Dopaminergic Mechanisms in Idiopathic and Drug-Induced Psychoses

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Abstract

Stimulant drugs such as cocaine and amphetamine are among the most commonly abused substances by schizophrenic patients. This may be due in part to aspects of the illness and treatment side effects that impel patients to use dopamine agonist drugs. Dopaminergic neural systems have been shown to mediate both stimulant drug effects and schizophrenia. Because of the hypothesized overlap in the pathophysiology of schizophrenia and the neurobiological effects of chronic stimulant use, the potential for serious complication of the primary disease by substance abuse exists. This article reviews the neurobiological mechanisms of behavioral sensitization and neurotoxicity associated with chronic stimulant administration in the context of pathophysiological theories of schizophrenia. Discussion focuses on the potential impact of stimulant use on the disease process as well as the manifest phenomenology and course of schizophrenia.

Substance abuse comorbidity can complicate preexisting major mental disorders in various ways. If severe enough, substance abuse may become the primary problem and require treatment for addiction. It may cause impairment in function and disruption of the life of patients (beyond that which may already exist) necessitating additional supportive measures. Interactions of abused substances with treatment may alter the efficacy of pharmacological agents directed at the primary psychiatric disorder. Substance abuse may change the manifest phenomenology of psychiatric disorders as well as the timing of onset and the course of the illness. It has also been suggested that substance abuse comorbidity may interact with the primary disease at the pathophysiological level and produce persisting and potentially irreversible alterations of neural systems (Robinson and Becker 1986; Bowers 1987; Seiden and Ricaurte 1987). Although these concerns have been raised with regard to various mental disorders, they are particularly relevant to schizophrenia. The epidemic proportions of psychostimulant and hallucinogenic drug use among adolescents and adults combined with the vulnerability of schizophrenic patients to their devastating effects have made this an ominous concern. Since pathophysiological theories of schizophrenia and the pharmacological actions of these substances of abuse involve disturbances of dopamine (DA) neurotransmission, the behavioral effects of psychostimulant abuse by schizophrenic patients are believed to be mediated by DA neural activity.

The aim of this article is to review some of the evidence for DA neural activity in the pathophysiology of idiopathic and substance-induced psychoses and to consider the potential of stimulant drug abuse to influence the nature and course of schizophrenia.

Clinical Studies of Drug-Induced Psychosis

Studies of stimulant-induced psychosis form a cornerstone of the DA hypothesis of schizophrenia.

Reprint requests should be sent to Dr. J.A. Lieberman, Hillside Hospital, P.O. Box 38, Glen Oaks, NY 11004.
(Snyder et al. 1974). It has been well established that "stimulant loading," usually in doses of amphetamine greater than 100 mg within a 72-hour period, produce a psychotic syndrome including delusions, hallucinations, and thought disorder in subjects who do not have a psychotic diathesis (Connell 1958; Angrist and Gershon 1970; Griffith et al. 1972; Bell 1973). This condition spontaneously subsides soon after cessation of stimulant administration or can be reversed by neuroleptic medication (Angrist et al. 1974). In addition, stimulant drugs can provoke or exacerbate psychotic symptoms in schizophrenic patients in small doses that are subpsychotogenic in nonschizophrenic subjects (Lieberman et al. 1987). This acute psychotogenic response in schizophrenic patients is transient and spontaneously subsides within hours or can be reversed with neuroleptic medication. Psychotogenic vulnerability to low-dose stimulants is believed to reflect an enhanced sensitivity to DA stimulation in patients with schizophrenia (Lieberman et al. 1987). This phenomenon appears to be state dependent and occurs during the active or unstable stages of the illness (Janowsky et al. 1973; Lieberman et al. 1984). Thus, schizophrenic patients are not always susceptible to psychotic perturbation by psychostimulants. In addition, a small proportion of schizophrenic patients do not respond in this characteristic fashion, a finding that is believed to reflect the pathophysiological heterogeneity of the illness (van Kammen et al. 1982; Lieberman et al. 1987, 1989).

A spectrum of dose-related acute effects of stimulant intoxication (largely amphetamine and cocaine) has been described in nonschizophrenic subjects (Angrist and Szubinski 1978). The administration of relatively low doses of stimulants produces euphoria, alertness, and enhanced self-confidence and self-esteem (Fishman 1988), increased interest and curiosity in the immediate environment, social disinhibition, and decreased anxiety—all in the setting of a clear sensorium without hallucinations or cognitive impairments. This activated euphoria may become exaggerated to include euphoric disinhibition, impulsiveness, impaired judgment, irritability, grandiosity, compulsive repetitive and stereotypic behavior, and extreme psychomotor activation (Kramer et al. 1967; Gawin and Ellinwood 1988, 1989). With further increases in dose or duration of administration, a dysphoric anxiety state often accompanied by general sympathetic arousal occurs. Severe anxiety can resemble a panic episode with fears of impending doom and may be associated with paranoid ideation (Sherer et al. 1988). As previously described, florid psychosis ultimately occurs after sustained stimulant administration (Ellinwood 1967; Lesko et al. 1982; Manschreck et al. 1987). Moreover, certain effects of chronic stimulant abuse can persist long after cessation of use as evidenced by the behavioral hypersensitivity of former addicts to the psychotogenic effects of stimulants during reexposure (Utena 1966; Sato et al. 1983).

The spectrum of behavioral effects in schizophrenic patients is comparable to that in normal patients, but with the dose-response curve shifted markedly to the left (Post 1975). A single administration of a psychostimulant in low to moderate doses can activate psychotic symptoms in 40–60 percent of patients (Lieberman et al. 1989). The more severe psychotic exacerbations include motor symptoms that can take the form of wildly bizarre and disorganized behavior, catatonia, intense stereotypes, and perseverative self-stimulating behaviors in addition to the more commonly manifest affective, cognitive, and perceptual disturbances (Groves and Rebec 1976; Lieberman et al. 1989; Lieberman, unpublished data). These responses may reflect a continuum of severity of psychosis mediated by central DA neural activity (Post 1975; Gold and Bowers 1978; Sherer 1988). In view of the above findings, it is easy to understand why schizophrenic patients who use stimulants recreationally may experience symptom exacerbations and relapses. It is unfortunate that aspects of schizophrenic symptomatology (e.g., negative symptoms) as well as subjective side effects of schizophrenia treatment (e.g., dysphoria) may impel patients to use stimulant drugs (Schneier and Siris 1987).

**Psychostimulant Pharmacology**

The class of drugs called psychostimulants, which includes dextroamphetamine, methamphetamine, methylphenidate, d-ephedrine, and cocaine, have as a common pharmacological property catecholaminergic agonism (Snyder 1972; Jaffe 1985). Though largely indirect-acting catecholamine agonists, they are believed to produce their mood-activating and psychotogenic effects by increasing synaptic concentrations of DA through potentiation of presynaptic release and inhibition of reuptake (Groves and Rebec 1976; Kuczenski 1983; Nunes and Rosecan 1987). Indeed, the psychotogenic potency of these drugs is correlated...
with their DA agonist activity (Janowsky and Davis 1976; Lieberman et al. 1987). However, despite the apparent causal association between DA stimulation and psychotic behaviors, no consistent correlation between symptoms and measures of DA neuronal activity has been found (Javaid et al. 1988; Sherer 1988; Jody et al. 1989). In addition, the temporal dissociation between behavioral response (both the affective and psychotic components) and plasma drug concentrations indicates that the physiological actions initiated by drug administration extend beyond the transient changes in synaptic concentrations of DA (Angrist et al. 1987; Sherer 1988; Lieberman et al., unpublished data).

It has been hypothesized that repeated administration of stimulants may produce a supersensitive condition in the central nervous system (CNS) by upward regulation of postsynaptic DA receptors (Klawans and Margolin 1975; Dacks and Gold 1985). This occurs as a result of postsynaptic DA depletion and lowered tonic basal DA levels that may follow the drug-mediated surge of DA synaptic activity. Coincident with this DA surge, autoreceptor subsensitivity may also develop, thereby reducing the inhibition of presynaptic DA synthesis and release (Antelman and Chiado 1981). This could result in a dysregulation of presynaptic and postsynaptic mechanisms which contributes to increased DA neurotransmission. Such neuroadaptive phenomena as alterations and dysregulation of presynaptic and postsynaptic mechanisms that occur in response to pathological states of endogenous DA activity (either through illness or substance abuse) are believed to play a role in the pathogenesis of psychosis. Our understanding of such mechanisms is limited, however, and it is primarily inferential. Moreover, the impact of chronic stimulant abuse on schizophrenic pathophysiology has not been well studied and is largely unknown.

Preclinical Studies of the Behavioral Pharmacology of Stimulant Drugs

Since invasive in vivo studies of brain physiology in humans are not feasible, we necessarily turn to animal models of substance abuse and psychosis to examine neural mechanisms.

Acute Dose Studies. The complex pattern of behavioral effects produced by stimulants in rodents parallels that seen in humans. Acute treatment with low doses of amphetamine (0.25–1.0 mg/kg s.c.) produces an increase in locomotor activity that is accompanied by continuous sniffing. As acute doses increase, locomotor hyperactivity is interrupted by brief periods of stereotyped behavior consisting of focused sniffing and repetitive movements of the head and limbs. At higher doses (>2.5 mg/kg), the initial locomotor activation quickly fades into a period of intense focused stereotyped behaviors characterized by continuous sniffing and head weaving, and the appearance of gnawing, chewing, and licking behaviors. As stereotypy wanes, locomotor hyperactivity reemerges (Segal and Schuckit 1983). All of these behavioral components are mediated by DA. However, other (in vitro) studies have shown that extracellular levels of striatal DA reach their maximum values as the amphetamine dose approaches 3 mg/kg, while focused stereotypies appear at higher doses (5 mg/kg) (Kuczynski 1983, 1986). Extraneuronal catabolism of excess axon-released DA may establish this ceiling. Despite this limit, the progressive increase in stereotyped behaviors may reflect the development of a dissociation between presynaptic neuronal activity and postsynaptic DA receptor stimulation. Thus, at lower amphetamine doses, locomotor hyperactivity is the behavioral consequence of increased postsynaptic receptor activation occurring within the constraints of presynaptic regulatory mechanisms. Higher amphetamine doses may maximally stimulate postsynaptic receptors yet also dysregulate presynaptic neuronal activity in the substantia nigra from the striatum, producing the appearance of focused stereotyped behaviors (Kuczynski 1983). The behavioral activity of the direct DA agonist apomorphine, which, unlike amphetamine, produces predominantly focused stereotypies, supports the notion that such stereotypy reflects postsynaptic receptor stimulation uncoupled from the influence of DA neuron firing (Geyer et al. 1987).

The dissociation of synaptic DA concentrations and behavioral response is also seen with in vivo microdialysis studies (Sharp et al. 1987; Kuczynski and Segal 1989). These studies demonstrate that stereotyped behaviors are triggered by an early rise in DA release but are maintained despite a fall in DA levels. This suggests an uncoupling of a postsynaptic effector mechanism from receptor stimulation after a large, rapid presynaptic release of DA.
A report by Barnett and Kuczenski (1986) also suggests that increased DA release may desensitize postsynaptic D1 receptors, which could contribute to the development of focused stereotypies through alteration of relative D1 to D2 postsynaptic activity (Rosengarten et al. 1986; Murray and Waddington 1989). D2 receptors are believed to mediate the antipsychotic effects of neuroleptic drugs (Creese et al. 1976), which suggests that they are upwardly regulated in psychosis. If D2 receptors exist in a reciprocal balance with D1 receptors, then desensitization of D1 receptors and the consequent upward regulation of D2 receptors may facilitate the onset of psychosis.

The induction of intense, focused stereotypy by acute, high-dose amphetamine indicates a possible uncoupling of postsynaptic receptor stimulation from either presynaptic DA neuronal activity or postreceptor effector mechanisms. Such dysregulated neurotransmitter action may contribute to the psychotogenic effects of stimulants in humans.

RepeateD Dose Studies. When administered in an intermittent or repetitive pattern and in low to moderate doses, psychostimulants produce in animals an increased locomotor and stereotyped response to the acute challenge of the drug. This condition of reverse tolerance to psychostimulant effects is termed behavioral sensitization (for extensive review, see Segal and Schuckit 1983; Robinson and Becker 1986). This widely replicated but poorly understood phenomenon is characterized in rats by enhanced locomotor activity, more rapid onset, and greater intensity of stereotypy, including a shift toward more focused stereotyped head, limb, and oral movements, and a prolonged poststereotypy locomotor hyperactive phase. After drug withdrawal, no abnormalities in activity are seen unless the animal is challenged with an acute dose of amphetamine (Segal and Mandell 1974). Components of the sensitization response may persist for several months following drug withdrawal (Hirabayashi and Alam 1981; Leith and Kuczenski 1982).

Despite the robust nature of this phenomenon, the neurochemical basis for behavioral sensitization is unknown. Since chronic amphetamine treatment may also sensitize rodents to subsequent challenge with the direct DA agonist apomorphine (Klawans and Margolin 1975; Bailey and Jackson 1978; Kilbey and Ellinwood 1978; Nelson and Ellison 1978; Weiner et al. 1979; Nishikawa et al. 1983), an upward regulation of striatal postsynaptic DA receptors has been hypothesized as mediating behavioral sensitization in a manner analogous to behavioral hypersensitivity resulting from chronic neuroleptic-induced DA receptor increases (Burt et al. 1977). The findings of studies that have examined alterations in postsynaptic receptor binding, however, are inconsistent (Burt et al. 1977; Klawans et al. 1979; Muller and Seeman 1979). In fact, if anything, a downward regulation of striatal DA receptors has been more frequently reported following repeated amphetamine administration (Howlett and Nahorski 1979; Akiyama et al. 1982; Daigui and Meltzer 1982; Sibley et al. 1982), as well as after chronic continuous amphetamine treatment may also desensitize rats in either nigrostriatal or mesolimbic terminal fields (Kuczenski and Leith 1981). There is evidence, however, that sensitized animals have an enhanced release of DA in nigrostriatal and possibly in mesolimbic and mesocortical regions when challenged with amphetamine, an effect that can be demonstrated for up to several weeks after amphetamine discontinuation (Robinson and Becker 1982; Nishikawa et al. 1983; Kolta et al. 1985; Castaneda et al. 1988). When rats receiving mid-range doses of amphetamine chronically are stratified according to their variance in locomotor and stereotypy predominance, then differences in drug-induced DA release across DA systems become more apparent, suggesting that a shift from nigrostriatal to mesolimbic or mesocortical increased DA release may influence the transition from locomotor to stereotyped behavior (Segal and Kuczenski 1987).

The cellular mechanism by which repeated amphetamine treatment may lead to the increased release of DA upon rechallenge is unclear. Electrophysiological studies provide evidence for the development of DA autoreceptor subsensitivity in the substantia nigra, an effect that would attenuate feedback inhibition of DA release (Antelman and Chiodo 1981; Kamata and Rebec 1984). A reduction in striatal tritiated apomorphine binding after chronic amphetamine has been interpreted as...
indicating a diminished density of presynaptic autoreceptors (Muller and Seeman 1979). Another explanation involves increased availability of DA for release in sensitized animals (though the overall concentration of presynaptic DA is not increased). Increased availability could occur if there were a shift in the distribution of DA within the presynaptic axon terminal from the reserpine-sensitive storage pool to the readily releasable cytoplasmic pool (Robinson and Becker 1986). An alternative explanation is that repeated amphetamine administration sensitizes neuronal afferents to DA terminals (such as glutamatergic neurons) which facilitate DA release (Kandel and Schwartz 1982; Robinson and Becker 1986).

Behavioral sensitization has been demonstrated after repeated cocaine administration in the rat (Post and Rose 1976). Repetition of low doses selectively produces locomotor sensitization that appears to be mediated by the mesolimbic rather than the nigrostriatal DA system and seems to be sensitive to environmental conditioning (Post et al. 1988). A stereotypy component of behavioral sensitization develops after a single large dose or after repeated moderate doses of cocaine and is relatively independent of conditioning effects (Post et al. 1988). Chronic cocaine may also produce a subsensitivity of somadendritic autoreceptors on mesolimbic DA neurons which might contribute to enhanced DA release upon cocaine rechallenge (Duffy and Kalivas 1988).

Limbic structures such as the amygdala, hippocampus, and perirhinal cortex may mediate the development of electrical and lidocaine-induced kindling, which represents a form of electrophysiological reverse tolerance characterized by the progressive development of increasing afterdischarge activity and ultimately major motor convulsions during the repetitive application of subthreshold electrical stimulation or subconvulsive doses of lidocaine to the limbic system (Post et al. 1988). Chronic cocaine in high doses which are subthreshold for seizure induction may lead to the emergence of seizure activity. It is hypothesized that behavioral sensitization, following repeated cocaine administration, which may involve the limbic system, may potentially activate a kindling mechanism, which once established, may be responsible for the persistence of the sensitization phenomenon as well as for its extension into other pathological responses (Post et al. 1988).

It is intriguing that the development of behavioral sensitization to repeated amphetamine (Tadokoro 1978; Kuczenski and Leith 1981; Kuribara and Hirabayashi 1985) and cocaine (Post et al. 1988) can be blocked by the concurrent administration of neuroleptics; once the pattern has been established, however, neuroleptics may not block the sensitized response that appears on rechallenge (Kuribara et al. 1986; Post et al. 1988). This suggests that the behavioral alterations of sensitization may be perpetuated by non-dopaminergic mechanisms, such as kindling, and implies a possible model for the induction of neuroleptic-refractory schizophrenic psychosis (Post et al. 1988).

**Behavioral Sensitization and Schizophrenia**

Behavioral sensitization has obvious relevance to schizophrenia and drug-induced psychosis. The phenomenon consists of an evolution of a particular behavioral pattern induced by chronic exposure to DA agonism that is characterized by exaggerated perseverative behaviors. This condition is covert in that it is only manifest upon acute pharmacological perturbation and persists for extended periods after cessation of the induction process. Moreover, the induction of this condition may be blocked by neuroleptic drugs, but not the provocation of its manifest behaviors once sensitization has developed. Finally, this process occurs and persists in the absence of any clearly apparent neurological abnormalities. This bears a marked resemblance to what is seen in the natural course of schizophrenia. The pathogenesis of schizophrenia is hypothesized to involve enhanced DA neural activity in specific anatomical regions, yet no direct evidence of this increased neurochemical activity has been found (Haracz 1982). Patients with schizophrenia may be stable for long periods before developing exacerbations in the wake of environmental stressors, following stimulant abuse, or after discontinuing neuroleptic medication (all are occurrences that alter DA neural tone) (Wyatt et al. 1988a). In addition, patients experience exacerbations and relapse in the aftermath of stressful events or stimulant abuse despite apparently adequate maintenance neuroleptic treatment. Thus, behavioral sensitization as a pathophysiological model for schizophrenia has considerable face validity.

**Neurotoxic Effects of Stimulant Drugs**

The prolonged high-dose administration of methamphetamine and structurally related derivatives to laboratory animals produces persistent depletion of DA that leads to...
neuroaxonal degeneration (Ellison and Eison 1983; Trulson et al. 1986; Seiden et al. 1988). Administration over a 1- to 2-week period is sufficient to produce DA reductions, although degeneration of axon terminals in the striatum can be seen 48 hours after a single large methamphetamine injection to rats. The reductions in DA, its synthetic enzyme tyrosine hydroxylase, and reuptake sites, as well as the presence of axonal swellings, all indicate that these psychostimulants induce degeneration of DA axon terminals in the striatum, frontal cortex, nucleus accumbens, and amygdala, while midbrain DA cell bodies appear to be less or not at all affected (Robinson and Becker 1986; Seiden et al. 1988). The depletion of DA may be permanent, at least as seen in the caudate of nonhuman primates (Seiden and Ricaurte 1987).

A possible mechanism for neurotoxicity is that the massive release of DA and inhibition of monoamine oxidase by stimulants results in the nonenzymatic conversion of released DA into 6-hydroxydopamine. This toxic metabolite is transported via the DA uptake carrier into the presynaptic neuron causing the axon terminal to degenerate (Seiden and Ricaurte 1987). Another mechanism of neurotoxicity involves glutamatergic neurons projecting from the cortex to striatal and limbic DA neurons. The neurotoxic effects of methamphetamine can be blocked by the N-methyl-D-aspartate antagonist MK-801 (Sonsalla et al. 1989). This suggests that stimulant-enhanced excitatory amino acid activity in glutamatergic neurons may lead to DA neurotoxicity, though the exact process by which this occurs is not known. Glutamate neurons are also involved in the induction of behavioral sensitization by the psychotogenic drug phencyclidine (Greenberg and Segal 1986; Iwamoto 1986). Thus, glutamatergic neurons may provide a common route of afferent stimulation of DA neurons for various pharmacological types of psychotogenic compounds.

As seen with the induction of behavioral sensitization, animals treated in the neurotoxicity paradigm display the effects of behavioral activation while receiving chronic stimulant administration, yet show no overt behavioral abnormalities after the drugs are withdrawn (Seiden and Ricaurte 1987). However, in contrast to behavioral sensitization, when subsequently rechallenged with methamphetamine or apomorphine after drug withdrawal, they exhibit reduced rather than enhanced behavioral sensitivity (Lucot et al. 1980; Finnegan et al. 1982). This reduced responsivity occurs in the absence of measurable alterations in postsynaptic DA receptors (Ricaurte et al. 1980; Finnegan et al. 1982), but it may be contributed to by supersensitivity of nigral somadendritic autoreceptors that could attenuate DA release (Ellinwood and Lee 1983).

Since it is not feasible to perform neurotoxicity studies in humans, the neurochemical consequences of chronic methamphetamine and cocaine abuse in humans are not fully known. A report of increased plasma prolactin levels in chronic cocaine abusers suggests reduced DA activity in the hypothalamus (Gawin and Kleber 1985). Recent positron emission tomography studies of cocaine addicts have found decreased DA neural activity in frontal cortical and striatal regions (Baxter et al. 1988). Anhedonic and amotivational behavior has been described in former amphetamine addicts (Utena 1966; Gawin and Ellinwood 1988). Recent reports of infants born to cocaine-using women also describe unresponsive behavior and indifference to the environment (Chasnoff et al. 1985), which may reflect a hypodopaminergic condition.

Dopamine and Stimulant Drug Dependence

Cortical and limbic DA neural systems have been implicated in the reward-seeking and reinforcement mechanisms that mediate cocaine and amphetamine dependence (Goeders and Smith 1982; Koob and Swerdlow 1988). Koob and Swerdlow (1988) have suggested that pathological alterations of mesolimbic activity induced by stimulants in humans might lead to psychotic states through the disruption of normal reinforcement contingencies. Though this explanation is plausible, it seems more likely that the euphoric effects of stimulants which are reinforcing and lead to dependence are mediated by additional mechanisms that induce psychosis. Gawin and Ellinwood (1988) have described the development of vivid, pleasurable memories of stimulant-induced euphoria which continually re-create the desire to use stimulants. Therefore, though it is the reward-seeking process that may lead schizophrenic patients and stimulant abusers to take stimulants repeatedly, the induction of psychosis is an overlapping but separate consequence of the accrued pharmacological actions.

Neural Substrates of Schizophrenia and Stimulant-Induced Psychosis

In humans, the natural history of behavioral changes in stimulant
abusers roughly corresponds to the evolution of psychopathology in some forms of schizophrenia. Individuals take stimulants recreationally for affective stimulation in a manner analogous to reward-seeking behavior in animals. They become more dependent on drugs for affective stimulation, use them more habitually and eventually sustain cognitive and perceptual alterations potentially including episodes of psychosis. With continued long-term use, they may develop behavioral changes evident during abstinent periods which include affective instability (depression and irritability), anhedonia, lack of motivation and the diminution of cognitive functions. "Burnt out" former "speed-freaks" have been described as being indifferent to their environment and as sitting around staring into space. Such individuals though appearing generally unresponsive are still hypersensitive to stimulant drug effects upon reuse as well as to psychological stressors (Utena 1966; Angrist and Gershon 1969; Utena et al. 1975).

Similarly, in schizophrenia periods of acute psychosis are characteristically seen in the early stages of illness, which are followed in some patients by the development of what has been called the defect state and is characterized by affective blunting, impoverished speech and thought, anhedonia, and asociality (Andreasen 1985; Crow 1985). Such patients may also have exacerbations of their illness in the form of increases in positive psychotic symptoms and are susceptible to symptom exacerbations with stimulation by DA agonists (Lieberman et al. 1989) and stressful life events (Dohrenwend and Egri 1981). Interestingly, neuroleptic drugs can reverse psychotic episodes and maintain states of remission but cannot completely prevent exacerbations in schizophrenic patients by stimulant drugs or psychological stressors (Dohrenwend and Egri 1981; Kane and Lieberman 1987; Lieberman et al. 1987, 1989). In the behavioral sensitization paradigm previously described, this may be analogous to the ability of concurrent neuroleptic treatment to prevent the induction of sensitization but its inability to prevent the exaggerated behavioral response in sensitized animals when they are rechallenged (Robinson and Becker 1986; Post et al. 1988).

At the cellular level, we would postulate the following processes as underlying the behavioral events just described: The initial neurochemical insult, be it of endogenous (i.e., schizophrenia) or exogenous (i.e., stimulant abuse) origins, occurs in the form of enhanced presynaptic DA neural activity. This gives rise to acute behavioral changes and causes disruption of normal presynaptic and postsynaptic regulatory processes. The continuation of increased DA stimulation produces a sensitization of DA neurons. This enhanced sensitivity to changes in basal as well as event-related neural dopamine tone may eventually, if sustained, produce neurotoxic effects through axonal neurotransmitter depletion, formation of toxic metabolites, or enhanced excitatory amino acid activity (Wyatt et al. 1988b; Olney 1989). Consequently, a state of partial denervation develops with reduced presynaptic neuronal viability and a resultant increase in postsynaptic neuronal sensitivity. This condition is less plastic than the initial state of behavioral sensitization and therefore may not be amenable to pharmacological or neuroadaptive restitution. A decrease in postsynaptic neuronal sensitivity, paradoxically, may follow more extensive degeneration of DA axon terminals (see figure 1).

Pathophysiological changes in DA neural systems may be propagated to other neurotransmitter systems resulting in a more extensive neurobiological disturbance. Other neurotransmitters potentially implicated by their interaction with DA neurotransmission in the pathogenesis of behavioral sensitization or schizophrenia include the endogenous opiates (Kalivas 1985), norepinephrine (Hornykiewicz 1982), glutamate (Olney 1989), serotonin, and acetylcholine (Moore 1978).

Schizophrenia and Drug Use Interactions

Our understanding of the neurobiological bases of schizophrenia and chronic stimulant drug effects suggests the potential for their interaction. Schizophrenic patients who abuse psychostimulant drugs incur several types of potential risk. At the very least, they can induce symptom exacerbations that otherwise might not have occurred. Beyond this, given the occurrence of behavioral sensitization and neurotoxic effects, chronic stimulant use could conceivably exacerbate the disease pathophysiology, resulting in an acceleration of the disease course and/or an increase in the ultimate level of severity to which the disease progresses. In addition, antipsychotic treatment responsiveness might be altered in an unfavorable direction. Fortunately, it appears that schizophrenic patients who abuse substances do so in smaller quantities than nonschizophrenic substance-abusing populations. Nevertheless, the dose-response
DA = dopamine; 6-OHDA = 6-hydroxydopamine; 1 = uptake site; 2 = impulse regulated DA release; 3 = postsynaptic receptors/effectors; 4 = axon terminal autoreceptor; 5 = intracellulal DA pool (cytoplasmic ["DA"] vs. storage granules [encircled]); 6 = neuronal impulse firing; 7 = hyperpolarizing synapse (facilitates DA release).

Schematic model for alterations in the function of a conceptualized dopaminergic neuron and its postsynaptic cell that may be relevant to the induction of psychosis after progressively increasing exposure to amphetamine (AMPH). A—Acute AMPH effects: Through its interaction with uptake site (1), AMPH decreases DA reuptake and increases its release. D-1 postsynaptic sensitivity (3) may be diminished relative to D-2 sensitivity. Presynaptic neuronal firing rate (6) may be decreased. High-dose AMPH may induce neuronal dysregulation by uncoupling postsynaptic receptor stimulation from either presynaptic neuron activity or postsynaptic effector mechanisms. B—Repeated AMPH effects (early): Behavioral sensitivity may be secondary to enhanced DA release (1,2). Terminal autoreceptor subsensitivity (4), redistribution of DA from storage granules to readily releasable cytoplasmic pool (5), increased neuronal firing (6), and hyperpolarization of axon terminal through a facilitatory presynaptic receptor (7) may all contribute to this increased DA release upon rechallenge. Increased postsynaptic sensitivity (3) may be secondary to D-2:D-1 predominance in receptor density or postreceptor effector. Possible neuronal dysregulation may occur at relatively low AMPH doses. C—Repeated AMPH effects (late): Consequent to presynaptic DA depletion (5), supersensitivity of terminal autoreceptors (4) and postsynaptic receptors (3) may develop; decreased neuronal firing (6) may be secondary to supersensitivity of somadendritic autoreceptors. Extraneuronal conversion of excessive synaptic DA to the neurotoxin 6-OHDA may develop during chronic AMPH administration. D—Neurotoxic AMPH effects: Decreased tyrosine hydroxylase and presynaptic DA depletion (5) may reflect DA axon degeneration secondary to the intraneuronal uptake of 6-OHDA. Decreased neuronal firing (6) may be secondary to supersensitivity of somadendritic autoreceptors. Decreased postsynaptic receptor sensitivity (3) may eventually develop.
parameters may also be different for schizophrenic patients. While schizophrenic patients should be counseled against all forms of substance abuse, they should be warned particularly against stimulant use (as well as phencyclidine) which in their case poses great potential for harm.

The question as to whether chronic stimulant abuse in persons who do not have a psychotic diathesis can engender a schizophrenia-like condition that persists without continued stimulant abuse is currently unsettled. Most reports suggest that the onset of schizophrenia may be precipitated in prepsychotic or latent schizophrenic patients, but that the illness is not directly caused by drug abuse (Breakey et al. 1974; Richard et al. 1985). However, one study has described the de novo development of schizophrenia in the setting of chronic stimulant abuse (McLellan et al. 1979).

**Conclusion**

Clinical and preclinical studies of chronic stimulant effects and schizophrenia demonstrate an overlap in the neurobiology of idiopathic and drug-induced psychoses. This has important implications for our understanding of the pathophysiology of stimulant abuse and schizophrenia as well as suggesting potential pathophysiological mechanisms by which substance-abusing patients with schizophrenia could complicate the nature and course of their illness. Further research into the interaction of stimulant, as well as other drug abuse and schizophrenia, is clearly needed.

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