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# An Hypothesis Regarding the Antipsychotic Effect of Neuroleptic Drugs

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FREED, W. J. *An hypothesis regarding the antipsychotic effect of neuroleptic drugs.* PHARMACOL BIOCHEM BEHAV 32(1)337–345, 1989.—The antipsychotic effect of neuroleptic drugs appears gradually over the course of several weeks of chronic drug administration. Neuroleptic drugs are thought to act by blocking dopamine receptors; however, the dopamine-blocking effect of neuroleptics appears rapidly. One effect of dopamine antagonists which develops slowly is dopaminergic supersensitivity. It is suggested that this dopaminergic supersensitivity is related to the development of tolerance to some of the acute sedative properties of neuroleptics, but not to the antipsychotic effect. A population of glutamate receptors which are postsynaptic to the cortico-striatal afferents is located on the same neurons as striatal dopamine receptors. These glutamate synapses are located on the heads of dendritic spines of striato-nigral projection neurons, while the dopaminergic synapses are predominantly located on the necks of these same dendritic spines. Similar relationships could exist for mesolimbic and mesocortical dopamine systems. In peripheral systems, postjunctional denervation supersensitivity is known to be nonspecific; in other words, denervation of a single innervation of an excitable cell can alter the response to a range of stimuli. The antipsychotic effect of neuroleptics is therefore suggested to be due to nonspecific postjunctional subsensitivity at glutamate synapses, which develops concomitant with supersensitivity at dopaminergic synapses.

Neuroleptics Denervation supersensitivity Glutamate receptors Cortico-striatal pathway
Schizophrenia Psychosis Dopamine Excitatory amino acids

THE antipsychotic effect of neuroleptic drugs is enhanced by chronic administration, rather then diminished. In this respect, neuroleptic drugs are unlike agents such as barbiturates, ethanol, or opiates. The effects of these agents are diminished by chronic administration, i.e., they undergo tolerance. Yet, there is ample evidence that tolerance does develop to some effects of neuroleptic drugs: when administered acutely to animals these drugs block the effects of dopaminergic agonists and increase dopamine turnover, and these effects undergo tolerance after chronic administration (16, 53, 69). Tolerance also develops to some behavioral effects and to some of the early nonspecific sedative effects of neuroleptics in both animals and in man (2, 4, 19, 26). Thus, upon closer examination, neuroleptics and other agents are not so dissimilar, in that tolerance to the acute effects develops after chronic administration. For neuroleptics, a second effect—the antipsychotic effect—develops gradually over the course of several weeks of chronic administration (13, 19, 44, 75). This "therapeutic latency" is not related to changes in drug blood levels or metabolism (18).

Many experiments have shown that chronic neuroleptic administration causes a supersensitivity of central dopamine receptors, as well as a behavioral supersensitivity to dopamine agonists (11, 69, 78, 79, 82). The time course of development of this dopaminergic supersensitivity is similar to the time course for the development of antipsychotic effects. It has often been presumed that dopaminergic supersensitivity is somehow related to the therapeutic latency phenomenon.

Dopaminergic supersensitivity is thought to consist of proliferation of postsynaptic dopamine receptors (11, 17, 79). If neuroleptics do indeed act through antagonism of dopamine receptors, development of dopaminergic supersensitivity would only be expected to overcome the acute effect of dopamine receptor blockade. Other studies have noted time-dependent changes in dopaminergic systems induced by neuroleptics such as increased turnover and decreased activity of substantia nigra cells (10, 53, 69), but these changes also would tend to either counteract or augment the acute neuroleptic effect. In fact, any unidimensional change in the efficacy of transmission at dopaminergic synapses could in theory be achieved acutely, by administration of dopamine agonists or antagonists. For that reason, it is the contention of this paper that any alteration which is entirely restricted to the brain dopamine system is insufficient to explain the therapeutic latency of neuroleptics. Similar reasoning has previously led others to conclude that "although the antipsychotic effect may depend on dopaminergic blockade, such blockade may be necessary only in order to allow other, longer-term processes to take place" [(44); 851].

## NIGRAL AND CORTICAL STRIATAL AFFERENTS

The dopamine-mediated nigrostriatal system is one of the major afferents to the corpus striatum (1, 21, 41). Dopamine is generally thought to be inhibitory for striatal neurons (5,72), although excitatory effects have also been reported (60,86). Recently, Herrling and Hull (38) observed that dopamine induced a slow depolarization of striatal neurons, with reductions of ongoing firing rate. During these depolarizations, cortically-evoked potentials were inhibited. Chiodo and Berger (15) also reported that dopamine inhibited glutamate-induced excitation in the striatum, but at very low concentrations of dopamine glutamate-induced excitation was enhanced. At odds with most microiontophoresis experiments, Wilson and co-workers (86) found that stimulation of the substantia nigra produced a complex response in striatal neurons with inhibitory and excitatory components. When cortical and thalamic striatal afferents were removed, however, nigral stimulation produced only excitation of striatal cells, suggesting that the direct effect of nigral neurons upon striatal neurons is one of excitation. Some of these effects might, however, be due to alterations in striatal function caused by cortical lesions, and substantia nigra stimulation might also activate nondopaminergic ascending fibers. Most other data suggest that dopamine inhibits corticostriatal transmission (8, 70, 81). The present hypothesis will be developed with the assumption that the predominant effect of dopamine is inhibition. It is recognized that dopamine can have excitatory effects, and probably exerts a modulatory effect on striatal neurons which is neither entirely excitatory nor inhibitory. The predictions of the present hypothesis would largely be reversed if subsequent findings do show that dopamine is, in fact, excitatory.

A second major striatal innervation is the cortico-striatal system (33,45). This system is mapped topographically so that, in a rough sense, various parts of the frontal cortex innervate the closest parts of the striatum (12,84). There is strong evidence that glutamate is the neurotransmitter for the cortico-striatal pathway (35, 55, 87). The effects of glutamate are almost always excitatory (57,83).

There appear to be three types of excitatory amino acid receptors which have been characterized as N-methyl-D-aspartate ($AA_1$), quisqualate ($AA_2$), and kainate ($AA_3$) receptors (14, 25, 57, 83). The receptors for the cortico-striatal afferents appear to be of the $AA_2$ type (37). Activity of striatal cells evoked by cortical stimulation can be effectively blocked by glutamic acid diethyl ester (74), a partially specific antagonist of the $AA_2$ receptor (40,57). Antagonists of the $AA_1$ receptor do not block cortically-evoked striatal responses (39). Relatively high concentrations of the $AA_2$ receptor are present in the striatum (42,58).

The topography of the dopaminergic innervation of the striatum has recently been described at the ultrastructural level (6, 27, 35, 50, 73). Tyrosine hydroxylase immunoreactive synapses (presumably dopaminergic) are found at the necks of the dendritic spines or less frequently on dendritic shafts of striato-nigral projection neurons (6,27). The cortico-striatal synapses are often found to be coincident not only on the same neurons, but on the same dendrites or dendritic spines. Whereas the tyrosine hydroxylase immunoreactive synapses are often found on dendritic spine shafts, the corticostriatal afferents tend to synapse more distally, on dendritic spine heads (27). It is therefore apparent that the location of dopaminergic synapses in the striatum is ideally situated to modulate the efficacy of the cortico-striatal synaptic link (27). Activity at these dopaminergic synapses could therefore serve to modulate cortico-striatal transmission (8,81).

The present hypothesis is based entirely on the nigrostriatal system, primarily because detailed data is not available on interactions between dopaminergic afferents and other coincident inputs to the mesolimbic and mesocortical dopamine systems. Thus, the nigrostriatal system is employed in the present hypothesis as a model. The suggestions of this hypothesis could apply equally to other dopamine terminal regions.

## DENERVATION SUPERSENSITIVITY

This returns us to the original issue; that is: How can chronic neuroleptic administration produce alterations that cannot be obtained on an acute basis, either by administration of neuroleptics or dopamine agonists? The present hypothesis is that these changes occur in the glutamatergic cortico-striatal system, and specifically, that these changes take the form of altered postjunctional sensitivity at the glutamatergic cortico-striatal synapse.

How can this occur, as neuroleptics are dopamine antagonists and produce dopaminergic supersensitivity? There is, in fact, a phenomenon which is well-established in the literature that could account for such a change. Numerous studies have shown that peripheral denervation supersensitivity is of two types: prejunctional and postjunctional. Prejunctional supersensitivity is due to the loss of presynaptic neurotransmitter reuptake, and is specific for the denervated transmitter system. The more interesting and more profound type of supersensitivity is postjunctional. Postjunctional supersensitivity is due to a proliferation of postsynaptic receptor molecules (and possibly also to changes in the properties of membranes). What is not commonly recognized is that postsynaptic supersensitivity is highly nonspecific (23, 24, 51). For example, a classic experiment by Hudgins and Fleming (43) examined the contractile responses of rabbit aortic strips subjected to chronic reserpine treatment to deplete presynaptic norepinephrine. As expected, supersensitivity to norepinephrine was found. In addition, the aortic strips became supersensitive to acetylcholine and to potassium. There was no alteration in the response to histamine, serotonin, or angiotensin, but the sensitivity to tyramine was decreased. Many other studies have also found that postjunctional supersensitivity in peripheral excitable tissues is nonspecific; in fact, in some cases changes in responsivity to secondary agents is greater in degree than the altered response to the agonist which is subject to the primary denervation (23,24). Denervation supersensitivity is nonspecific in the sense that responsivity to multiple transmitters is altered; nevertheless, the changes are not indiscriminate or homogenous. The response to each agent shows a different yet predictable degree of change (24). No examples of nonspecific denervation supersensitivity have been documented for the central nervous system.

It is not entirely surprising that denervation supersensitivity would be nonspecific, in that the signal for receptor proliferation would have to be intracellular, rather than localized to the synapse itself. Denervation supersensitivity of muscle involves a spread of acetylcholine receptor, including de novo synthesis of acetylcholine receptor molecules (3,7). The signal which initiates receptor proliferation would presumably be coupled to electrical excitability of the cell,

and would therefore not be restricted to the denervated transmitter only, but to all similar transmitters involved in regulating cellular excitability. That is, denervated excitable cells appear to undergo a generalized homeostatic response which tends to correct any internal abnormality caused by denervation or altered external stimulation. It is probable that the nonspecificity of denervation supersensitivity is due to a number of mechanisms, including changes in numbers of more than one kind of receptor as well as to changes in membrane proteins other than receptors which are involved in regulating the resting membrane potential (23,65).

## HYPOTHESIS

Thus, the following precise hypothesis is suggested (Fig. 1A–C):

1) Psychosis is related to cortico-striatal excitatory transmission. Exactly how is not within the scope of the current hypothesis, but the current hypothesis implies that the cortico-striatal system is a crucial link in the manifestation of psychosis (see next section).

2) Acute neuroleptic administration blocks dopamine receptors. Direct blockade of these synapses may cause some sedation, but not the changes in transmission which are responsible for amelioration of psychosis.

3) After long-term administration of neuroleptics, dopaminergic supersensitivity counteracts the dopamine-blocking effect of neuroleptics. This ameliorates some of the acute sedative effects of neuroleptics.

4) Concomitantly, excitatory glutamate synapses become subsensitive, dampening cortico-striatal transmission and producing the antipsychotic effect.

## CAVEATS

First of all, it should be emphasized that this does not necessarily mean that psychosis is directly caused by overactivity of the cortico-striatal pathway. Others have previously suggested a role of the cortico-striatal glutamate system in psychosis (47,48). Several specific hypotheses about the origin of psychosis could, however, be consistent with the present hypothesis. For example, psychosis could be caused by an abnormality in the substantia nigra, but its expression could be stimulated by an overactive striato-nigral system. Or, psychosis could be generated entirely within the cortex, but its expression might be ameliorated through damping of cortico-striatal transmission. The present hypothesis does imply that the cortico-striatal pathway plays a crucial role in the expression of psychotic symptoms.

It is also probable that much of the sedative effect of neuroleptics is due to other mechanisms, in particular, antagonism of $\alpha$-adrenergic receptors (63,64). The present hypothesis suggests, however, that there is a tranquilizing or nonspecific sedative component of the acute effect that is caused directly by dopaminergic blockade. This initial effect may dampen some of the manifestations of psychosis. With chronic neuroleptic administration, this relatively nonspecific effect is suggested to disappear or coalesce into the antipsychotic effect.

The first objection to this hypothesis which is likely to come to mind is that the dopaminergic and glutamatergic synapses are located on the same neurons. Thus, why would alterations in glutamate synapses be any more likely to alleviate psychosis than alterations in the dopamine synapses? The answer is that the dopamine system is a relatively diffuse modulatory system, which tends to regulate overall activity of the striato-nigral output neurons. Although there is some degree of patterning or compartmentalization of the nigrostriatal dopaminergic system (34), this system is extensively branched, so that there is a considerable overlap between the areas of striatum innervated by individual nigral neurons (61,76). In contrast, the cortico-striatal system is intricately patterned, and the activity of this system occurs in concert with patterns of cortical activity. Thus, abnormal transmission in this system may produce disordered thought patterns, hallucinations, delusions, and other psychotic symptoms, or these symptoms may originate elsewhere but are facilitated by cortico-striatal transmission. Direct dopaminergic blockade may produce a uniform modulation of cortico-striatal activity, whereas desensitizing the glutamate system may dampen the specific symptoms of psychosis without impairing the overall functioning of the system. In other words, the acute neuroleptic effect involves the whole population of striatal neurons, whereas chronic adjustments involve the cortico-striatal connections, not all of which are active at the same time. It is also conceivable that certain cortico-striatal links which are particularly hyperactive are the most susceptible to dampening by dopamine blockade.

The overall situation is undoubtedly more complex than is presented here, and particularly in situations where more than one of the striatal innervations is altered. The dopaminergic target cells receive other innervations than the glutamate- and dopamine-mediated inputs to the dendritic spines that have been so far discussed. Of particular significance are cholinergic striatal interneurons, which are also thought to synapse on dendrites of the same dopamine target cells. There is evidence of reciprocal interactions between striatal cholinergic and dopaminergic systems (52). Chronic neuroleptic treatment alters the behavioral response to cholinergic drugs (31,54). Chronic neuroleptics have also been reported to alter responses to cholecystokinin (20), a GABA agonist (26) and adrenergic agents (22). Responsivity to serotonergic drugs is unchanged (16,45). Therefore, although glutamate-mediated synapses are the synapses most closely associated with dopaminergic terminals, it is also possible that chronic neuroleptics alter the efficacy of other kinds of striatal synapses, and that the antipsychotic effect of neuroleptics could be mediated at least in part by changes in other synapses located on these same dopamine-target cells.

Bouyer and co-workers (6) also observed that a minority of the nigro-striatal and cortico-striatal terminals come into direct contact with each other. No synaptic contacts between the two types of afferents were seen, but there is the possibility of nonsynaptic communication between the two types of terminals. In addition, there is evidence that glutamate stimulates striatal dopamine release and that dopamine inhibits glutamate release and reuptake (59,66); thus, interactions between striatal dopamine and glutamate systems other then adjustments in synaptic efficacy probably exist.

Also, the conclusion that dopamine is "inhibitory" is almost certainly an oversimplification. Dopaminergic deafferentation does increase the spontaneous firing of striatal neurons (70). Most of the published data suggest that dopamine inhibits cortically evoked striatal activity (8,81). Dopamine does, however, have excitatory effects under some conditions (15,38). A completely precise formulation of the current hypothesis will therefore have to await additional data on the nature of the effect of dopamine on striatal neurons. Thus, although changes in cortico-striatal and nigro-striatal responses generally appear to be opposite in

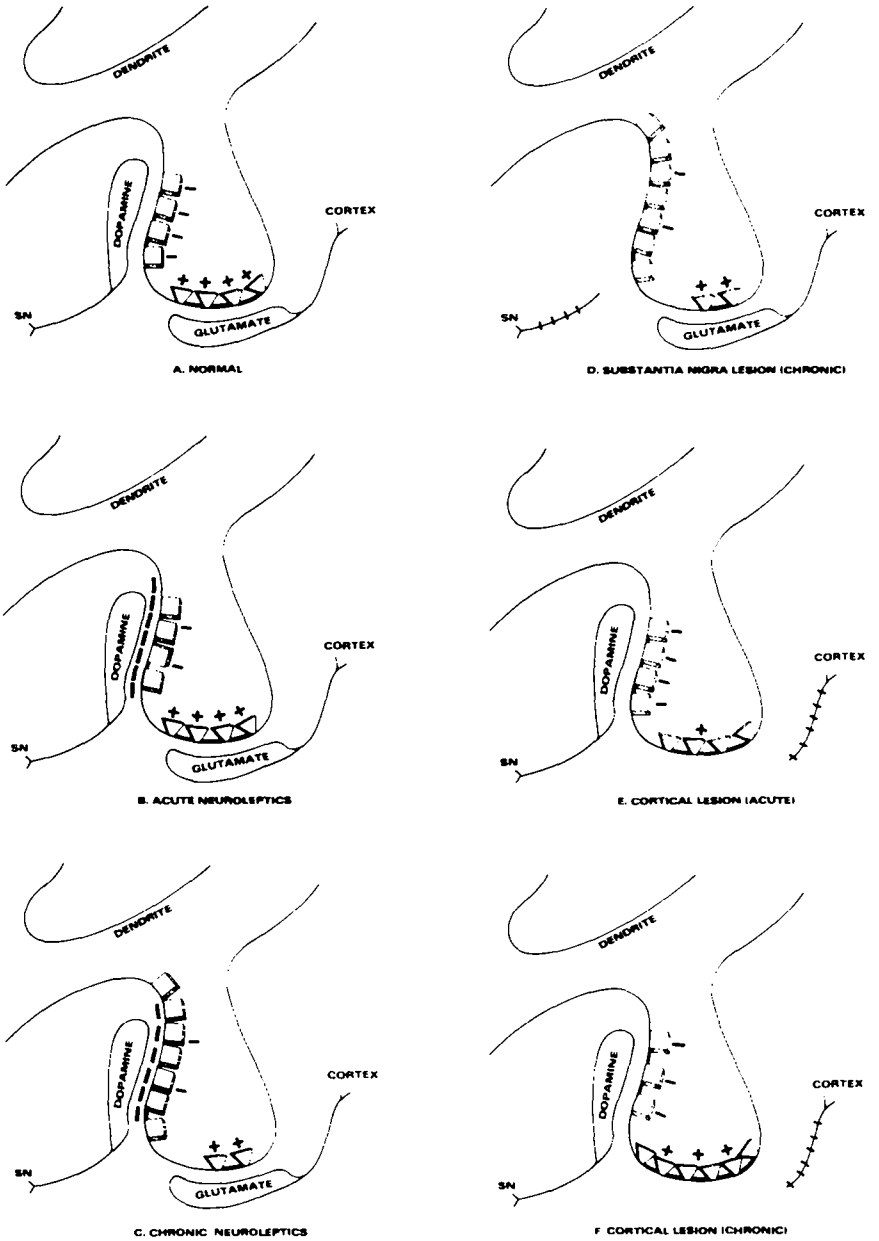


FIG. 1. Symbolic representation of the current hypothesis, based on a model of the relationship between afferents to the striatal output neurons developed by Bouyer *et al.* (6) and Freund *et al.* (27). (A) Under normal conditions, dendrites of the striato-nigral projection neurons receive a dopamine-mediated input from the substantia nigra and a glutamate-mediated input from the cerebral cortex. The dopaminergic synapses are predominantly located on the necks of dendritic spines, while the glutamate-mediated synapses are predominantly on the heads of the same spines. The relative number of dopamine receptors is illustrated by the number of square symbols, and glutamate receptors are represented by triangles. Postsynaptic excitation is represented as "+" symbols and inhibition as "−" symbols; four symbols represents a normal number of receptors or a normal amount of postsynaptic effect. The presence of a pharmacological antagonist is represented by the presence of dashes in the synaptic cleft. As the present hypothesis does not favor any particular theory of the cause of psychosis, no distinction is made between normal and psychotic conditions. (B) *Acute neuroleptics:* When the dopaminergic input is reduced by administration of a neuroleptic drug, the level of dopamine-mediated inhibitory input is decreased and the glutamate-mediated input remains constant. The cell then experiences an overall excess of excitation. (C) *Chronic neuroleptics:* If neuroleptics are present chronically the cell responds to this excess excitation by increasing the inhibitory input (by dopaminergic supersensitivity) and decreasing the excitatory input (by glutamatergic subsensitivity). Additional alterations in membrane proteins and other receptors also may occur. This normalizes the overall excitatory state of the cell, but under this condition sensitivity to cortico-striatal input is reduced. (D) *Substantia nigra lesions (chronic):* Removal of the dopaminergic innervation by substantia nigra lesions produces changes analogous to those which are produced by chronic neuroleptics. (E) *Cortical lesions–Acute effect:* Immediately after a cortical lesion, the excitatory input to the cell is reduced, and the cell experiences an excess of inhibition. (F) *Cortical lesions–Chronic effect:* At some time after the cortical lesions, the cell responds to the excess of inhibition by attempting to increase excitatory input (by glutamateric supersensitivity) and concomitantly by decreasing the inhibitory input (by dopaminergic subsensitivity). These changes normalize the overall excitatory state of the cell.

direction, it would not be surprising to find some other forms of interaction between striatal dopaminergic and glutamate systems. There are some experiments which suggest functional interactions between cortico-striatal and nigro-striatal afferents opposite to that proposed here (29,32).

### SPECIFIC DATA SUPPORTING THE HYPOTHESIS

There are some specific data which can be interpreted to support this hypotheses. The experiment which most closely approximates a specific test was reported by Roberts and colleagues (67). These investigators found that lesioning of the substantia nigra with 6-hydroxydopamine to destroy the nigro-striatal pathway decreased striatal glutamate receptors by about 40%. The explanation that was offered for this finding was that some of the cortico-striatal synapses are located presynaptically, on dopaminergic terminals. Ultrastructural data suggests, however, that the cortico-striatal synapses are located on dendritic spines, not on dopaminergic terminals (6). An at least equally plausible explanation of these data, therefore, is that dopaminergic denervation of the striatum induced by substantia nigra lesions causes subsensitivity of glutamate receptors concomitant with supersensitivity of dopamine receptors (Fig. 1D).

Data reported by Schultz and Ungerstedt (70) may provide a physiological corollary of these changes in receptors. Striatal cells which responded to cortical stimulation were selected. These cells were found to have very low spontaneous discharge rates (about one impulse per 25 seconds). This impulse rate was increased seven-fold three days after a substantia nigra lesion, but firing rates reverted to baseline levels one year after the lesion. These investigators considered the possibility that the reversion in discharge rates was due to development of dopaminergic supersensitivity, even though the remaining dopamine was present in "exceedingly small amounts" (70). These investigators also stated that "It is conceivable that the activities of other neuronal systems afferent or intrinsic to the striatum are changed to compensate the effects of the lesioned dopamine input" (70). A decrease in glutamate binding sites after substantia nigra lesions such as that reported by Roberts and colleagues (67) could reduce the excitatory input to these cells and might have contributed to the reductions in firing rates observed by Schultz and Ungerstedt (70).

A corollary of the suggestion that dopaminergic supersensitivity causes excitatory amino acid subsensitivity is that denervation of the cortico-striatal pathway will cause an increase in glutamate receptors (supersensitivity) and a decrease in dopamine receptors (subsensitivity). Decortication increases striatal glutamate binding (67) and increases the sensitivity of striatal neurons to iontophoretically-applied glutamate (56). Several studies have also reported that, in fact, decreases in striatal dopamine receptors occur following decortication, but all have interpreted their data in other ways. For example, one study (71) found that decortication decreased striatal binding of tritiated haloperidol (a measure of the "D2" type of dopamine receptors). Substantial decreases (about 40%) were found by six days after the lesion. A maximum decrease of 50% was observed after 18 days, after which there was a slight increase. There were no changes in dopamine-stimulated adenylate cyclase activity (71) and, interestingly, dopamine-stimulated adenylate cyclase activity is not altered by chronic haloperidol either (82). Several other experiments have also found decreases in striatal spiroperidol and sulpiride binding (both measures of D2 dopamine receptors) after decortication (28, 68, 80). These studies have concluded that some striatal D2 receptors are located on cortico-striatal afferents, because removal of these afferents decreased these receptors. Again, later studies found that the dopaminergic afferents to the striatum do not synapse with axon terminals (6, 27, 50, 73). An equally plausible explanation of these results, therefore, is that cortical lesions cause dopaminergic subsensitivity in concert with a supersensitivity of the excitatory amino acid receptors which are postsynaptic to the cortico-striatal afferents (Fig. 1E,F).

A recent study by Paturle and co-workers (62) confirmed that cortical lesions decreased the density of dopamine receptors (spiroperidol binding sites) in the striatum, but found that combined lesions of the substantia nigra and cortex caused an increase in binding sites similar to that produced by substantia nigra lesions alone. These results are essentially identical to earlier results reported by Rosenblatt and co-workers (68), in which the effects of combined cortical ablation and chronic haloperidol treatment were employed. Both studies found that although cortical lesions alone decreased striatal dopamine receptors, the levels of binding after SN lesions (or chronic haloperidol) were similar to those observed when cortical lesions and SN lesions (or chronic haloperidol) were combined. Under the combined lesion condition, it may be that both the dopamine and glutamate receptors become supersensitive. This interpretation would be consistent with the conclusion that dopamine is neither strictly inhibitory nor exictatory, but instead serves as a modulatory influence on cortico-striatal inputs. Nevertheless, the findings of Paturle *et al.* (62) and Rosenblatt *et al.* (68) are paradoxical for previous interpretations. For example, if some of the dopamine receptors were on the cortico-striatal afferents, they should have been removed by cortical lesions whether or not there had also been a nigrostriatal system lesion. Thus, if some dopamine receptors are located on the cortico-striatal afferents, cortical lesions should invariably reduce dopamine receptors. The latter study (62) interpreted the decrease in dopamine receptors after cortical lesions in terms of transsynaptic degeneration, since by the time of their experiment axo-axonal synapses between dopaminergic and cortico-striatal afferents were known to be rare (6). A transsynaptic degeneration explanation (36) is untenable in this case, because combined cortico-striatal and nigro-striatal denervation would be expected to be even more likely to cause transsynaptic degeneration than either denervation alone. The most parsimonious explanation of the reductions in striatal dopamine receptors following cortical lesions is, therefore, in terms of nonspecific postjunctional denervation sensitivity changes.

There is some evidence that chronic administration of haloperidol alters the behavioral responsivity of animals to glutamatergic agents (Freed, Cannon-Spoor, and Rodgers, submitted). In normal, untreated animals the glutamate agonist quisqualic acid (administered intracerebroventricularly) and the antagonist GDEE (administered intraperitoneally) both decrease behavioral activity. Behavioral effects of both agents were measured in animals that had chronically received haloperidol or vehicle and were then withdrawn for four days, so that no haloperidol was present during testing. Behavioral responsivity to both quisqualic acid and GDEE was decreased by chronic haloperidol treatment (Fig. 2). For both compounds, the greatest differences were observed at the lowest dosages which caused substantial behavioral effects in normal animals. These data are consistent with the

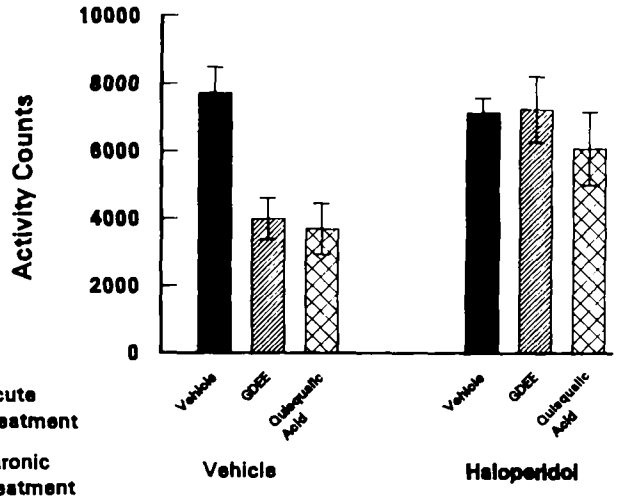


FIG. 2. Total horizontal activity counts in 30 min (means±S.E.M.) as a function of acute treatment with vehicle, GDEE, or quisqualic acid following withdrawal from chronic haloperidol or vehicle administration. Mice received either haloperidol or vehicle for 28 days, followed by withdrawal for four days. Animals were then treated acutely with GDEE 480 mg/kg IP or vehicle or, in a separate experiment, with quisqualic acid 0.03 $\mu$g into the lateral cerebral ventricle 10 min prior to testing. Only the dosages for which the largest differences occurred are shown. Data have been rearranged from Freed, Cannon-Spoor and Rodgers, submitted.

hypothesis that chronic neuroleptic administration induces subsensitivity of striatal glutamate receptors.

## FURTHER CONSIDERATIONS AND HYPOTHESIS TESTING

If one considers the remarkable ability of the brain to adapt to conditions imposed by chronic drug administration, it is indeed remarkable that psychological and neurological abnormalities can be corrected by chronic drug administration in any brain system. For example, a number of chronic pain syndromes clearly respond to opiates. The beneficial effect of opiates for pain, however, is diminished markedly by the development of tolerance after chronic administration. It is also interesting that a therapeutic latency has been observed for other psychopharmacological agents, most notably for the tricyclic antidepressants (4). On the other hand, some agents, such as anticonvulsants, can be effective both acutely and chronically. It is tempting to speculate that the therapeutic latency phenomenon is ubiquitious for drugs which act through postsynaptic effects on neurons. In order to obtain a chronic change in CNS function through drugs which exert a postsynaptic effect on neurons, it may always be necessary to influence a system other than that which requires alteration, but closely juxtaposed on the same neurons.

The present paper has emphasized the nigro-striatal dopamine system, primarily because the relationship between dopamine terminals and other afferents has not been extensively studied for other systems. It may be that similar relationships exist in other dopamine terminal areas, although at the present time insufficient information is available. Clozapine, a drug which is thought to have minimal activity in the nigro-striatal dopamine system (9,85), has antipsychotic activity (77). This may indicate that dopamine terminal areas other than the striatum are important for antipsychotic activity. Nevertheless, changes in glutamatergic synapses associated with nigrostriatal dopaminergic synapses could serve as a model for changes that take place in other brain regions.

The validity of the present hypothesis can be tested primarily by studies of quisqualate ($AA_2$) receptors in animals and in human patients exposed to neuroleptics. The simplest test would involve measurements of $AA_2$ receptors following chronic neuroleptic administration. Several weeks of neuroleptic administration would be predicted to decrease $AA_2$ receptors in the dopamine-terminal regions, but not in other brain areas (such as hippocampus). As is the case for dopamine receptors, changes in glutamate receptors induced by neuroleptics should be correlated with clinical potency. In human post-mortem brain tissue, the current hypothesis would make a similar prediction; that is, $AA_2$ receptor density should change as a function of chronic neuroleptic administration. This change should be correlated with the potency of these drugs in blocking dopamine D2 receptors, rather then with any effects on amino acid receptors. This change in amino acid receptors should occur in dopamine terminal areas (such as nucleus accumbens and corpus striatum), but not in other brain areas (such as hippocampus). Changes in amino acid receptors in neuroleptic-free schizophrenic patients may also be present, in striatum or in other brain regions (46). It may eventually be possible to test the current hypothesis by means of PET scan studies or other techniques which would allow for repeated in vivo measurements of amino acid receptors in a single patient. In this way, it might be possible to look for temporal relationships between changes in amino acid receptors and the emergence of antipsychotic effects after chronic neuroleptic administration.

The present hypothesis does not necessarily suggest a role for glutamate agonists or antagonists as antipsychotic drugs. Glutamate agonists might desensitize glutamate receptors when administered chronically. Nevertheless, it is doubtful that administration of such drugs would be useful. First of all, glutamate receptors are found everywhere in the brain, not only in the striatum. More importantly, glutamate agonists would be predicted to exacerbate psychosis when administered acutely. This prediction would be difficult to test experimentally; in part because such an experiment would be dangerous and probably unethical, and also because no $AA_2$ agonists which cross the blood-brain barrier are currently known.

Antagonists such as GDEE might alleviate psychosis acutely, but when administered chronically glutamate antagonists would be expected to cause glutamate supersensitivity. Drug withdrawal would then be predicted to exacerbate psychosis or induce a "supersensitivity psychosis" when sensitized receptor sites are unmasked. Nevertheless, there is a possibility that agents which alter glutamate receptors could be employed acutely or as adjuncts to current neuroleptic therapy. On the other hand, the present hypothesis predicts that neuroleptic withdrawal would produce increased activation and arousal, by unmasking sensitized dopamine receptors. Since the glutamate receptors would not be affected, however, there would not be a supersensitivity psychosis per se after neuroleptic withdrawal. In fact, evidence for the existence of a supersensitivity psychosis is controversial (30,54) and most of the clinical phenomena seen during neuroleptic withdrawal appear to be related to cholinergic properties of neuroleptics (30,54).

SUMMARY

It is the contention of this hypothesis, therefore, that both the acute and chronic effects of neuroleptics are indeed due to antagonism of dopamine receptors. On the other hand, only acute effects, possibly including some components of nonspecific sedation, are suggested to be due directly to reduced efficacy of transmission at dopaminergic synapses. When neuroleptics are administered chronically, dopamine supersensitivity would tend to overcome the neuroleptic effect and partially restore the efficacy of transmission at dopaminergic synapses toward normal levels. The antipsychotic effect is suggested to be due to secondary changes in other receptors related to the nonspecific nature of postjunctional denervation supersensitivity (24). In particular, glutamate-mediated synapses occuppied by terminals of cortico-striatal afferents are closely juxtaposed with dopaminergic synapses, on the same dendrites and dendritic spines (6,27). Dopamine is thought to be predominantly inhibitory in the striatum, while glutamate is excitatory. Thus changes in glutamate synapses, probably in the direction of subsensitivity, are suggested to mediate the antipsychotic effect which occurs after chronic administration of neuroleptic drugs.

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