Abstract

It is suggested that the antidopaminergic effects of neuroleptics are not directly responsible for the antipsychotic effect but, rather, that the antipsychotic effect is related to secondary changes in the efficacy of transmission at corticostriatal excitatory synapses. Arguments are presented in support of the following: (1) acute dopaminergic antagonism produces a relatively nonspecific sedation or deactivation, but most of the amelioration of psychosis develops slowly; (2) the development of dopaminergic supersensitivity is responsible for tolerance to the sedative effects of neuroleptics; and (3) excitatory synapses of the corticostriatal pathway, mediated by glutamic acid, are located on the same dendritic spines as the striatal dopaminergic synapses. Concomitant with the development of dopaminergic supersensitivity, these glutamate synapses become subsensitive. The glutamatergic subsensitivity is a result of the nonspecific nature of postsynaptic denervation supersensitivity. It is suggested that subsensitivity of striatal glutamate-mediated synapses is directly responsible for the antipsychotic effect of neuroleptic drugs. In support of this hypothesis, chronic neuroleptic administration was found to decrease the behavioral responsiveness of mice to the glutamate agonist, quisqualic acid, and to the antagonist, glutamic acid diethyl ester.

One of the greatest paradoxes of psychopharmacology is the latency of the antipsychotic effects of neuroleptics. Neuroleptic drugs are thought to act primarily through direct antagonism of dopamine receptors. Although the onset of dopaminergic blockade occurs rapidly following administration of neuroleptics, the antipsychotic effect slowly emerges over a period of weeks or even months (Casey et al. 1960; Curry 1974; Spohn et al. 1977; Johnstone et al. 1978). In the present article, recent findings on the ultrastructure of dopaminergic synapses in the striatum will be described and related to a classic series of experiments on the pharmacology of denervation supersensitivity in an attempt to resolve this paradox.

Chronic neuroleptic administration does, indeed, produce a number of slowly developing alterations in the functioning of the brain's dopaminergic systems. Foremost among these is the development of dopaminergic supersensitivity. A number of studies have shown that chronic administration of neuroleptics increases the $B_{\text{max}}$ for binding of various putative dopamine-receptor agonists and antagonists. For example, Burt et al. (1977) demonstrated an increase in the $B_{\text{max}}$ for binding of haloperidol to striatal membranes following chronic haloperidol administration (also cf. Theodorou et al. 1981a). Behavioral supersensitivity to dopamine agonists has also been observed after withdrawal from chronic neuroleptics (Tarsy and Baldessarini 1974; Von Voigtlander et al. 1975; Christensen et al. 1976). An increase in the sensitivity of dopamine receptors alone cannot, however, account for the therapeu-
tic latency of neuroleptics, because an increase in dopamine receptor sensitivity would be expected merely to counteract the acute effect of dopamine receptor blockade. Because neuroleptic drugs occupy or block some of the available dopamine receptors, increases in the total number of receptors would be equivalent to a lessening of the neuroleptic dosage. Other explanations of therapeutic latency have also focused on chronic changes in the efficacy of transmission in dopaminergic systems (for example, conduction block; cf. Bunney et al. 1980). It is not clear, though, how additional increases or decreases in dopaminergic transmission, resulting from mechanisms such as conduction block, would produce effects dissimilar to those produced by acute receptor blockade. Others have also concluded 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” (Johnstone et al. 1978, p. 851).

This therapeutic latency is dissimilar to the tolerance effects seen after chronic administration of many other drugs. For example, chronic administration of opiates results in an initial euphoria and analgesia. Tolerance develops to both effects, so that increasing dosages are required to achieve the same result. In contrast to the effects produced by neuroleptics, there is no pronounced state produced by chronic opiate administration that is qualitatively unlike the effects observed from acute administration. Neuroleptics induce sedation or deactivation after acute administration. As is the case with opiates, tolerance to this sedation is seen after chronic administration (Rupniak et al. 1983; Baldessarini 1985). Unlike opiates, however, chronic neuroleptics induce an antipsychotic effect that appears primarily after chronic administration.

**Denervation Supersensitivity**

Postsynaptic denervation supersensitivity is unquestionably one of the major forms of adaptional plasticity that occurs in the nervous system. Moreover, the time course for the development of denervation supersensitivity induced by neuroleptics roughly parallels the time course for the development of antipsychotic effects. Is there, then, any other way in which denervation supersensitivity could account for the therapeutic latency phenomenon?

Denervation supersensitivity involves a proliferation of postsynaptic receptor molecules. These molecules are, of course, synthesized inside the cell, and ultimately transported to and incorporated into synaptic membranes. The signal for the development of denervation supersensitivity must, therefore, be an internal signal rather than a signal that is received and processed entirely within the synapse (cf. Axelsson and Thesleff 1959; Brookes and Hall 1975).

A single neuron may have receptors for several neurotransmitter substances. Although different neurotransmitters may be linked to different ion channels or secondary messenger systems, the synaptic input to each cell is primarily linked to the regulation of the overall excitation of the cell. It has therefore been suggested that denervation supersensitivity, as it is commonly observed, is but a special case of the homeostatic functioning of neurons that serves to maintain an overall stable level of activity. More generally, neurons may alter their overall level of excitatory and inhibitory inputs by changing various receptor molecules and membrane proteins in order to maintain a stable level of activity (cf. Robbins 1974; Fleming 1976).

In fact, there is ample evidence that this is the case, in other words, denervation supersensitivity is nonspecific. In most experiments, wherever an excitable cell is sensitive to more than one neurotransmitter, removal of one innervation results in changes in the sensitivity of that cell to more than one of the agents to which that cell is sensitive (Trendelenburg and Weiner 1962; Westfall 1970; Fleming et al. 1973; Langer 1975; Fleming 1976). For example, in one classic study by Hudgins and Fleming (1966), the effects of chronic reserpine treatment on sensitivity of aortic strips were measured. The tissues became supersensitive to norepinephrine, as expected. In addition, supersensitivity to acetylcholine and potassium was observed. There was no change in the response to serotonin, histamine, and angiotensin, but the tissues became subsensitive to tyramine. Many other experiments have observed similar phenomena using a variety of tissues and denervation techniques (cf. Fleming et al. 1973). In general, denervation supersensitivity is nonspecific, although not indiscriminate or homogeneous. That is, specific and predictable alterations are seen for each of the molecules to which a target cell is receptive.

**Hypothesis: Part I**

Thus, the literature on peripheral
postjunctional denervation supersensitivity suggests that changes in responsivity of a cell brought about by denervation are not restricted to a single agonist. It has been repeatedly confirmed that denervation induces changes in responses to many of the agents to which a target cell can respond, and that these changes vary in degree and sometimes also in direction—that is, supersensitivity or subsensitivity. Moreover, changes in responsivity to ions and changes in resting membrane potential have been observed, suggesting that membrane proteins other than neurotransmitter receptors may also be altered (Robbins 1974; Fleming 1976). It is therefore suggested that dopaminergic supersensitivity, induced by chemical denervation (as in 6-hydroxydopamine lesions of the substantia nigra) or by pharmacological denervation (induced by chronic administration of haloperidol), will be accompanied by changes in the sensitivity of the striatal target cells to at least one other agent in addition to dopamine.

**Anatomy of Striatal Afferentation**

Where would we look for this secondary alteration? First of all, the synapse most likely to be changed concomitantly with a change in the efficacy of dopaminergic synapses would be that which is most closely coincident with the dopaminergic synapses. Recently, the location of dopaminergic synapses and other striatal synapses has been described at the ultrastructural level (Kitai et al. 1976; Bouyer et al. 1984; Freund et al. 1984). A second major input to the striatum, in addition to the dopaminergic innervation, is the corticostriatal pathway (Webster 1965; Kemp and Powell 1970), which is mediated by the excitatory amino acid neurotransmitter glutamic acid (McGeer et al. 1977; Young and Bradford 1986). In recent ultrastructural studies (Bouyer et al. 1984; Freund et al. 1984), dopaminergic synapses were located by tyrosine hydroxylase immunocytochemistry. Corticostriatal afferents were located by degeneration following cortical lesions. The dopaminergic nigrostriatal afferents and the excitatory corticostriatal afferents were both found to synapse not only on the same nigral projection neurons but also on the same class of dendrites or dendritic spines. Corticostriatal synapses tended to be found on the heads of the dendritic spines, while the dopaminergic synapses were found on the necks of the same spines (Bouyer et al. 1984; Freund et al. 1984).

The corticostriatal pathway is known to be excitatory and is mediated by the putative amino acid neurotransmitter glutamic acid (McGeer et al. 1977; Young and Bradford 1986). There are thought to be three types of excitatory amino acid receptors, distinguished by their responsivity to the three agonists N-methyl-d-aspartate, quisqualic acid, and kainic acid (Watkins and Evans 1981). The receptors for the corticostriatal afferents appear to be of the second quisqualate-prefering type, because striatal potentials evoked by cortical stimulation can be effectively blocked by glutamic acid diethyl ester (Spencer 1976), a partially specific quisqualate antagonist (Watkins and Evans 1981). Antagonists of the N-methyl-d-aspartate type of receptor do not block cortically evoked striatal potentials (Herrling et al. 1983).

**Hypothesis: Part II**

Thus, all information needed to suggest a specific hypothesis on the action of neuroleptics is available (Freed, in press). It is suggested that (1) neuroleptics block dopamine receptors upon acute administration, producing a relatively nonspecific sedation or deactivation; (2) chronic administration of neuroleptics causes the development of supersensitivity to dopamine; (3) this dopaminergic supersensitivity counteracts the dopamine antagonism produced by the neuroleptics and is responsible for tolerance to some of the sedative effects of neuroleptics; (4) concurrent with the supersensitivity of dopamine receptors, subsensitivity of nearby quisqualate-prefering glutamate receptors also develops; and (5) the subsensitivity of these glutamate receptors is responsible for the antipsychotic effect (figure 1).

**Implications**

First, it must be emphasized that this hypothesis does not make a clear prediction about the brain abnormalities that can give rise to psychosis. The type of abnormality that would be most readily accommodated by the current hypothesis would be an irregular or intermittent overactivity of corticostriatal transmission. Intermittent overactivity is not effective in producing receptor desensitization. Thus, if such an overactivity were intermittent, it would not decrease the sensitivity of corticostriatal synapses on its own, but could be dampened by subsensitivity at these synapses induced by other means. It is difficult, however, to imagine an abnormality that is present only intermittently.
Overactivity of the corticostriatal pathway, or of some elements of the corticostriatal pathway, could also originate elsewhere in the brain. The corticostriatal pathway might be only a final common pathway that is susceptible to pharmacological manipulation.

On the other hand, it might equally well be imagined that the efficacy of transmission in the corticostriatal pathway is chronically and continuously impaired. This might induce supersensitivity of striatal glutamatergic synapses. Then, when activity of all or part of the corticostriatal afferents was intermittently normal, perhaps during stress or activation, psychotic symptoms would occur.

Finally, it is conceivable that psychosis originates elsewhere. For example, an abnormality occurring in the substantia nigra, the striatum, or any other area that connects with these systems might be implicated. It may be simply that the location of the dopaminergic and glutamatergic synapses on the primary striatal output neurons is the most readily manipulable link in a chain of obscure events and that psychosis can originate as an abnormality in one or more of the components of this system.

One obvious objection to the current hypothesis is that the dopaminergic and glutamatergic synapses are very closely associated. Why, therefore, would changes in the glutamate synapses be any more likely to influence psychosis than would changes in efficacy of the dopaminergic synapses? The difference between the two systems is one of patterning. While the dopamine system is a relatively diffuse or disseminated modulatory system, which influences all or large parts of the striatum simultaneously, the corticostriatal system is intricately patterned. A single dopaminergic neuron in the substantia nigra may innervate a very large number of striatal neurons (Andén et al. 1966; Hokfelt and Ungerstedt 1969). On the other hand, the corticostriatal system is topographically mapped, with specific parts of the cortex mapped onto specific parts of the striatum (Webster 1965; Kemp and Powell 1970; Goldman and Nauta 1977). Thus, subsensitivity of the entire corticostriatal system might be induced by chronic neuroleptic administration. This could serve to dampen irregularities of transmission in the corticostriatal system, while leaving intact the overall functioning of the striatonigral projection.

**Supporting Evidence**

Roberts et al (1982) found that lesions of the cerebral cortex produced an increase in striatal glutamate receptors, consistent with the presence of striatal denervation supersensitivity to glutamate. When the substantia nigra was lesioned by stereotaxic administration of 6-hydroxydopamine, a manipulation known to produce supersensitivity of dopamine recep-
tors, striatal glutamate receptors were decreased by about 40 percent. One possible explanation of these data is that the dopaminergic denervation of the striatum caused a subsensitivity of glutamate receptors concomitant with supersensitivity of dopamine receptors. A possible electrophysiological corollary of this change in receptors has been described by Schultz and Ungerstedt (1978).

Conversely, the current hypothesis would predict that cortical lesions should not only cause increases in glutamate receptors (Roberts et al. 1982) but also cause decreases in dopamine receptors. Several experiments have, in fact, produced findings of decreased dopamine receptors in the striatum following decortication (Garau et al. 1978; Schwarcz et al. 1978; Jenner and Marsden 1981; Theodorou et al. 1981b; Parent et al. 1987). Most commonly, these changes have been interpreted as suggesting that some dopamine receptors are located on the corticostratal afferents. Ultrastructural studies have not, however, found that dopaminergic synapses contact axon terminals in the striatum (Kitai et al. 1976; Bouyer et al. 1984; Freund et al. 1984). An at least equally plausible interpretation, therefore, is that these changes represent nonspecific subsensitivity of striatal dopamine receptors which develops concomitant with supersensitivity of striatal glutamate receptors.

In an earlier version of this hypothesis (Freed et al. 1980), which was developed before the specific anatomy of nigrostriatal and corticostriatal synapses was known, it was thought that the synapses most closely convergent with dopamine synapses would contain γ-aminobutyric acid

Figure 2. Effects of acute and chronic neuroleptic administration on behavioral responsivity to imidazole acetic acid (IMA), an agonist of γ-aminobutyric acid (GABA)

A. ACUTE HALOPERIDOL—CUMULATIVE ACTIVITY

B. CHRONIC HALOPERIDOL—CUMULATIVE ACTIVITY

C. CHRONIC HALOPERIDOL—15 MINUTE INTERVALS

Behavioral activity (counts) is shown as a function of time after administration of 82 mg/kg IMA or vehicle. (a) Effects of IMA on cumulative behavioral activity in animals pretreated with a single injection of haloperidol or vehicle. (b) Effects of IMA on cumulative behavioral activity in animals pretreated chronically for 28 days with haloperidol or vehicle and withdrawn for 3 days. (c) Same data as shown in b for each individual 15-minute period of activity testing.
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Figure 3. Behavioral activity of mice following administration of vehicle, glutamic acid diethyl ester (GDEE) (480 mg/kg i.p.), or quisqualic acid (.03 µg) in the lateral cerebral ventricles

Activity Counts

Chronic Treatment

Acute Treatment

Vehicle

GDEE 480 mg/kg i.p.

Quisqualic Acid 0.03 µg i.c.v.

Mice had previously received haloperidol mixed with their drinking water for 28 days (HAL) or vehicle (VEH) followed by 4 days of withdrawal. Note that both GDEE and quisqualic acid substantially decreased behavioral activity in vehicle-pretreated animals, but not in animals pretreated with haloperidol. The differences in activity scores between VEH and HAL animals were statistically significant for the animals given GDEE or quisqualate (p < 0.01, Scheffe tests), but not for the vehicle-treated mice (p > 2).

(GABA) When animals were chronically administered haloperidol for 28 days followed by 3 days of withdrawal, a marked alteration in the behavioral response to imidazole-4-acetic acid, a postsynaptic GABA agonist, was seen. In haloperidol-treated mice, imidazole-4-acetic acid acted as a powerful stimulant, whereas the same dosage caused sedation in vehicle-treated mice. These changes were most consistent with a subsensitivity to the GABA agonist, as lower dosages of imidazole-4-acetic acid were found to cause slight stimulation in other groups of control animals. Acute administration of haloperidol did not alter the behavioral response to imidazole-4-acetic acid (figure 2).

Electrophysiological studies have shown a mutual antagonism between glutamate-induced excitation and GABA-mediated inhibition in the brain, in that glutamate-induced neuronal excitations can be inhibited by GABA (Curtis and Watkins 1960, Davies and Watkins 1972). In intact synaptic membrane preparations, GABA was found to inhibit glutamate binding allosterically using an equilibrium dialysis binding assay (Michaelis et al. 1974). When the membranes were solubilized, or when other binding assay methods were used, this inhibition could not be detected (Michaelis 1975; Michaelis et al. 1981). It is therefore tempting to speculate that the altered behavioral response to a GABA agonist in mice treated chronically with haloperidol reflects an alteration of glutamate sensitivity induced by chronic exposure to haloperidol. These alterations are also consistent, however, with alterations in GABA receptors in the substantia nigra (Gale 1980).

To test the current hypothesis more specifically, the effects of chronic haloperidol on behavioral responses to the glutamate agonist quisqualic acid and the antagonist l-glutamic acid diethyl ester HCl (GDEE) were investigated (Freed et al. 1988). Mice were chronically given haloperidol or lactic acid vehicle mixed with their drinking water for 4 weeks as described previously (Freed et al. 1980). Haloperidol administration was discontinued and testing was conducted after 4 days, so that haloperidol was not present during testing. Animals were given GDEE (Sigma Chemical Co.) intraperitoneally or quisqualic acid (Sigma) into the lateral cerebral ventricles by a freehand injection technique (Clark et al. 1968) in various dosages. Starting 10 minutes after injection, behavioral activity was measured for 30 minutes using photocell-activated activity monitoring cages.

In normal, untreated animals both GDEE and quisqualic acid tend to decrease behavioral activity. This effect of both agents was markedly diminished by haloperidol withdrawal (figure 3). Haloperidol withdrawal alone (in animals treated acutely with vehicle) caused only a slight and nonsignificant decrease in activity. In animals chronically treated with vehicle, 480 mg/kg GDEE caused a 44 percent decrease in activity and .03 µg quisqualate caused a 48 percent decrease in activity (as compared to acute vehicle treatment). In animals
chronically treated with haloperidol, however, the decrease in activity caused by GDEE was only 6.1 percent, and that caused by quisqualate was only 21 percent. The differences between haloperidol and vehicle-treated animals in activity following administration of either 480 mg/kg GDEE or .03 μg quisqualate were statistically significant ($p < .01$, Scheffe test following significant main effects from analysis of variance). Thus, chronic haloperidol administration decreased the behavioral responsivity of animals both to quisqualic acid and GDEE. Studies of glutamate binding sites in chronic neuroleptic-treated animals are currently in progress.

Conclusion

The current hypothesis deals only with striatal dopaminergic systems, because the ultrastructural relationships between terminals containing dopamine and those containing other neurotransmitters are not known for dopamine terminal areas other than the striatum. Nevertheless, it is suspected that similar relationships would occur in other brain regions. The present hypothesis would predict, for example, that if the antipsychotic effect of neuroleptics primarily occurred in the nucleus accumbens, neuroleptics would be found to produce alterations in nondopaminergic synapses closely associated with the dopaminergic synapses of that brain region.

It is suggested that only some of the acute sedating effects of neuroleptics are directly due to dopaminergic blockade. This relatively nonspecific sedation or deactivation may mask or dampen some of the manifestations of psychosis, but does not produce the primary antipsychotic effect. The specific antipsychotic effect of neuroleptics is suggested to be a secondary effect of chronic dopaminergic antagonism. Specifically, when dopamine receptors are chronically blocked by neuroleptics, the development of dopaminergic supersensitivity tends to alleviate the acute sedation. The striatal dopamine synapses are closely juxtaposed with glutamate synapses; the glutamate synapses are located on the heads of dendritic spines of striatonigral projection neurons, while the dopaminergic synapses tend to be located on the necks of these same dendritic spines (Bouyer et al. 1984; Freund et al. 1984). Concomitant with supersensitivity at these dopaminergic synapses, it is suggested that nonspecific postsynaptic subsensitivity develops at the associated glutamate synapses. It is suggested that this glutamate subsensitivity rather than any change in the dopaminergic system is directly responsible for the antipsychotic effect of neuroleptic drugs.

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