organism at the time of treatment (Martin-Iverson et al., 1988; see also Chapter 4 by Martin-Iverson, this volume). Intermittent vs continuous treatment with DA agonists can also strongly affect the behavioral results of the treatment (Nielsen, 1981; Eison et al., 1983), and thus alter the modeling value for mania.

The activity of DA systems can also be modified by blocking the systems directly with neuroleptics, or by changing the dopamine/serotonin (DA/5-HT) balance, which is normally in favor of DA during activity and in favor of 5-HT during rest. In a similar manner, other neurotransmitters (GABA, ACh) and neuromodulators (β-endorphins) are also seen as affecting the DA/5-HT relationship. This viewpoint is used as a "working hypothesis" for the present discussion of neuromethods for mimicking the effects of mania in humans.
1.1. Clinical Manifestations of Mania and the Working Hypothesis

Mania is frequently accompanied by a spurt of creative energy, accompanied by a strong feeling of elation, and some artists and writers accomplish their best work during a manic phase (Andreasen and Powers, 1975). As the mania becomes more intense, the rapidly changing behavior either results in a superficial sampling of continuously changing ideas, or in a form of perseveration, where the same idea occurs so repeatedly that it blocks further progress. The manic individual becomes “hung up” in a narrowly focused set of behaviors, and this stage frequently is followed by irritability and depression.

Certainly, two aspects of manic hyperactivity tend to separate it from other types. One difference lies in the way the manic hyperactivity tends to evolve into a specific and limited behavioral form, in which the individual wholeheartedly pursues a single activity for such long periods that it evokes protest from others, and is oblivious to social pressures. For instance, a guest in a house, on discovering one dull kitchen knife, insists on sharpening every knife in the house, including the host’s fine table silverware, and proceeds to do this over the host’s open protest. Another example is that of the author who locks herself in her room, typing continuously and refusing food, water, social contact, or sleep until she can finish her manuscript. These examples illustrate the “focused” nature of the hyperactivity, which distinguishes it from simple hyperactive exploration, or excessive energy devoted to whatever is at hand or is socially appropriate to the situation.

The second difference in manic hyperactivity is its excessive emotional tone, which is out of all proportion to the actual situation. For instance, there is tremendous elation if the activity is allowed to continue without disturbance, as well as a quick change to irritation and rage if this activity is prevented.

In terms of neurotransmitters, the depressive stage most commonly resembles the behavioral state produced by a continuous overstimulation of the noradrenergic (NE) and DA sys-
tems, which reduces the supply of available dopamine. This may explain why DA stimulant drugs often produce a temporary, but noticeable, upward swing in activity and mood in depressive patients (Beckmann and Heinemann, 1976; Brown and Mueller, 1979). However, given that the nervous system in this illness continues to overstimulate these systems, the exhaustion and depression soon returns. Surely, this is too simple a hypothesis to explain all that happens in depression, but it does indicate that DA activity reduction is, at least, a concomitant feature of depression.

1.2. How Animal Models Relate to the Present Working Hypothesis

The above reasoning suggests that animal models for mania should probably include a direct or indirect stimulation, or overbalance, in favor of the dopaminergic systems, and that models of depression will tend to be found with methods producing DA and NE depletion. However, long-term stimulation of DA systems can lead to severe depletion of DA resources and behavior resembling the post-amphetamine “crash” syndrome, and the like, that displays many elements of behavioral depression. It has even been suggested that the aftereffects of large doses of amphetamine be used to model depression directly (Gerner et al., 1976). Certainly, the phenomenon of “crashing” fits well with the supposition that the early phases of intense mania are principally related to DA overstimulation. The purpose of this chapter is to examine how well this initial working hypothesis bears up under scrutiny from both pharmacological and behavioral viewpoints.

1.3. Problems of Definition for Animal Models

There is a great temptation to place too much emphasis on hyperactivity in defining the symptom characteristics for animal models for mania. Robbins and Sahakian (1980) reviewed the animal literature related to mania, and they suggested that irritability and elation should also be included among the basic attributes of such models. Lyon (1990) has gone further in attempting to define elation and irritability in terms of behavioral
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features recognizable in an animal model. Table 1 summarizes in an extremely brief fashion some of the essential criteria that can be seen in animal models to have close parallels with human symptomatology in mania. In proposing any methods for inducing manic-like states in animals, it may be helpful to look more closely at this table. The most important point for any animal model must be that it does not simply mimic one of these potential symptoms, but several of them, in the same way that diagnostic systems such as DSM-III require the simultaneous appearance of several indicators.

A few points deserve special mention. Elation is often supposed to be a uniquely human feature of emotional experience, with few measurable parallels among animals. The present chapter takes the view that an excessive valuation placed on secondary reinforcements is a proper measure of elation. Secondary reinforcements are seen as the cognitively associated reinforcing value, which is not so directly mixed with the satisfaction of basic physiological needs as are primary reinforcers, such as food and water. Hence, the value of a secondary reinforcer, like that of beauty, lies "in the eye of the beholder," and consequently, can be under- or overvalued, according to the emotional content of the moment in which it appears. An excessive emotional reaction of a positive sort is presumably what we call elation. Since the overvaluation of secondary reinforcers can be measured in animals, and, if carefully done, separated from the mere stimulation of response activity (Hill, 1970; Robbins, 1976), we have a relatively distinct measure of elation in animals.

The rapid shifting of mood that occasionally appears in mania, where depressive episodes intrude on moments of elation, and vice versa, is also a feature that needs to be modeled in animal studies. However, direct measurement of shifts in mood can be difficult to assess behaviorally in animals. Irritability is one feature of the shifting mood function, and it is relatively easy to measure in animals since they shift readily to aggressive behaviors when irritated. Very few studies, however, have taken the time to investigate the level of irritability exhibited, or to compare it properly with control levels. A related phenomenon may be the kindling, or sensitization by electroconvulsive shock or
<table>
<thead>
<tr>
<th>Human symptoms</th>
<th>Measurable animal correlates</th>
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<tr>
<td>Elation</td>
<td>Highly increased value of secondary reinforcement</td>
</tr>
<tr>
<td>Inflated self-esteem</td>
<td>Assumes inappropriate dominant role responses</td>
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<tr>
<td>Irritability</td>
<td>Intense vocalization, Increased startle response, Easily provoked aggression</td>
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<tr>
<td>Rapid mood switching</td>
<td>Sudden and inappropriate changes in vocalizing, bodily posture, and response to stimuli</td>
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<td></td>
<td>Abrupt changes in secondary reinforcement value, Abrupt changes in thresholds for startle and aggression</td>
</tr>
<tr>
<td>Increased intensity of social contact</td>
<td>Increased social vocalization, More approach, contact, and grooming of others</td>
</tr>
<tr>
<td>Increased aggression</td>
<td>Increased threat by voice or posture, Unprovoked attack and biting</td>
</tr>
<tr>
<td>Increased frequency of sexual contacts</td>
<td>Increased mating calls, presenting postures, Increased sexual investigation, foreplay, copulation</td>
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<tr>
<td>Hyperactivity</td>
<td>Hyperactivity in vocalization, locomotion, and responding in general</td>
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<td>Pressure of speech</td>
<td>Increased rate of vocalization or any other form of direct social communication</td>
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<tr>
<td>Flight of ideas</td>
<td>Increased and inappropriate switching between social, aggressive, and sexual behaviors</td>
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<td>Decreased sleep</td>
<td>Decreased sleeping time</td>
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<td>Distractibility</td>
<td>Behavior easily disrupted by irrelevant stimuli</td>
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<td>Impaired judgment and impulse control</td>
<td>Avoidance learning loss with escape and memory intact, Loss of passive avoidance in GO/NO-GO task</td>
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<tr>
<td>Perseverative and/or stereotyped responses</td>
<td>Constant repetitions of behavioral patterns or perseveration in a single response</td>
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repeated low-dose drug effects, which cause sudden shifts to occur in mood and activity functions when some threshold is exceeded (Post et al., 1984). What is most relevant here is that following the initial kindled episode, the threshold for further stimulation is markedly reduced, thus leading to more rapid shifting of reactions when a new stimulus is applied. Emotional lability is the clinical name for such abrupt shifting, and it appears to find here a close animal parallel.

Finally, much criticism of animal models of mania is directed at the supposedly patent absurdity of measuring accelerated thought processes in animals, as opposed to human subjects. The present view, however, is that accelerated thought processes are actually very effectively communicated by animals in the speed of their reaction on tasks requiring serial reaction that do not require exact repetition of a response sequence. For instance, operant conditioning techniques using several manipulanda that must all be operated, but in any desired order (Thompson, 1973; Vogel and Annau, 1973). Such responding tends to develop into fixed patterns for each individual, which represent a series of thought processes (Schwartz, 1986), and rate changes in the execution of these patterns can be directly related to acceleration of thought processes.

Furthermore, there is an increasing number of psychophysiological techniques that allow measurement of the speed of reactive brain processes as “thinking” proceeds (Hiramatsu et al., 1984). The speed with which evoked potentials have their effects, and the rapid shifting of mood mentioned above, are both measurable by direct physiological techniques.

**1.4. Plan for the Present Chapter**

The models are subdivided somewhat arbitrarily, according to their emphasis on causal factors, into the following groups: catecholaminergic, indoleaminergic, lithium-response, opioid, cholinergic, glutamic acid/GABA, brain lesions, intracranial self-stimulation, and kindling/sensitization. There is, of course, considerable overlap between many of these model types, and only certain of them have been selected here for presenting methodological detail.
2. Animal Models of Mania

2.1. Catecholaminergic Models

Amphetamine models are the oldest and most investigated of all animal models of mania, but in recent years, a number of other drugs (i.e., cocaine, methylphenidate, apomorphine) with actions affecting dopamine (DA) have been added to this group (for reviews, see Murphy, 1977; Robbins and Sahakian, 1980; Iversen, 1986; Lyon, 1990). Methodologically, these models can be separated into treatment categories of

1. Large acute injections;
2. Once-daily injections for several days;
3. Several treatments per day repeated over days;
4. Subcutaneous mini-pumps, or implanted capsules, with slow-release lasting for several days, or even weeks.

The single, large injection methods yield, for the most part, only evidence of hyperactivity, which is an important, but not definitive, symptom of mania. However, when combined with operant conditioning methods to test for changes in secondary reinforcement (see Table 1), even these treatments can produce signs of elation, defined here as a sharp increase in secondary reinforcement values. Amphetamine is not preeminent in the latter effect, with pipradrol and methylphenidate producing more obvious effects (Hill, 1970; Robbins, 1975, 1976).

In such operant experiments, careful attention must be paid to separating the effects of these drugs on simple response rate from the effects owing to changes in the secondary reinforcing value proper. This problem, of separating simple rate changes from other measures of reinforcing value, is ubiquitous in experiments with DA stimulant drugs (Lyon and Robbins, 1975).

Behaviorally, studies of amphetamine, methylphenidate, pipradrol, and other catecholaminergically active agents produce many of the symptoms of mania, including hyperactivity, elation (as above), increased irritability and aggression, increased startle reactions, interference with sexual activity, and insomnia. As in humans, many of these symptoms, especially in the
early stages, lead to greater social interactions, and even to improvements in productive behavior on learned tasks. However, with continuing stimulation, the behaviors invariably tend toward excessive responding, strongly repetitive actions, and loss of normal social interactions.

Pharmacologically, amphetamine and similar drugs are acting principally on the DA systems in producing these effects. There appears, however, to be a functional separation within the DA systems of the brain, such that hyperactivity changes are most closely related to the basal ganglia, whereas the emotional tone (mood) accompanying the symptoms is apparently more closely related to the mesolimbic DA system, including the nucleus accumbens (NAC) (Stevens, 1975). DA stimulation of the NAC appears to increase the rapidity with which responses are made. Behaviorally, this would appear as overly rapid reactions, quickly shifting attention, behavioral switching, and the emotional concomitants of irritability, and rapid escalation to aggression. At the same time, the DA stimulation of the basal ganglia would be presumed to be leading in the direction of repetition of responding and perseveration in behavior, with the end result being stereotyped activity (Iversen, 1977).

In the initial phases of mania, the characteristics of behavior would be increased switching of behavior, and in the later phases, a repetitive and stereotyped ("hung-up") type of response that is also characteristic of schizophrenia (see Lyon et al., 1986; Lyon and Gerlach, 1988). The behavioral changes may also be related to changes in neurotransmitter balance, rather than to DA alone. For instance, lithium (Li), which has an excellent antimanic effect, tends to dampen hyperactivity produced by amphetamine, yet there is little evidence that Li reduces DA per se. What apparently happens is that Li increases 5-HT levels, and this acts to counterbalance the overstimulation of DA systems (Gerson and Baldessarini, 1980). This fits well with the knowledge that 5-HT depletion with parachlorophenylalanine (PCPA) leads to hyperactivity, which has been compared with manic hyperactivity, and this type of depletion is aided by the effect of Li.
2.1.1. Examples of Methods

Using Catecholaminergic Changes

The first method chosen to illustrate the measurement of variables relevant to mania was not originally intended as such (Hill, 1970; Robbins 1975, 1976, 1978; Robbins et al., 1983). However, this method provides one of the few available assessments of what is defined here as elation. If elation is indeed closely related to sudden and intense increases in secondary reinforcing strength, then this animal model could be extremely important in relation to mania.

2.1.1.1. Measuring Secondary Reinforcement as a Parallel to Elation

Robbins et al. (1983) have described an excellent method for measuring secondary reinforcement. The method does not depend on responses during extinction of an operant, but rather on the acquisition of a totally new response in which secondary reinforcement is the only source of reward.

The following is a brief description of this method.

Rats were trained in an operant conditioning chamber to push open a panel in order to reach a water feeder. Training consisted of a 0.5-s light flash above the dipper feeder, followed by a 7.5-s presentation of the dipper with water. Water was given independently of responding, every 30 s on a fixed, and later on a random time schedule of reinforcement. To emphasize discrimination of the "light + dipper noise" combinations, the house light was turned off and the reinforcement schedule stopped if the animal poked its head into the dipper feeder when no light flash had been given. This was followed by a 3-s pause to prevent spurious "dipper + no-light" associations from forming.

There were also two levers present in the box, but during training, depression of the levers had no effect beyond being recorded. Training required about six sessions, arranged on alternate days. At the end of training, all animals consumed the water offered, and ignored the levers.

During the test trials for secondary reinforcement effects, no water was delivered, although the empty dipper and the flashing light were presented when correct (to be rewarded)
responses were made on one of the levers. One of the levers, counterbalanced among animals, was chosen as the correct lever, and produced flash + dipper closure on a random interval (RI) 5-s schedule, whereas responding on the other lever had no effect except being recorded. What was measured was the degree of acquisition of responding on the lever producing flash + dipper closure (secondary reinforcement). This preference was tested using, among others, the following drugs: pipradrol hydrochloride (1.5–13.5 mg/kg dissolved in a 1:2 mixture of polyethylene glycol and distilled water), d-amphetamine sulfate (0.25–2.9 mg/kg dissolved in 0.9% saline), cocaine hydrochloride (1.7–41.4 mg/kg dissolved in 0.9% saline), apomorphine hydrochloride (0.03–3.0 mg/kg dissolved by slow warming in 0.2% ascorbate in 0.9% saline and given subcutaneously in the flank), α-flupenthixol dihydrochloride (0.01–1.0 mg/kg dissolved in 0.9% saline), morphine hydrochloride (1.0–10.0 mg/kg dissolved in 0.9% saline).

Drugs were injected ip about 15 min prior to testing (which may not have been ideal for d-amphetamine’s peak action), except morphine and α-flupenthixol, which were given 30 min before sessions. During the pause, the injected animal was placed in a special holding cage. Sessions with varying drug doses and control treatments were counterbalanced using Latin-Square designs.

Pipradrol and d-amphetamine clearly produced increased responding on the correct (conditioned reinforcement) lever, whereas cocaine had little effect. Morphine and α-flupenthixol decreased responding on both levers, whereas apomorphine increased responding on both levers, thus not indicating an “elational” increase, but simply an “activity” increase. The results indicate the differential nature of responding under the drugs, and indicate that drugs such as d-amphetamine and pipradrol may be more closely related to this type of secondary reinforcement than cocaine and morphine, both of which have distinctly analgesic properties. As noted later, morphine may be reinforcing in a different manner than are DA stimulants per se. However this may be, the above method seems to provide an excellent tool for examining differences in elational properties.
The second method chosen for analysis here is that of infusion of dopaminergic agents directly into the nucleus accumbens (NAC). This method has the special merit that it affects, in a localized manner, one of the rostral structures connected with the mesolimbic system. As mentioned above, the NAC has been implicated in some behavioral functions having possible relationships to mania. A key finding was that of Kelly et al. (1975), showing that there is an apparent separation of neural control concerning hyperactivity (rate of response initiation) in itself, vs stereotyped, or intensely repetitive, behaviors. Iversen (1977) summarized some of this work, and suggested that the NAC was more closely related to response rate functions, whereas the nigrostriatal system was more closely related to stereotyped behavior (Randrup and Munkvad, 1968; Randrup et al., 1981). Since that time, Costall et al. (1984a,b) have shown that direct infusion of DA agonists into the NAC affects some behaviors in a cyclical fashion, and may demonstrate exceedingly lasting effects (>1 yr) on DA-related behaviors.

The latest work with infusion of DA agents into the NAC goes much more into depth with the behavioral changes produced, and provides evidence of DA effects on both conditioned and unconditioned (species-specific) behaviors (Taylor and Robbins, 1984; Jones et al., 1987,1989). Thus, it may provide clues relevant to both the learned and unlearned (biologically constraining) factors that are involved in mania.

The following is a brief description of the daily injection vs minipump infusion methods used by Costall et al. (1984a,b). It is suggested that with some methodological revisions, the comparison of these two methods, particularly as it reflects on the mesolimbic DA system under different treatment conditions, may come to provide some valuable insights into manic behavior.

Adult, male rats were used as subjects, and they were selected as either high (60–80 counts/5 min) or low (10–25 counts/5 min) in photocell activity cages. It should be noted that only about one-half of the animals fitted into these two categories. Selected animals were stereotaxically implanted with guide
cannulas for bilateral injection into the nucleus accumbens. Correct placement of cannulas was checked by killing at least three animals at the time of surgery and examining frozen sections of the brain. No mention is made of postmortem anatomical checks on the tested animals. The guide cannulas were of stainless steel and 0.65 mm diameter, and were held in place with perspex holders fastened to the skull. Guides ended 3.5 mm above the NAC and were kept open by means of a stylet protruding 0.5 mm below the end of the guide.

Drug treatment was given to one group by direct daily injections by microsyringe for 13 successive days. Doses of DA hydrochloride ranging from 1.56–50 µg were delivered in 1 µL of a 0.1% sodium metabisulphite solution bubbled with nitrogen. A second group was implanted with a 14-d minipump (Alzet®) attached to a short piece of polyethylene tubing fitted to a stainless steel injection unit inserted into the guide cannula and extending 3.5 mm beyond its tip. The minipumps were removed on d 13 to avoid a potential fall-off in drug infusion at the design limit of the pumps.

For subcutaneous injection, the dopamine agonist (-)-N-n-propylnorapomorphine ((-)NPA) was dissolved in 0.1% sodium bisulphite, and for ip injections, methysergide hydrogen malenate, piperoxan hydrochloride, and (+)propanolol were prepared with water. Haloperidol and (-)-sulpiride were dissolved in “minimum” quantities of lactic acid and hydrochloric acid, respectively. All peripheral injections were calculated as the base and given in a vol of 1 mL./kg body wt.

Behavior was measured by activity in the photocell cages, individually, and by Automex® activity meters in social groups of five animals. Unfortunately, no other behavioral measures are reported, although the activity measures were continued up to 98 d after DA withdrawal. This method provides two potentially useful parallels to mania.

The first parallel lies in a cyclic change in hyperactivity produced in both high and low base activity animals at a one-week interval with the minipump infusion method. The initial phase is hyperactive followed by a three-day return to baseline activity levels, and then followed by a second peak exactly seven days
after the first one. The peak in activity comes abruptly on the third and the tenth day of treatment, and activity is significantly above baseline levels for 3–4 d. This strongly suggests (although the authors do not mention it) that the hyperactivity is correlated with the general activity in the laboratory, including the two weekends in the 13-d test period. Since control animals did not show this peak, it appears that quiet/active periods in the laboratory are associated with a significant change in the incidence of hyperactivity. Furthermore, this is only a function of the minipump infusion method, since the injection procedure seems to show only one prolonged peak of hyperactivity lasting ten days or more. The exact causal factors in this apparent sensitivity of the infusion paradigm to laboratory activity suggests an important parallel to the effects of daily activity stress on mania. The infusion method is also one of the better methods (but see comparison with the implanted capsule method, Eison et al., 1983) for mimicking the relatively stable DA stimulation, which must occur in the natural course of manic illness. The injection method does not offer this parallel so exactly since peak drug levels are constantly changing between injections. It is unfortunate that stereotyped behavior, and some form of conditioned behavior were not examined by Costall et al., since these might have provided still further evidence of parallels to mania.

The second potentially important parallel to mania in these studies is that Costall et al. (1984b) have shown that hypersensitivity to DA challenge is retained more than one year after intracerebral treatment with haloperidol. This suggests that some changes resulting from this injection treatment have more or less permanent effects on sensitivity to DA stimulant drugs. Such an effect resembles the apparently permanent tendency to relapse in unmedicated manic patients, even after periods of many months without the illness.

That it is the change in DA levels in the accumbens and striatum that is the relevant variable for the changes seen is strongly supported by the studies of Jones et al. (1987) and Kuczenski and Segal (1989), using in vivo dialysis of these regions to demonstrate DA activity changes. It is of great interest that the effects seen are so long-lasting, but one severe detri-
ment to these studies is the failure to examine other behaviors than simple motor activation (activity counts). However, the method itself provides an excellent means of investigating the potentially manic effects of localized NAC injections of DA stimulants.

2.1.2. Other Catecholamine-Related Models

Most of the other potential models for manic behavior in this section are based on such relative modulation of neurotransmitters, but it is contended that the basic feature of change is always most closely related to dopamine. For instance, it will be seen that lithium, which acts more on serotonin than on dopamine, has little effect directly on amphetamine-induced behavior (Fessler et al., 1982), but indirectly, lithium's effect on serotonin may allow dopamine to achieve an increased dominance in certain types of behavioral initiation.

2.1.2.1. Alpha-Methyl-Para-Tyrosine (AMPT)

Agents that interfere with dopamine formation, such as AMPT, which interferes with the process of tyrosine conversion to L-dopa, may reduce the hyperactivity induced by amphetamine (Davies et al., 1974). Some antimanic properties have been reported for AMPT in humans (Brodie et al., 1971). In addition to those drugs directly affecting dopamine, some agents primarily affect norepinephrine, acetylcholine, and serotonin levels, with corresponding changes in the relative effect of dopamine stimulation.

2.1.2.2. Amphetamine/Chlordiazepoxide Model

U'Prichard and Steinberg (1972) suggested a potential model for prolonged hyperactivity induced by amphetamine injections combined with the benzodiazepine chlordiazepoxide. The behavioral methods applied (see also Davies et al., 1974) included measures of locomotor activity, and studies of hole-board activity (Poitou et al., 1975). Although it was initially suggested that amphetamine stereotypy (repetitive sniffing, licking, and head movements) was dampened by the chlordiazepoxide pretreatment, later studies did not support this distinction (Poitou et al., 1975). The latter authors suggested that the combination
of chlordiazepoxide and amphetamine caused an imbalance in the normal relative levels of norepinephrine and serotonin, and they cited the partial correction of this behavioral effect by lithium to support their view.

2.1.2.3. Catecholamine Super- or Subsensitivity Models for Mania

2.1.2.3.1. Supersensitivity. There has also been speculation that super- or subsensitivity induced in DA receptors might be the main feature of mania. Robbins and Sahakian (1980), after reviewing the evidence for DA receptor supersensitivity, as induced by localized NAC lesions with 6-OHDA, suggested that this model should be further investigated. There are several points arguing against this direct hypothesis of induced supersensitivity. Chronic pretreatment with amphetamine does not produce supersensitivity as measured by constant hyperactivity or stereotypy, over the entire period of treatment (Huberman et al., 1977; Nielsen, 1981; and Jackson et al., 1981, all in rats; Mehrabian, 1986, in humans). Instead, there appears to be an initial phase of increased activity and perseverative behavior, which is accompanied by lack of sleep and increased irritability. This phase is followed by one in which the activity and stereotypy is reduced, while feeding and resting behaviors gradually increase, though not to normal levels in most cases.

2.1.2.3.2. Subsensitivity. Antelman and Chiodo (1981) have suggested that the principal feature in the induction of amphetamine psychosis, which has many symptomatic features resembling mania, is dopamine autoreceptor subsensitivity, rather than postsynaptic receptor supersensitivity. According to this view, the autoreceptors, which normally function as “shutoff valves" for further DA release into the synapse, are subsensitive to the released DA, and therefore do not prevent further release. The result would be increased activity, and at least, a temporary respite from depressive symptoms. Since tricyclic antidepressants and electroconvulsive shock both appear to induce subsensitivity of DA autoreceptors, this seems to support this possibility (Chiodo and Antelman, 1980).

The truly chronic treatment methods, especially those with slow-release capsules (Huberman et al., 1977), mini-pumps
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(Nielsen, 1981), and chronic infusion (Fischman and Schuster, 1974), show that continuous treatment with central stimulants produces a cessation or weakening of stereotypic motor acts, and less overall bodily activity. However, this may be caused simply by temporary exhaustion and the effects of almost continuous physiological stress induced by DA/NE overstimulation. In short, the outward behavior may have changed, but the sensitivity of the DA system may largely be intact.

2.1.2.4. Monoaminergic/Cholinergic Sensitivity Balance Model

Dilsaver and Greden (1984) have suggested that there may be an important interaction between cholinergic and monoaminergic systems in the production of mania and the subsequent depression that so often accompanies it. The idea is still at the theoretical stage, but may be worth considering in developing methods to mimic the switching between mania and depression that is so characteristic of these disorders.

Basically, the concept of Dilsaver and Greden is that when the brain neurotransmitter balances are disturbed, the opposing systems will attempt to restore balance by changing the sensitivity of pre- and postsynaptic receptors. For instance, cholinergic overstimulation may lead to an increased synthesis of tyrosine hydroxylase in noradrenergic and dopaminergic neurons, with resulting overstimulation of these systems, which, indeed, seems to be the case in mania. However, overestimation of the DA and NE systems would then gradually lead to counteracting changes in the cholinergic system, with subsensitive autoreceptors on presynaptic endings, and supersensitive postsynaptic receptors. This would lead to another cyclic switch from mania to depression. The concept seems relevant, but methodology for separating these effects is not yet available.

2.1.3. Summary of the Catecholaminergic Models

The catecholaminergic models provide a very important set of parallels with manic behavior. The combined stimulation of the DA and NE systems does not seem to be necessary, as most of the symptoms can be produced by models that are essentially dependent on only the DA systems.
The principal features modeled here are hyperactivity, elation, and switching of mood tone. Secondary reinforcement strength is used as a prime measure of elation, and direct stimulation of the nucleus accumbens of the mesolimbic system, and the corpus striatum of the nigrostriatal system have been suggested as models for the induction of manic symptoms.

2.2. Indoleamine Related Models

Serotoninergic systems have often been implicated in models of mania, but careful attention must be paid to methodology, since many of these models include pretreatment with monoamine oxidase inhibitors (MAOIs), which automatically increases the level of available monoamines as well. This criticism applies particularly to models purporting to demonstrate manic behaviors produced by increasing the amount of normally available serotonin (Grahame-Smith, 1971; Green and Grahame-Smith, 1974; Jacobs, 1976; see also, Summary in Iversen, 1986). Further doubt is cast on the likelihood that excessive serotonin is the prime factor in mania by the finding that ICSS rates are reduced, rather than increased, by treatment of rats with the serotonin precursor L-tryptophan, together with the MAOI pargyline (Herberg and Franklin, 1976). This suggests that elation effects are reduced rather than increased by this treatment, although the caveat regarding interpretation of ICSS rate decreases as purely motivational in causation must be recalled.

However, it should be noted that with high doses of amphetamine, 5-HT levels are increased in the corpus striatum of rats (Kuczenski and Segal, 1989). This is a dose-dependent effect, and several other researchers (see review by Gerson and Baldessarini, 1980) have concluded that the increased 5-HT levels are associated mainly with the stereotyped behavior phase of amphetamine stimulation. In any case, serotoninergic actions must be seen against the background of the DA stimulation, which they appear to modulate, rather than control fully.

Similar criticisms may be applied to some lysergic acid diethylamide (LSD) models of mania in cats, such as that reported by Jacobs et al. (1976), which is said to depend on the antagonism of 5-HT receptors by this drug. The symptoms described
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following the LSD treatment include features known to be typical of dopaminergic overstimulation, such as fractionation of behaviors (Schiorring, 1971; Sudilovsky, 1975; Ellinwood and Kilbey, 1977) and continuous switching between a limited number of forms of activity (Evenden and Robbins, 1983). Since Kelly and Iversen (1975) have shown that LSD may also work directly as a DA agonist on mesolimbic structures, it seems doubtful to attribute these effects to serotonergic systems alone.

In contrast to the questionable nature of serotonin (5-HT) increases as causative factors in mania, there appears to be good evidence that depletion of 5-HT by para-chlorophenylalanine (PCPA) is followed by hyperactivity, increased frequency of social and aggressive acts, and increased irritability to novel stimuli (Fibiger and Campbell, 1971; Ellison and Bresler, 1974; Marsden and Curzon, 1976). Whereas PCPA does have effects on other neurotransmitter systems (Miller et al., 1970), it has been shown that the behavioral effects mentioned here can be reversed by treatment with tryptophan or 5-HT itself. Furthermore, the PCPA-induced hyperactivity is not readily reduced by the specific DA receptor blocker pimozide, whereas the increased aggression can be blocked by lithium. These facts tend to increase the likelihood that specific 5-HT effects are at work in addition to any DA overbalance that might occur as a result of the depleted serotonin following PCPA treatment. Because this model includes changes in social behavior, including aggression and irritability, as well as the more commonly reported hyperactivity, it is a model deserving further research.

2.2.1. Summary of Indoleamine Related Models

These models suffer from the fact that reductions in 5-HT are unfailingly followed by a relative overbalance of the opposing monoaminergic system (DA + NE). Whereas some features of behavior are clearly influenced by the 5-HT levels alone, it is virtually impossible to separate the indoleaminergic from the monoaminergic effects. However, as several studies have suggested, the DA/5-HT balance may be a critical factor in mania, and this may be the principal cause of the manic-like symptoms produced by 5-HT depletion models.
2.3. Opioid Related Models

2.3.1. Morphine Models

The opioid related models of mania have a special interest in comparison with the DA related models discussed above. The reasons are that behavioral changes produced by opioid stimulation include, but are not limited by, increases in bodily activity, and also, that opioid effects appear to be more specifically related to elational and behaviorally reinforcing actions (Barchas et al., 1985).

Morphine was long thought to produce diverse behavioral effects in different species, with cats being prone to "feline mania" under its influence, although rats were frequently sedated. Recent work has shown that most of this diversity was simply the result of dose response differences along a steeply climbing curve of dose effect (Ayhan and Randrup, 1973; Villablanca et al., 1984). However, a second difference exists. Morphine tends to stimulate the frequency of abrupt changes in the types of activity being engaged in, with sudden shifts in the morphine-treated rat between such diverse activities as locomotion, social interaction, eating, and grooming (Ayhan and Randrup, 1973; Schiørring and Hecht, unpublished). The relatively rapid shifting between these more complicated behaviors appears somewhat different from the increased shifting between simpler motor acts, which is so characteristic of the DA overstimulation models (Lyon and Robbins, 1975). The result is that the DA models yield manic-like behaviors that are more limited in scope and become more rapidly stereotypical and repetitive, whereas the opioid models disrupt behavior by producing disorder in the normal sequence of events. The common feature of both DA and opioid models is that behavior becomes fractionated, and eventually inappropriate, as the shifting of behavioral patterns increases. Behavior under opioids may also become stereotypical and repetitive, but it seems that this end result is reached more slowly.

Besides the above differences between opioid and DA models, there are also differences in the strength of elational and reinforcing effects, which have traditionally been supposed to be extremely high with opiates. However, it is also known that
the DA systems are closely related to reinforcing effects, with the mesolimbic DA system being most important in this context. ICSS in the hypothalamic regions containing many mesolimbic fiber projections can be used as a reinforcing effect in its own right, although DA cells may be only indirectly involved (Gallistel, 1986).

The relationship of these reinforcement measures to those involving morphine euphoria is also difficult to assess, since lithium itself has a slightly dysphoric effect in humans, and does not counteract morphine-induced euphoria (Jasinski et al., 1977). This finding also militates against the acceptance of morphine stimulation as a model for the euphoric/elational aspects of mania, which apparently can be counteracted by Li.

If morphine is able to induce a state similar to mania by its effect on opioid receptors sites in the brain, then morphine receptor antagonists, such as naloxone and naltrexone, should be capable of producing at least a temporary reduction of manic symptoms. However, the effects of naloxone on mania are equivocal, with some positive response, but more frequently, no improvement (Berger and Barchas, 1982).

2.3.2. Endogenous Opioid Models

Morphine may not be the best of the opioid substances for modeling the effects of mania. Katz (1982) has suggested that endogenous opioids may be the actual source of manic disorder. His experiments with mice tend to bear this out, with $d$-Ala2-substituted amides of Leu and Met enkephalins producing stereotyped running very similar to that seen following morphine treatment. Kyotorphin, which inhibits the catabolic enzyme enkephalinase, given intraventricularly in $<$30 s, tends to potentiate enkephalin activity and also produces increases in rearing on the hind legs at lower doses (ca. 75 $\mu$g in 5 $\mu$L), and stereotyped intensive running at high doses (ca. 150 $\mu$g in 5 $\mu$L). At doses higher than 150 $\mu$g, there is a period of intense stereotypical responding lasting no longer than 30 min and followed by convulsions and death.

Probably the most interesting of the models employing endogenous opioids is that of Schwartz et al. (1982), who pretreated rats with morphine or lactose via implanted subcutane-
ous Silastic® capsules, and then tested them during the hypersensitivity induced following removal of the morphine capsules by injecting beta-endorphins into the ventral tegmental area. During the supersensitive postmorphine period, morphine, but not amphetamine, challenge was followed by greatly increased activity. Furthermore, gamma-endorphins themselves can apparently induce a haloperidol-like supersensitivity, yet amphetamine and apomorphine challenge treatments indicate that these changes are independent of changes in striatal DA function. The following is a brief resume of the methods used by Schwartz et al. (1982).

Adult male Wistar rats were anesthetized with Chloropent® ip, and implanted with stainless steel guide cannulas bilaterally aimed at the ventral tegmental area (VTA). The cannulas were cemented to the skull and blocked with a stylet during surgical recovery of 1 wk. All animals were then tested with a single 0.5 μg infusion of β-endorphin (0.3 nmol total dose) and locomotor activity was recorded in a photocell box for 2 h. Rats were then paired with respect to similar locomotor activity scores and one member of each pair assigned to receive morphine or placebo pellet implants.

Silastic® pellets were prepared (McGinity and Mehta, 1978) that contained either 100 mg morphine sulfate or lactose, and left implanted sc for 3 d. Two additional pellets were then implanted for 3 more d. At the end of this procedure, all pellets were removed and animals received 0.4 mg/kg of the opioid antagonist naloxone hydrochloride, sc. The presence of ptosis, wet-dog shakes, and diarrhea were confirmed during the next 90 min in the morphine group, but not in the placebo group.

Microinfusion through the cannulas into the VTA of β-endorphin was performed using 1 μL of solution infused over a period of 105 s by a syringe pump. The injection cannulas were left in place for 1 min after infusion, then stylets were placed in the cannulas and activity counts were taken over a 2-h period.

One day after pellet removal and naloxone treatment (as above), animals were subjected to either 0.5 or 1.0 μg/μL β-endorphin, and on d 4 post-pellet, they received the opposite dose.
On d 6, animals were given saline infusions, on d 7 d-amphetamine was injected sc, and on d 8, they received 5.0 mg/kg morphine sc.

The results showed that pretreatment with morphine resulted in a change from hypo- to hyperresponsiveness over the next 3 d, whereas lactose had no effect. Schwartz et al. (1982) suggest that this change models the switch from hypoactivity to mania, and that the morphine pretreatment followed by β-endorphin infusion into the mesolimbic pathway at the VTA provides an improved model for the induction of mania. It should be noted that this model implicates the mesolimbic DA system in an opioid-controlled behavior. Exactly how this is accomplished is not yet clear. Joyce and Iversen (1979) demonstrated, however, that injections of morphine into the substantia nigra pars compacta did not cause the hyperactivity that resulted when the VTA was treated. The further use of this model should provide answers to the question of DA/opioid interactions in mania.

2.3.3. Summary of Opioid Related Models

It is possible that in evaluating opioid models of mania, that the mesolimbic DA system from ventral tegmental area to nucleus accumbens should be considered separately from the nigrostriatal DA system that is responsible for amphetamine stimulation of motor activity (Schwartz et al., 1982; Van Ree et al., 1982). It is also possible, as Stevens (1975,1979) has often suggested, that GABA stimulation of limbic structures is more important than DA stimulation of the striatum in producing the typical symptoms of mania.

The most problematic feature of the opioid related models, so far, is that the evidence is conflicting on whether naloxone, which blocks opiate receptor activity, can produce any improvement in mania (Berger and Barchas, 1982). This suggests that the effects of morphine, and possibly of the endogenous opiates as well (de Wied, 1979), are mainly owing to effects produced in other neurotransmitter systems than those directly controlled by the opiate receptors. The problem of defining which opioid receptor types might be involved in mania remains to be solved.
2.4. Acetylcholinergic Factors in Mania

Janowsky and J. Davis and their colleagues (Janowsky et al., 1972a,b) were among the first to advance a NE/ACh hypothesis for mania and depression. According to the original form of this hypothesis, high NE and low ACh would be associated with mania, whereas low NE and high ACh would accompany depression. Whereas present views give more emphasis to DA as well as NE in this relationship, there is no doubt that ACh, at the very least, can act as a modulator for the monoaminergic effects. Some of the earliest studies with manics treated with the cholinesterase inhibitor physostigmine reported a complete reversal of mania, even resulting in depression in 8/8 patients tested (Janowsky et al., 1973). However, later studies of ACh and mania have shown that physostigmine acts principally on the rate increases in thought production and bodily activity induced by mania, and it had much less effect, if any, on the thought content or emotional tone (J. Davis et al., 1978). Physostigmine tended to make euphoric manic patients feel tired, listless, and ill or nauseated, with clearly depressive overtones, yet it failed to alter the state of irritable manic patients, even resulting in increased irritability on cessation of the physostigmine infusion (K. Davis et al., 1978).

Animal studies with physostigmine seem to support the above description, with an initial depressant effect on behavior, followed by excessive overactivity. On the other hand, the ACh antagonist, atropine, tends to produce a more perseverative form of behavior ("behavioral trapping"), with an apparent lack of habituation that seems to mimic partially the effects of DA agonists (De Vietti et al., 1985).

2.4.1. The Effects of Lithium (Li) on Cholinergic Functions

Lithium was originally reported to have little significant effect on cholinergic systems (Boissier, 1975), but more recent work indicates that it may be important in allowing the brain to retain more choline, or to increase the concentration of brain ACh. Such an effect would explain the effectiveness of Li in prevent-
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...ing the return of the massive mood swings in bipolar affective illness, not by a direct effect on the DA/NE systems (for which there is less clear evidence anyway), but by insuring the constant presence of adequate amounts of ACh when this neurotransmitter must act to balance the presumed changes in the DA/NE systems.

Putting this and other evidence together, Dilsaver and Greden (1984) have proposed an adrenergic/cholinergic model similar to that originally proposed by Janowsky and J. Davis (see above), but in this case, attempting to explain how the bipolar mood changes are initiated. Adrenergic excess leads to mania, whereas cholinergic excess favors behavioral inhibition, and possibly leads to depression. Therefore, Dilsaver and Greden suggest that since anticholinesterases and cholinomimetic drugs both work to increase available ACh, these agents will, in turn, antagonize the monoaminergic systems. The particular importance of the Dilsaver and Greden theory, however, lies in the attempted explanation of the mania/depression switching, which they hypothesize is caused either by autoregulatory receptor reactions at pre- and postsynaptic monoaminergic sites, which would be accompanied by an increase in cholinergic receptor sensitivity (leading to the mania/depression switch), or by increased production of tyrosine hydroxylase by cholinergic hyperfunction (leading to the depression/mania switch).

2.4.2. Summary of ACh Related Models of Mania

There is little doubt that ACh in combination with the catecholamines provides part of the balance that is disturbed in mania. However, it is a telling point in comparing this model to human mania, that the emotional component of behavior is not easily altered by large changes in ACh. In short, there seems to be a separation of the motor activation from the elational aspects of mania. Nevertheless, as a comparison model with those involving combined changes in these variables, the manipulation of ACh levels may be quite useful. What is needed for progress in this area is a viable model of the Dilsaver/Greden hypothesis, using agents with both adrenergic and cholinergic influences in combination.
2.5. Glutamic Acid (Glu) and Gamma-Amino-Butyric Acid (GABA) Factors in Mania

Models involving the adrenergic/cholinergic interactions may be useful for studying the switching effect from mania to depression, and they may also have direct relevance to the next grouping of models that implicate the excitatory effects of glutamic acid and the inhibitory action of GABAergic systems (Fonnum, 1984; Scheel-Kruger, 1986) as they are reflected in behavior.

The potential and known interactions of the brain's most widely distributed excitatory and inhibitory neurotransmitters (Glu and GABA, respectively) are too complex to be dealt with here. Only a few relevant findings will be considered in relation to mania.

GABA is formed from glutamate by the removal of a carboxyl group. It is perhaps the most ubiquitous of all neurotransmitters, with over one-third of all nerve terminals in the CNS staining for its presence (Fonnum, 1984). GABA is an inhibitory neurotransmitter at the postsynaptic junction, but the end result can be excitatory if it inhibits a normally inhibitory pathway.

2.5.1. Excitatory Amino Acids and the Hippocampus

Several interesting relationships have been suggested between the effects of excitatory neurotransmitters, such as glutamic acid (Glu) and aspartate (Asp), and the neural activity of the hippocampus (Cooper et al., 1986). The NMDA receptors in this limbic region seem to be of particular importance, since they have relationships to long-term potentiation, which may be important in learning and short-term retention, yet these same receptors are vulnerable to a neurotoxic effect if overstimulated by glutamate in the absence of calcium (Ca²⁺) channel blocking by either a blocking agent (such as MK-801), or magnesium (Mg²⁺) within a specific temperature range. If the calcium channel is not blocked sufficiently often, a process begins that may end with the death of the cell.

These facts may be relevant to mania for a number of reasons. First, there is a large amount of independent evidence linking cellular damage in these same regions of the hippocam-
pus with the major psychoses (Bogerts et al., 1985; Kovelman and Scheibel, 1984). Second, lithium-induced increases in Mg\textsuperscript{2+} tend to be correlated with that drug's effectiveness in reducing mania (Pavlinac et al., 1979), and a close relationship between Mg\textsuperscript{2+} deficiency and catecholamine functions and aggressivity has been documented by Kantak (1988). These changes could be related to the NMDA receptors, but further investigation is needed to establish the possible roles of not only Mg\textsuperscript{2+}, but also of Ca\textsuperscript{2+}, zinc, and glycine at the NMDA site.

Cocaine also magnifies kindling effects produced by electrical stimulation of the amygdala and hippocampus, which have been suggested to be dependent on excitatory amino acid (Glu) functions. If intensified by repeated stimulations over time, these local effects can lead to the kindling of seizures within the limbic system (Post et al., 1984). The kindling itself leads to a state in which the initial neurochemical stimulation is no longer necessary to invoke the disturbance of hippocampal electrical activity (see also Kindling and Sensitization Models).

To prevent the development of these seizures, Post tried various antiepileptogenic compounds, and discovered that carbamazepine blocked both cocaine and lidocaine-induced hippocampal seizure activity. On this basis, Post suggested that carbamazepine should also act as an antimanic medication. This has proved to be correct, at least for a subgroup of manic patients (Rubin and Zorumski, 1985).

2.5.2. The Role of GABA

Originally, it was thought that the relationship of GABA to the DA systems was mainly as a direct inhibitory effect of striatonigral GABA neurons inhibiting the action of the nigrostriatal fibers arising in the pars compacta of the substantia nigra. However, this is not what happens at normal levels of GABA activation. Instead, the striatonigral GABA neurons act principally on the cells of the pars reticulata of the substantia nigra, and indirectly affect thalamocortical relationships (Scheel-Kruger et al., 1981; Scheel-Kruger, 1986; Carlsson, 1988), which then, in turn, affect the corpus striatum once more. Furthermore, stimulation with the GABA agonist muscimol of the VTA results in different reactions from the rostral and caudal ends of
that structure (Arnt and Scheel-Kruger, 1979). GABA stimulation of the caudal VTA results in:

...a dose-dependent increase in non-explorative locomotion, a strong aggression shown as immediate attack of everything presented and violent fighting after placing two rats in a single cage...increased food intake in satiated rats...no stereotypies (sniffing, head movements, licking or gnawing) after bilateral injection or turning after unilateral injections...(Scheel-Kruger et al., 1980, p. 263).

On the other hand, muscimol injected into the rostral VTA causes a decrease in spontaneous activity that eventually becomes sedative, with a hunch-back posture and some rigidity of the limbs. There is no aggressive behavior or induced eating.

These behavioral descriptions fit reasonably well with the symptoms of mania, including the fact that limited behavioral stereotypies are not the most prominent symptom as they tend to be in schizophrenia (Bleuler, 1950). Stevens (1975) reported extreme emotional responses of fear, hypervigilance, and apparent "hallucinations" following GABA blockade of the VTA with the GABA antagonist bicuculline in the cat. Scheel-Kruger et al. (1980) found that bicuculline and picrotoxin in the rostral VTA of the rat induced strong hypermotility and vertical activity (rearing on the hind legs, an investigatory movement in uncertain situations). From this, one might guess that Stevens' injections mainly reached the rostral VTA. Stevens' conclusion was that disturbances of the mesolimbic system had much to do with schizophrenia, but it may be that lesser doses would produce the equivalent of manic behavior.

It is also extremely interesting that the only two long-axon pathways involving GABA neurons are the striatonigral path already mentioned, and the output axons of Purkinje cells in the cerebellum, which terminate in the basal cerebellar and vestibular nuclei (Fonnum, 1984). These pathways are of interest because the first of these pathways is quite possibly involved in mania, as mentioned above, and the cerebellar path has been suggested to have a potential role in the abnormal eye movements seen in schizophrenia (Karson et al., 1990).
2.6. Brain Lesion Models

Robbins and Sahakian (1980) made an attempt to review thoroughly the various ways in which hyperactivity following brain lesions might be seen as a model for mania. They concluded appropriately that hyperactivity alone may not be a sufficient index of manic-like behavior in animals. This is because such a wide variety of agents affecting the brain can cause excessive activity. However, in the following, the various lesion models have been grouped roughly according to the structures that they affect, rather than according to the degree of hyperactivity they produce.

Before assessing the effectiveness of various lesioning procedures in modeling mania, rather than for producing simple behavioral activation, it would be wise to recall the two major aspects of manic hyperactivity as discussed in the introduction. Manic hyperactivity (1) tends to evolve into a specific and limited behavioral form after a period of intensely active switching between such forms; and (2) exhibits an excessive emotional tone, whether of elation, irritability, or aggression.

Using the above differences in manic hyperactivity as criteria, many of the supposed parallels to manic hyperactivity in animals are not convincing. Heavy metal poisoning often involves a strong deposition of the metal in the hippocampus, a structure frequently suggested to be implicated in psychosis. However, the hyperactivity produced by poisoning with lead, cadmium, or rubidium (Silbergeld and Goldberg, 1974; Rastogi et al., 1977; Meltzer et al., 1969) is "paradoxically" reversible by treatment with amphetamine or methylphenidate, which is not the typical case in mania, although occasional decreases in manic symptomatology are reported in the literature following central stimulant drug treatment. In any case, the present lack of knowledge about the fundamental effects and localization of heavy metal toxicity makes it difficult to use these treatments as a source for modeling.

The same criticisms apply to methods used by Norton et al. (1976). They compared the behavioral effects of X-irradiation at gestational d 14–15, carbon monoxide exposure on postnatal d 5,
and direct electrolytic lesions of the globus pallidus. However, we do not yet know enough about the effects of agents limited to d 14–15 of gestation in the rat, or to the exact effects of postnatal d-5 treatment. Destruction of the globus pallidus, which contains the major descending output of the corpus striatum, would be expected to remove a large part of the inhibitory influence on motor reactions, and thus, to effectively raise the level of muscular activity, and hasten the rate of change between various activities by allowing a more rapid initiation of new responses. This is exactly what Norton et al. (1976) found, using these methods. Explorational behavior, measured by videotape analyses of behavioral acts at 1-s intervals, occurred more frequently, but with briefer durations, and there appeared to be a more random, and more frequent, switching between behaviors. It should be noted that at the 14th gestational day, the cells in the cortex of the parahippocampal gyrus had not fully migrated to their cortical layering, and disturbances at this anatomical position have been found in the brains of schizophrenic patients (Jakob and Beckmann, 1986). Postnatal hypoxia induced by the carbon monoxide treatment on d 5 may also affect the hippocampus, as well as the neocortex, thalamus, and sensory pathways of the midbrain (inferior colliculus, and so on), since these regions are still under steady development at this time. Finally, the cerebellum still contains immature and only partially migrated cells destined for the lateral cerebellar cortex, including their input to the basal cerebellar nuclei (Gilles et al., 1983; Lyon and Barr, in press). Although the behavioral effects of lesions at these developmental stages are similar to mania, we are once again without precise localization. Hence, the methods used by Norton et al. (1976) are not well designed for basic modeling of mania, although their methods for measuring behavior are excellent for this task.

2.6.1. Lesion Methods Related to Serotonergic Systems

Several methods have been applied to the destruction of 5-HT systems, and two of these will be mentioned here: selective destruction of 5-HT cells by neurotoxins, and electrolytic lesions of the raphe nuclei in the brain stem (Lorens et al., 1976).
The selective neurotoxins 5,6- and 5,7-dihydroxytryptamine (DHT) can be used to destroy 5-HT cells in the CNS. This can be done either by microinjections into selected areas, or by periventricular injections, which affect a much broader periventricular area (Diaz et al., 1974; Green and Grahame-Smith, 1974). This method should be compared with PCPA injections, which do not destroy the 5-HT cells, but do lower the amount of 5-HT available. The lesion method with 5,6-DHT has a dose-related effect. A lower dose, injected intraventricularly in rats, produces an initial increase in whole body locomotion and a reduction in rearing, whereas a higher dose reduces whole-body locomotion but increases rearing on the hind legs.

This effect is reminiscent of the effects reported with low and high doses of amphetamine in rats responding on a shock avoidance task, in which such increased locomotion and increased rearing disturb, respectively, passive and active avoidance (Lyon and Randrup, 1972). As mentioned previously, such parallels suggest that perhaps changes in DA balance, rather than 5-HT activity per se, is the relevant variable in producing these changes. However, the activity changes may not be as long-lasting in the case of the DHT lesions. Mailman et al. (1981) reported that 5,7-DHT lesions given 2-d postnatally, resulted in hyperactivity 14 d later, but only hypoactivity 28 d posttreatment. Once again, this is consistent with the suggestion that the activity changes can be compensated for by DA systems over time.

Lesions of the raphe nuclei have been studied with both electrolytic and neurotoxic lesions (Lorens et al., 1976). As with many other systems, the effects of these two lesion methods do not produce the same behavioral effects. Electrolytic lesions were followed by increases in whole body locomotion, but not by increases in rearing or sniffing at the floor of the cage. In addition, running wheel, and open-field, activity also were increased. These effects are similar to those seen with low doses of d-amphetamine, and once again, suggest an indirect relationship with DA system overbalance produced by decreasing the normal 5-HT levels of activity (Gerson and Baldessarini, 1980; Balsara et al., 1979). However, 5-DHT lesions of the median raphe did not produce the same symptoms, which suggests that part of the reason for the increased locomotion may be the result of fibers
coursing through the region of the median raphe, but without
direct connection with 5-HT systems.

Furthermore, it appears that the dorsal nucleus of the ra-
phe is more closely connected to the caudate-putamen, whereas
the median raphe nucleus has more extensive connections with
the hippocampus, medial preoptic area, suprachiasmatic nucleus,
and anterior hypothalamus (Van de Kar and Lorens, 1979). These
connections suggest that the dorsal nucleus may have more to
do with the rapid repetition of responding seen in mania, whereas
the median nucleus is more closely related to the potential kin-
dling effects in the hippocampus (see below under Kindling and
Sensitization Models).

2.6.2. Lesion Methods Related to DA Systems

Selective lesioning of specific neurotransmitter systems be-
gan with the use of 6-hydroxydopamine (6-OHDA), a neurotoxin that appears to be relatively specific to DA systems. It is
perhaps one of the most widely used of all neurotoxins, and
several of its uses result in behavioral symptoms with an apparent
relation to mania. In the following, a few of these experiments
have been selected in order to show some of the internal neural
arrangements that may be dysfunctional in mania. Once again,
the two basic DA systems that are considered for such a role are
the nigrostriatal, and the mesolimbic systems.

Lesions of the nigrostriatal system involving DA cells lead
to a loss of motor activity, principally through the lack of initia-
tion of movement by the corpus striatum and associated struc-
tures. Lesions caused by disease result in Parkinsonism, and more
recently, the abused drug 1-methyl-4-phenyl-1,2,3,6-tetrahy-
dropyridine (MPTP) has been shown to produce the same losses
of DA cells in the substantia nigra, and the same symptoms as
Parkinsonism (Heikkila et al., 1984). The only parallels with
mania lie in the supersensitivity to DA of the remaining nigral
cells, which may temporarily result in overly repetitive actions,
either as facial or limb tics, uncontrollable tremors of the
extremities, or simply inordinately perseverative repetitions of
some otherwise normal behavioral sequences. However, since
the basic course of the disease leads to less and less active
responding, any further parallels with mania are difficult to find. Furthermore, it is particularly symptomatic of Parkinsonism that facial expressions and normal social interactions are diminished or lost. In short, there is reduced reaction to environmental stimuli, and increasing impairment in the initiation of acts.

On the other hand, lesions of the mesolimbic system, dependent on where in this broader system they occur, tend to produce other effects than do the nigrostriatal lesions. Selective destruction of DA neurons in the nucleus accumbens of the rat is followed by a decrease in amphetamine-induced hyperactivity, but to increases in locomotor reactions produced by apomorphine, a direct DA receptor agonist. However, the timing of the behavioral test is very important in this context. For a few days after the 6-OHDA treatment of the nucleus accumbens, there may be a decrease in activity initiated by stress or amphetamine (Evetts et al., 1970), but several weeks later, such stimulation may increase activity again.

There is also a possibly confounding factor in activity analyses following accumbens lesions. Lesions involving damage to the lateral ventricles and septal region, as most NAC lesions are bound to do, sometimes result in a period of hyperesthesia, which was originally described as "septal hyperemotionality." However, the effect has nothing to do with specific septal nuclei (Harrison and Lyon, 1957), and may depend on a transient denervation supersensitivity. This might explain, in some cases, why apomorphine increases activity in 6-OHDA accumbens lesioned rats.

This suggestion fits well with the observation that mania does not necessarily lead to excessive motor activity (although it may do so). What is more characteristic of mania is the increased irritability, hypersensitivity to external stimuli, increased aggressive responses, and increased vocalization. These are all important symptoms of manic behavior, and the question now is, how are they related to periventricular brain structures?

Petty and Sherman (1981) introduced the intraventricular injection of 6-OHDA as a possible animal model for mania. They pointed out that 6-OHDA injected into the ventricles was known to deplete NE sharply, without severe effects on 5-HT and GABA.
Furthermore, animals treated in this manner showed "...strikingly increased irritability, aggression, hyperemotionality, hyperreactivity, and vocalization" (Nakamura and Thoenen, 1972; Coscina et al., 1973). These behavioral changes became worse if the animals received intraventricular NE, yet the behaviors were reduced by neuroleptics and by intense handling (Coscina et al., 1975). Petty and Sherman also recognized the importance of testing lithium, tricyclic antidepressants, neuroleptic drugs, and electroconvulsive shock treatments with their model. From the present point of view, we would not expect tricyclic antidepressants or shock treatment to be very effective in treating mania, since these treatments are not as commonly used, or found particularly effective, for the manic end of the bipolar mood disorder continuum. However, lithium and neuroleptic drugs are both supposed to be beneficial in mania, with lithium restoring DA/5-HT balance gradually, whereas neuroleptics act more immediately to block the hyperdopaminergia found in the early stages of mania.

The major problem with the Petty and Sherman study was the lack of differentiating behavioral tests. Only hyperreactivity, especially following an intense electric shock, was tested, using a Coulbourn modular test cage that was mounted on a BRS/LVE swinging pendulum activity meter.

On each test day, the initial stage was a 2-min familiarization period in the activity cage, followed by measurement of activity until the animal reached a criterion of 5 s with no measurable activity. After this, ten test trials were given, in which each test trial began with a 1 mA foot-shock for 1 s, followed by activity measurement until there was again a 5 s period of no activity. A 20-s intertrial interval separated the test trials. Responses of >40 counts on the activity meter were scored as hyperreactivity.

Separate groups were tested with
1. No drug or other treatment; reactivity test;
2. 6-OHDA by intraventricular injection; groups of animals tested on days 0, 2, 4, 6 after 6-OHDA; saline injection only; each group tested only once;
3. 6-OHDA as above; groups tested on days 0, 2, 4, 6 after
6-OHDA; lithium lactate injections (0.75 mmol/kg) twice
daily after the 6-OHDA treatment; each group tested only
once;
4. 6-OHDA as above; one group tested only on d 4 after
6-OHDA; chlorpromazine (5 mg/kg, ip) given once on
d 4 with testing occurring only 1 h later;
5. 6-OHDA as above; one group tested only on d 2 after
6-OHDA; imipramine (3 mg/kg, ip) given once on d 1 and 2.
6. 6-OHDA as above; one group tested only on d 6 after
6-OHDA; electroconvulsive shock (110 mA, 0.3 s) given
through earclip electrodes twice daily on d 2–5. Each ani-
mal had a tonic-clonic seizure of at least 20 s duration at
each treatment session. Testing occurred at least 18 h after
the last convulsive shock.
7. 6-OHDA as above; one group tested only on d 6 after
6-OHDA; subconvulsive shock (30 mA, 0.3 s) given on
d 2–5; no animals showed seizures at any time. Animals
were tested at least 18 h after their last shock.

Petty and Sherman found no changes in general activity
between treatments before testing began with electric foot-shock. Animals receiving only 6-OHDA treatments were progressively
hyperreactive to the shock over days, with a 67% increase on
d 6. Lithium treatment prevented this progressive increase in
reactivity, and animals were essentially at the normal level by
d 6. Chlorpromazine also significantly reduced the hyperreact-
itivity to shock, whereas imipramine, as predicted above, caused
a greater reactivity than 6-OHDA treatment alone on d 4. Chronic
electroconvulsive shock, but not the subconvulsive shock, had
some effect on the hyperreactivity to foot-shock, but did not bring
about a complete return to normal reactivity. These results fit in
very favorably with the suggestion that this method provides a
good model for mania. What is missing, in particular, is a good
measure of elation. It is suggested that such a measure be added
to future studies with this model.

There are also a number of interesting anatomical points
concerning this model. It should be noted that among the struc-
tures separated from CSF only by the ependymal lining of the ventricles (in the rat at least) are the nucleus accumbens, corpus striatum, hypothalamus, hippocampus, and periaqueductal gray matter. Theoretically, agents in the ventricular fluid that are able to pass the CSF/brain barrier will easily affect all of these structures. Thus, injection of 6-OHDA into the ventricles has the potential to affect directly DA transmission in both the mesolimbic and the nigrostriatal systems. In both cases, the rostral part of the systems is most clearly affected. The substantia nigra and the ventral tegmental area, from which the neurons arise that will most affect DA functions rostrally, are spared from the direct effect of intraventricular injection. From a methodological point of view, it is interesting to note that the nucleus accumbens and the hypothalamus, of the mesolimbic system, lie in the most ventral regions of the ventricles, so that fluids with a heavier mol wt might tend to gravitate to these regions following injection into the dorsal part of the ventricular system.

Perhaps of special significance for the Petty and Sherman model is the fact that the 6-OHDA treatment resulted in a lasting hypersensitivity to electric shock, and that this hypersensitivity increased in strength of a period of several days. Such an effect shows important parallels with the kindling model suggested by Post et al. (1984). Furthermore, this hypersensitivity could be reduced by lithium and, to some extent, by chlorpromazine and electroconvulsive shock, and was increased by the tricyclic antidepressant imipramine. These features make this model one of the most attractive of all the models for mania yet introduced.

2.7. Intracranial Self-Stimulation (ICSS) Models

ICSS has often been suggested as a good model for the elational effects of mania, on the assumption that the systems yielding a positive increase in responding to ICSS are also those most intimately connected with reinforcement. However, this assumption does not always bear up under close scrutiny. Electrical stimulation of the brain leads to an increasing motor activation, more frequent repetitions of the response preceding stimulation, and so on, but this does not totally negate the motor
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stiratory effects of the brain stimulation, which also exist
(Phillips et al., 1976). The problem then becomes one of judging
whether the rate increases typically measured in ICSS paradigms
can be directly compared with elational effects. Certainly, ICSS
thresholds provide a more secure measure of reinforcing
strength, than do simple rate measures (Robbins and Sahakian,
1980). The definition of elation in terms of animal models prob-
ably requires a secondary reinforcement paradigm, in which the
experimenter has control over the conditioning strength of the
positive (elation-provoking?) alternatives (Lyon, 1990).

Leith and Barrett (1980) suggested that ICSS in combina-
tion with prolonged amphetamine treatment could be used to
model the changes from mania to depression. They were able to
show that as the amphetamine treatment continued, the ICSS
rate was initially stimulated and then later depressed. This, they
suggested, was owing to the initial DA stimulating effect of am-
phetamine, which is eventually followed by a depression in rate
as the monoamine neurotransmitter resources are used up by
the continual DA stimulation (see also Gallistel, 1986). The logic
of this model is reasonable to a certain extent, and the fact that it
addresses the problem of bipolar illness is unusual, but it is un-
clear from this how the full cycle, including the depression/mania
change, would be achieved. This, added to the uncertain-
ties surrounding the ICSS rate measure as a yardstick for ela-
tion, leaves the model with a suggestive, but not convincing,
parallel to mania.

Perhaps ICSS could be used in combination with a model,
such as that suggested by Dilsaver and Greden (1984) discussed
above, which attempts to account for both directions of switch-
ing between the manic and depressive states. At this time, the
ICSS model appears only to relate to single aspects of the manic
syndrome, and even these are not entirely clear.

2.8. Kindling and Sensitization Models

Kindling refers to the gradual growth of sensitivity to peri-
odic subconvulsive electrical stimulation of brain structures, until
finally a convulsive episode occurs to the previously ineffective
stimulus. Furthermore, if convulsions are elicited a number of
times by this method, an independent convulsive cycle may be established, such that convulsions may be elicited without the priming effect of the subconvulsive stimulus (Goddard et al., 1969).

There is excellent evidence that the hippocampus, amygdala, and the nearby transitional cortex are very susceptible to the induction of long-term potentiation and kindling effects (Post et al., 1984). Increasing dose levels, as well as frequent repetition of small doses, leads to cocaine sensitization, and eventually to seizures and death (Post et al., 1988). The sensitization is partially context-dependent, which agrees with the context dependent behavior frequently found with d-amphetamine and other DA agonists (Fischman and Schuster, 1974).

Recognition of this phenomenon has led to a reevaluation of the causes for convulsive episodes, and also to further study of the periodicity in these events. Post et al. (1981) showed that periodic effects of kindling could be produced by electrical stimulation of the amygdala in the rat, and Wake and Wada (1975) demonstrated essentially the same phenomenon in kindling of the frontal cortex in the cat. Perhaps even more important in the context of mania and depression, was the fact that these researchers were able to show a cyclic variation in sensitivity to the electrical stimulation, with a periodicity of several days. Thus, this method seemed to reproduce the basic cyclic nature of the bipolar mood disorders. However, the cycling time is short, compared with the human manic/depressive cycle, and the behaviors produced during the sensitization to amygdaloid stimulation are not exactly like those that best characterize mania.

In a second paradigm, Post (1977) showed that repeated low-dose treatment with cocaine in monkeys resulted in a phase of behavioral activation followed by an “inhibitory syndrome” consisting of reduced motor activity, catalepsy, and abnormally strong staring and visual preoccupation with minute details in the environment. This resembles the results obtained by Lyon and Nielsen (1979), and by Nielsen et al. (1983) on the effects of continuous amphetamine treatment of vervet monkeys with implanted amphetamine capsules (see Chapter by Lyon on Models of Schizophrenia in this book for details of method). It is not surprising perhaps that cocaine and amphetamine treatments
can provide similar results, but the fact that a very low-dose treatment can kindle, over time, a sort of high-dose effect is intriguing. It implies that within the amygdala, frontal cortex, and hippocampus, and perhaps elsewhere, there is some form of long-term effect that is perhaps characterized by the hippocampal effect known as long-term potentiation (LTP) (Brown et al., 1988).

As with LTP, the kindling effect fades over time if it is not elicited, and in this way, is dissimilar to long-term memory, which remains intact over such periods. However, it is reasonable to suppose that lengthy periods of overstimulation of Glu-modulated systems, such as those involving the NMDA receptors in the hippocampus and elsewhere, can result in the dysfunction and eventual destruction of the cells, with a relatively permanent hypersensitivity as a result.

3. Summary

The present review of models for mania suggests that very important behavioral effects resembling mania can be found after manipulation of DA and Glu related systems. It appears that the DA systems obtain an overbalance as mania increases, and that the resultant effects can be modulated by other neurotransmitter systems, such as those related to ACh, 5-HT, and some neuropeptides. The origin of the DA overbalance may lie in the LTP effects of excessive stimulation of the NMDA receptors in the hippocampus and/or amygdala, with an end result of relatively permanent hypersensitivity (kindling effect). The cycling of mania and depression appears, from this view, to be resulting from the natural corrective tendencies of the brain in response to an overbalance of a particular neurotransmitter influence. However, this mechanism can have only a temporary effect, and on repeated insult, severe and long-lasting depression becomes increasingly probable.

The models for mania that seem most promising at this time are therefore those related to DA overstimulation of mesolimbic structures, as demonstrated by the dialysis method of Kuczenski and Segal, and by the intraventricular infusion method of Petty and Sherman. For studying the modulating effects of 5-HT on
this basic DA model, PCPA treatment provides an excellent model. The role of opioid receptors and the relationship of endogenous opioids to mania can best be studied by using morphine stimulation compared with specific beta-endorphins.

Lithium antagonism of an agent's effect should not be taken as the ultimate measure of a particular treatment's relationship to mania. On the other hand, both lithium and neuroleptic antagonism of model effects should be considered with regard to NMDA and DA receptor mechanisms.

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