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Comorbidity of Substance Abuse with Other Psychiatric Disorders

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Substance abuse is a frequent comorbid condition with other psychiatric disorders including schizophrenia and depression. These disorders may share a common substrate at the neurotransmitter or neurocircuit level. One candidate is hypofunction of the glutamate system. Several lines of evidence suggest that N-methyl-D-aspartate (NMDA) receptors may hypofunction in schizophrenia. Thus, NMDA receptor antagonists are schizophrenogenic; postmortem and imaging results point to reduced NMDA receptor function in schizophrenic brains; a number of genes that have been linked to schizophrenia code for proteins that influence NMDA function; and there is preliminary evidence that pro-NMDA drugs may be therapeutic in the treatment of schizophrenia. One of the most effective therapeutics for the treatment of substance abuse in schizophrenic people is clozapine, and clozapine may act at the glycine modulatory site to enhance NMDA receptor function. This preliminary line of evidence may link schizophrenia and drug abuse to a common neurochemical base, subnormal NMDA receptor function. People with schizophrenia and drug abusers similarly show deficits in tasks known to be sensitive to ventromedial prefrontal cortical damage, and both groups show decreased activation in the ventral striatum during reward anticipation in functional magnetic resonance imaging studies. These observations implicate common prefrontal cortical-striatal circuits and their modulation by hippocampal projections in schizophrenia and substance abuse. Withdrawal from substance abuse and depression both have been linked to changes in the function of several neurotransmitters including serotonin, dopamine and glutamate. These findings suggest possible common substrates and novel therapeutic approaches. Further studies are needed to fully characterize the neurocircuits and transmitters involved in various psychiatric disorders and their possible common elements in comorbid drug abuse.

Keywords: Comorbidity; Schizophrenia; Depression; Drug abuse; Glutamate; Serotonin; Dopamine; GABA

INTRODUCTION

Substance dependence or addiction is defined by a number of features including tolerance, withdrawal, uncontrolled substance use, a preoccupation with taking the substance to the detriment of usual social and occupational activities and persistent

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substance use in spite of knowledge that it is harmful. Substance abuse involves a pattern of substance use characterized by any one of neglect of usual occupational or social responsibilities, increased physical risk to self and others, substance-related legal problems and an inability to desist in spite of a negative impact on one's life (American Psychiatric Association, 1994). Psychiatric symptoms are classified as a substance-induced disorder if other primary disorders can be ruled out as accounting for the symptoms. When substance abuse co-occurs with a suite of psychiatric symptoms, the challenges for diagnosticians are substantial. Often the accuracy of phenotyping of disorders is critical to the success of studies of the neurobiologial and genetic mechanisms of the disorders (Palomo *et al.*, 2004). These challenges of diagnosis of comorbidly existing substance abuse and other psychiatric disorders and the tools developed to meet them are discussed by Torrens *et al.* (2006). Diagnosis remains an important issue in studies of the comorbidity of substance abuse and other psychiatric disorders.

Substance abuse disorder frequently co-occurs with other psychiatric disorders including schizophrenia and affective disorders. For example, the risk for substance abuse (except abuse of nicotine) in schizophrenia is three to four times greater than that found in the general population (Regier *et al.*, 1990; Kavanagh *et al.*, 2002) and there is a high co-morbidity of drug abuse and depression (Kessler *et al.*, 2005; Paykel *et al.*, 2005). It may be that substance abuse reflects the deinstitutionalization of chronically and severely mentally ill patients who find themselves as a result to have access to substances through their social circumstances. A second possibility is that substance abuse results from iatrogenic effects of medications used to treat the classical psychiatric disorders or that it reflects self-medication. A third is that substance abuse disorder and other psychiatric disorders may issue from the dysfunction of neurobiological mechanisms that they have in common.

Krystal *et al.* (2006) considered the first possibility in their discussion of environmental risk factors for substance abuse and schizophrenia. People with schizophrenia who abuse substances are more likely to have characteristics such as fewer years of education, homelessness and childhood conduct problems that increase their exposure to illicit substances (Swartz *et al.*, 2006). Their higher rates of unemployment and social isolation may increase the attraction of acceptance into a drug-using group. Schizophrenic people may have an increased exposure to traumatizing events that increase the probability of substance abuse (Gearon *et al.*, 2003). The convergence of these factors with the deinstitutionalization of psychiatric patients may contribute to their significantly enhanced frequency of drug abuse.

There is some evidence that drug abuse may be related to the use of antipsychotic medications. Drug abusers have been found to have significantly reduced dopaminergic functioning in ventral striatal regions (see Krystal *et al.*, 2006; Paterson and Markou, 2007). If antipsychotics produced such a state in schizophrenic patients, they might be more susceptible to drug abuse as drugs of abuse would enhance dopaminergic neurotransmission in this region. Some evidence for this possibility can be found in the observation that schizophrenic patients treated with clozapine are less likely to abuse drugs than similar patients treated with other antipsychotics (Drake *et al.*, 2000; Procyshyn *et al.*, 2002; Green *et al.*, 2003; Noordsy and Green, 2003; Coyle, 2006). In studies of immediate early gene induction in animals, it was found that clozapine was more potent in the frontal cortex than in the striatum whereas typical antipsychotic medications or risperidone affected the striatum but not the frontal cortex (Robertson and Fibiger, 1992; Wan *et al.*, 1995; Deutch and Duman, 1996; Fujimura *et al.*, 2000; Kovacs *et al.*, 2001). Although clozapine, typical antipsychotics and risperidone were found in the same studies to affect the nucleus accumbens equally, the differential action of these agents in the striatum coupled with the finding that striatal dopamine function is reduced in drug abusers provides a rationale for the suggestion that drug abuse in schizophrenia may be affected by the use of antipsychotic medications. From the same point of view, it is less clear why depressed patients might abuse drugs.

A related hypothesis is that drug abuse represents a form of self-medication; according to this hypothesis, people with schizophrenia take drugs that ameliorate an underlying deficiency. Moghaddam (2007), for example, recognized that schizophrenic patients may suffer from hypofunction of gluta-

matergic N-methyl-D-aspartate (NMDA) receptor-mediated neurotransmission (see below); she suggested that drugs of abuse are reinforcing in these patients because they overcome this underlying NMDA deficiency. One point of support for this argument is that many abused substances act via D_1-like receptors to increase the surface expression of nucleus accumbens α-amino-3-hydroxy-5-methyl-isoxazole (AMPA) receptors (Boudreau and Wolf, 2005) that would enhance glutamatergic neurotransmission. What is unclear from this hypothesis is why non-schizophrenic people would abuse the same drugs. Furthermore, if drugs abused by schizophrenic people were ameliorating symptoms, it might be expected that drug-abusing schizophrenic people would be less symptomatic or show a better outcome. However, the opposite is the case; in comparison with psychiatric patients diagnosed with a single disorder, those with comorbid substance abuse have higher psychopathological severity, more emergency admissions, increased rates of psychiatric hospitalization, higher prevalence of suicide, show increased rates of risk behaviors and infections, higher unemployment and homelessness and greater frequencies of violent and criminal behavior (see Torrens *et al.*, 2006). As reviewed by Coyle (2006, see below), there is still only weak evidence that pro-glutamatergic agents are effective therapeutics in treating schizophrenia. Thus, there is not strong evidence that schizophrenic patients abuse drugs to self-medicate.

Based on a review of many findings, a number of researchers favored the third possibility that substance abuse disorder and other psychiatric disorders issue from the dysfunction of neurobiological mechanisms that they have in common. One problem for this view is that the heritable risk for schizophrenia is distinct from the heritable risk for drug abuse; people with comorbidity of these disorders have heritable vulnerabilities to both disorders (Krystal *et al.*, 2006). If substance abuse and psychiatric disorders share a common substrate they might be expected to show some common heritability. One possibility is that both disorders involve complex interacting systems and that each involves a part of the overall mechanism. Some possible mechanisms will be discussed in this paper.

The topic of comorbidity was taken up recently at a meeting sponsored by the Fundation Cerebro y Mente of Madrid entitled, "Implications of comorbidity for etiology and treatment of neuropsychiatric disorders", held in Mazagon (Huelva), Spain, 19-23 Oct. 2005. In their presentations and papers, some of the authors discussed a number of neurobiological mechanisms that have been implicated in psychiatric disorders including schizophrenia and depression and the possibility that the high level of comorbid substance abuse seen in these patient groups might result from dysfunctions in these same mechanisms. Results continue to converge on a new synthesis pointing to various connections within multiple interacting neurotransmitter systems where dysfunctions may contribute to both classical neuropsychiatric disorders and substance abuse. In this paper, we provide an overview of several mechanisms that have been identified as possible common substrates of substance abuse and other psychiatric disorders.

GLUTAMATE IN SUBSTANCE ABUSE AND SCHIZOPHRENIA

For many years, the neurotransmitter dopamine was the focus of research into the dysfunctional neurobiological mechanisms underlying schizophrenia, and many data implicated dopaminergic systems in drug abuse. These continue to be areas of intense research. However, in recent years a number of findings have suggested the possibility that the dysfunction of dopaminergic systems may be secondary to a dysfunction of glutamatergic neurotransmission and a subsequent cascade of neurotransmitter interactions involving at least glutamate, γ-aminobutyric acid (GABA) and dopamine in several brain regions, leading to the observed symptoms. One beauty of the new synthesis is that it incorporates the hypothesis that dopamine is dysfunctional in schizophrenia rather that rejecting it for an alternative.

The dopamine hypothesis originated in two major observations and has been further supported in recent years by two additional lines of evidence. In what is now one of the classic findings of modern neuroscience and biological psychiatry, Seeman *et al.* (1975) showed that there was a high positive correlation between the average daily dose of antipsychotic medications needed to control positive symptoms in schizophrenia and the ability of

these drugs to block fifty percent of the binding of radio-labeled haloperidol to striatal dopamine D_2-like receptors. This result strongly implicated dopamine receptor blockade in the action of antipsychotic medications and suggested that hyperactive dopaminergic neurotransmission was the source of positive symptoms. Corroborative evidence was found in the observation that normal humans who abused psychomotor stimulants including amphetamine or cocaine developed psychotic symptoms like those seen in schizophrenic patients (Connell, 1958; Snyder, 1972) and that schizophrenic patients in remission were particularly sensitive to these psychotogenic effects of even low doses (Angrist, 1983). These constituted the first two pillars of the dopamine hypothesis of schizophrenia stating that positive symptoms resulted from hyperactive dopaminergic neurotransmission.

The somewhat newer evidence for the dopamine hypothesis came from direct observations of the brains of schizophrenic patients and from genetics. The former was dogged for years by possible effects of medications. Thus, postmortem measurements of dopamine D_2-like receptor binding showed elevations in schizophrenic patients, but it was also known from animal studies that such elevations could be produced by chronic treatment with dopamine receptor-blocking antipsychotic drugs (Crow and Johnstone, 1986). As most deceased schizophrenic patients would have been treated with antipsychotic drugs, observed elevations could have resulted from these treatments and therefore not have been intrinsic to the disease. The advent of single photon emission computerized tomographic imaging made it possible to evaluate indices of dopaminergic neurotransmission in the brains of living schizophrenic patients before they were treated with antipsychotic medications, making it possible to tease apart the possible effects of these medications versus the disease itself on dopamine D_2-like receptor number. Results showed elevated levels of dopamine receptors in the brains of newly diagnosed schizophrenic patients (Abi-Dargham *et al.*, 2000), further supporting the dopamine hypothesis.

Genetic studies in recent years have identified several risk genes for schizophrenia that may code for protein products that are involved in dopamine function. Linkage and association studies have implicated the *COMT* gene, coding for catechol-*O*-methyl transferase, an enzyme involved in the breakdown of catecholamines including dopamine (reviews: Harrison and Weinberger, 2005; Kirov *et al.*, 2005). Other genes that have been implicated include *RGS4* (regulator of G-protein signaling-4), *DISC1* (disrupted in schizophrenia 1) and *NRG1* (neuroregulin 1) (Harrison and Weinberger, 2005; Millar *et al.*, 2005). These and related genes involved in signal transduction may influence the long-term effects of dopamine on learning and memory, functions that have been linked to the effects of hyperfunctioning dopamine on positive symptoms (Beninger, 2006). Genetic studies, although providing some support for the dopamine hypothesis, are still in the early stages, and further studies are awaited. Thus, there are four pillars of support for the dopamine hyperfunction hypothesis of schizophrenia: the therapeutic actions of antagonists, the psychotogenic action of agonists, postmortem and imaging findings of elevations in dopamine receptors, and findings that genes relating to dopamine function are linked to schizophrenia.

In a well-organized and clearly presented review, Coyle (2006) discussed the hypothesis that NMDA receptors *hypofunction* in schizophrenia. The evidence for this hypothesis can be seen to form four pillars analogous to those supporting the dopamine hypothesis: NMDA receptor antagonists are schizophrenogenic, postmortem and imaging studies show altered glutamate structure/function in schizophrenia, genes related to glutamate are linked to schizophrenia, and glutamate receptor agonists may have therapeutic effects. Each line of evidence will be considered in turn.

It has been 45 years since Luby *et al.* (1962) described the schizophrenogenic effects of the dissociative anesthetics ketamine and phencyclidine in humans; both are NMDA receptor blocking drugs. The fact that children were relatively resistant to these effects provided further evidence that NMDA receptor antagonism might be specifically related to schizophrenia because diagnostic symptoms do not normally emerge until late adolescence or early adulthood (Reich and Silvay, 1989). The effects of these dissociative anesthetics can justifiably be called schizophrenogenic rather than simply psychotogenic because they produce not only positive symptoms but also negative and cognitive symp-

toms (Krystal *et al.*, 1994). Like the psychotogenic effects of dopamine agonists, the schizophrenogenic effects of ketamine were found to be particularly potent in schizophrenic patients in remission (Lahti *et al.*, 2001). Ketamine reproduced eye-tracking impairments in normal participants like those seen in schizophrenic patients (Radant *et al.*, 1998) and some of the electrophysiological abnormalities seen in schizophrenic people were also seen in normal participants treated with subanesthetic doses of ketamine (Umbricht *et al.*, 2000). The evidence for the first pillar seems quite good.

Many studies of postmortem brain tissue from schizophrenic people have revealed evidence of altered GABA function. There was reduced expression of the synthesizing enzyme glutamic acid decarboxylase (GAD 67) and the GABA transporter and increased levels of $GABA_A$ α_2 receptors on pyramidal neuron axonal initial segments (Akbarian and Huang, 2006; Lewis and Gonzalez-Burgos, 2006). Woo *et al.* (2004) showed a decrease in the number of neurons expressing GAD 67 that co-expressed the NR2A subunit of NMDA receptors in prefrontal cortex of schizophrenic brain. On the basis of this and related evidence, Coyle (2006) argued that these GABA neuronal abnormalities may be secondary to decreased NMDA receptor function. Supportive findings from basic research included the observation that chronic treatment of rats with the NMDA receptor antagonist dizolcipine led to decreased expression of GAD 67 and the GABA transporter in the frontal cortex (Paulson *et al.*, 2003); these were changes similar to those seen in schizophrenia.

N-acetylaspartylglutamate (NAAG) is an endogenous agent that acts at mGluR3 metabotropic receptors; these are found pre-synaptically on glutamate terminals where they inhibit glutamate release (Wroblewska *et al.*, 1997). NAAG is broken down by glutamate carboxypeptidase II (GCPII). Coyle (2006) reviewed several recent studies showing reduced levels of GCPII in postmortem schizophrenic brains suggesting a scenario involving elevated levels of NAAG, therefore elevated inhibition of glutamate release and reduced stimulation of NMDA receptors. This could result in reduced drive on GABA neurons bearing NMDA receptors, thus linking NMDA receptor hypofunction to reduced GABA function.

It is well known that schizophrenic patients show ventricular enlargement even at the time of disease onset, that there is some progression of this pathology over the early course of the illness and that there are corresponding decreases in cortical volume (*e.g.*, Miller, 1989). N-acetylaspartate is found in glutamatergic neurons in cortical regions including the frontal cortex and is reduced in schizophrenia (Sigmundson *et al.*, 2003). These results are consistent with the notion of reduced glutamatergic function in the cortex of schizophrenic patients. Taken together, the evidence from postmortem and imaging studies provides some support for the second pillar of the NMDA receptor hypofunction hypothesis of schizophrenia.

Genetics provides further evidence. Recent reviews of the current state of knowledge in the genetics of schizophrenia have identified several genes that point to a role for glutamate (Harrison and Weinberger, 2005; Kirov *et al.*, 2005). Two genes are *G72* and *DAAO*. *G72* encodes a protein that activates D-amino acid oxidase (DAAO), the protein coded by *DAAO*. DAAO breaks down D-serine, a modulator of the glycine site on the NMDA receptor. A change in the function of either of these genes that led to a reduction in levels of D-serine would lead to reduced NMDA receptor function. Another gene that has been linked to schizophrenia is *GRM3* that codes for mGluR3, a receptor that modulates glutamate release as discussed above. The genetic pillar of the NMDA receptor hypofunction hypothesis is growing in strength.

The final pillar of evidence is that agents that enhance NMDA receptor function will have therapeutic value in the treatment of schizophrenic symptoms. Coyle (2006) reviewed this evidence. The approach has been to target the glycine modulatory site of the NMDA receptor thereby mitigating the risk of excitotoxicity. Adding glycine itself, the full agonist D-serine, or the partial agonist at the glycine site, D-cycloserine, to a standard regimen of typical antipsychotic medication has led to some therapeutic effectiveness but not all trials have been successful. The prototypical atypical antipsychotic clozapine is well known for its efficacy in treating both positive and negative symptoms; Coyle (2006) suggested that the latter effect may be attributable to the action of clozapine at the glycine modulatory site. He reviewed several studies that provide

suggestive evidence for this hypothesis but further studies are needed. One interesting and relevant finding is that chronic smoking schizophrenic patients but not chronic smoking non-schizophrenic patients showed changes in NMDA receptor-related gene expression in hippocampal postsynaptic densities (Mexal *et al.*, 2005), suggesting that smoking may have a therapeutic benefit to schizophrenic patients! Overall, support for the pillar of evidence for therapeutic effectiveness of agents that enhance NMDA receptor function is weak.

So what about substance abuse? Is there evidence that NMDA receptor hypofunction may contribute to susceptibility to abuse substances? Coyle (2006) would argue that there is evidence and he reviewed it at the end of his paper. At best, the evidence is circumstantial; however, it is also provocative and provides a direction for future investigations. Coyle (2006) focused on the remarkable ability of clozapine to attenuate comorbid drug abuse in psychiatric disorders. Thus, clozapine, in comparison to other antipsychotic medications, significantly reduced alcohol abuse in alcoholic schizophrenic patients in one study (Drake *et al.*, 2000), tobacco use in another (Procyshyn *et al.*, 2002), and significantly reduced alcohol or cannabis abuse in a third (Green *et al.*, 2003). These results point to a unique action of clozapine in treating substance abuse, and previous results point to the possibility that clozapine may affect the glycine modulatory site. By linking these findings, Coyle (2006) suggests that schizophrenia (or at least the negative features of the disease) and drug abuse may have a common substrate.

VENTRAL STRIATUM AND RELATED CIRCUITRY IN SUBSTANCE ABUSE AND SCHIZOPHRENIA

Krystal *et al.* (2006) discussed the possibility that substance abuse and schizophrenia share a common basis in disturbances of motivation for reward and punishment. People with damage to the ventromedial prefrontal cortex have impaired performance on the Iowa Gambling Task that requires the choice of less attractive but also less risky reward alternatives for maximal performance (Bechara *et al.*, 1994; 1996; 1997; 1998; 2000a,b). A group of alcohol or stimulant abusers similarly showed impairments on this task (Bechara *et al.*, 2001; 2002), as did schizophrenic patients (Beninger *et al.*, 2003; Ritter *et al.*, 2004; Shurman *et al.*, 2005), although Beninger *et al.* (2003) observed the impairment in patients treated with atypical antipsychotics but not in those treated with typicals. If the impairment in schizophrenic patients is attributable to a disease-related dysfunction, then these finding converge on the hypothesis that a common ventromedial prefrontal cortical dysfunction may occur in substance abuse disorder and schizophrenia (*cf.*, Baler and Volkow, 2006). If the impairment in schizophrenic patients is attributable to the medication they are taking, the same conclusion is possible but the deficit in schizophrenia would be a consequence of the medication. Further studies are needed.

Krystal *et al.* (2006) discussed unpublished data from functional magnetic resonance imaging studies showing that individuals with a family history of alcohol dependence had less ventral striatal activation during the anticipation of rewards or punishments. Similarly, schizophrenic patients showed less activation in the ventral striatum during anticipation of reward or punishment (Juckel *et al.*, 2006). These findings raised the question of a common ventral striatal dopaminergic dysfunction in the two disorders. Studies of changes in dendritic spine morphology and scaffolding proteins in the postsynaptic density following chronic cocaine use further suggested changes in the ventral striatal region (Todo and Kalivas, 2007). The ventromedial prefrontal cortex projects to the ventral striatum where its input is gated by projections from the ventral hippocampus (Goto and O'Donnell, 2001). Disruption of this hippocampal modulatory input can lead to increased dopaminergic activity like that associated with schizophrenia (Goto and O'Donnell, 2002). As discussed in the previous section, there is growing evidence for the NMDA receptor hypofunction model of schizophrenia. Findings converge to suggest that disrupted activity in cortico-striatal and hippocampal-striatal circuits may underlie both schizophrenia and substance abuse.

NEUROTRANSMITTERS IN SUBSTANCE ABUSE AND DEPRESSION

Drug taking is maintained by the positively rewarding properties of the abused substances and by the negatively rewarding properties of withdrawal symptoms (Wise and Bozarth, 1987). Withdrawal

symptoms include depression-like aspects such as depressed mood, anhedonia, changes in appetite, sleep disturbances, fatigue, cognitive deficits and suicidal ideation (Markou *et al.*, 1998; Markou and Kenny, 2002). This suggests the hypothesis that the withdrawal aspect of substance abuse and depression may share common mechanisms and may similarly respond to medication. Indeed, smoking and depression are associated, and smokers with a history of depression find it significantly more difficult to quit (Glassman *et al.*, 1990). Paterson and Markou (2007) explored this hypothesis in their extensive review of animal models of treatment for comorbid depression and addiction.

In animal studies, possible blunted effects of rewarding stimuli can be assessed in a number of ways. Paterson and Markou (2007) focused on a technique that has been used extensively in Markou's lab over the years. Rats with chronically implanted electrodes are trained to rotate a wheel using electrical stimulation of the medial forebrain bundle as the rewarding stimulus. Trained rats can then be assessed for their preference for various intensities of brain stimulation by presenting them with a particular intensity in discrete trials and seeing if they respond for that intensity. Using this method it is possible to determine the threshold intensity needed to get the animal to respond. This provides a measure of how desirable the stimulation is to the rat. This technique can independently assess motor capacity as the latency to rotate the wheel after presentation of supra-threshold intensities of brain stimulation (Kornetsky and Esposito, 1979). When this technique was used to assess the intensity threshold of rats undergoing withdrawal, thresholds were elevated but latencies did not change (Paterson and Markou, 2007). Withdrawal from subchronic continuous infusion of nicotine (Epping-Jordan *et al.*, 1998) or amphetamine (Paterson *et al.*, 2000) elevated reward intensity thresholds. Results suggested that the normal effects of reward were blunted in rats undergoing withdrawal; this procedure provides a measure in animals analogous to diminished pleasure in people.

A number of neurotransmitters have been implicated in depression raising the question of their possible involvement in the reward threshold elevations seen during withdrawal. One is serotonin. Changes in serotonin receptors and neurotransmission in some brain regions have been reported in major depression (Mann, 1999). One of the main pharmacotherapies for depression is serotonin-selective reuptake inhibitors that are thought to normalize serotonergic neurotransmission in a two-stage process, beginning with stimulation of 5-HT_{1A} receptors, resulting in reduced synaptic serotonin followed by desensitization of those receptors and then elevated levels of serotonin; this therapeutic mechanism can be augmented by supplementing a serotonin-selective reuptake inhibitor with a 5-HT_{1A} receptor antagonist (Kinney *et al.*, 2000).

In rats undergoing cocaine or nicotine withdrawal changes in serotonerigic function similar to those seen in depression were observed including diminished serotonin release and receptor changes (see Paterson and Markou, 2007). Treatment of rats in withdrawal with the serotonin-selective reuptake inhibitor fluoxetine plus the 5-HT_{1A} receptor antagonist p-MPPI, but neither drug alone, reversed the threshold elevations in brain stimulation reward (Harrison *et al.*, 2001). In spite of these promising finding from animal studies, there is at present no strong evidence that antidepressants provide a beneficial effect in the treatment of human psychostimulant abusers.

Extracellular levels of dopamine in the nucleus accumbens of rats in withdrawal from subchronic continuous cocaine were reduced (Parsons *et al.*, 1991), and evidence of dopamine receptor changes also have been reported. Similar dopaminergic changes were seen in amphetamine or nicotine withdrawal (Paterson and Markou, 2007). The atypical antidepressant bupropion has been found to block dopamine and norepinephrine uptake and to block nicotinic cholinergic receptors. Bupropion attenuated the effects of nicotine withdrawal on brain stimulation reward thresholds (Paterson and Markou, 2007), and in humans has been shown to be an effective agent to assist quitting smoking. It could be the dopaminergic action of bupropion that is responsible for these effects; however, a beneficial effect of its actions on other neurotransmitter systems is also a possibility.

Withdrawal from chronic amphetamine use has been reported to alter norepinephrine levels in some brain areas (*e.g.*, Tonge, 1974); chronic cocaine decreased ligand binding to α_2-adrenoceptors in

rat cortex and hypothalamus (Giralt and Garcia-Sevilla, 1989) and chronic cocaine self-administration led to up-regulation of the norepinephrine transporter in several brain regions (Macey *et al.*, 2003; Beveridge *et al.*, 2005). These results show that noradrenergic neurotransmission was altered by chronic exposure to drugs of abuse. In related studies, the norepinephrine reuptake blocker tricyclic antidepressants desmethylimipramine and imipramine were found to attenuate brain stimulation reward threshold elevations observed following cocaine withdrawal (Kokkinidis *et al.*, 1980; Markou *et al.*, 1992), and chronic desipramine reversed the threshold increase seen during nicotine withdrawal (Paterson and Markou, 2007). Results may implicate norepinephrine in the anhedonic consequences of withdrawal from abused substances.

Glutamate has also been implicated; chronic amphetamine led to inhibition of glutamate release in the striatum (Kim *et al.*, 1981). Additionally, the glutamate mGluR2/3 receptor antagonist LY341495 reduced the threshold increase in brain stimulation reward produced by chronic nicotine (Paterson and Markou, 2007). Perhaps chronic nicotine leads to enhanced mGluR2/3 autoreceptor function and therefore enhanced inhibition of glutamate release. This might lead to enhanced reward thresholds and this effect might be blocked by inhibition of mGluR2/3 function. Results suggest a role for glutamate in the circuitry mediating the anhedonic effects of drug withdrawal.

Paterson and Markou (2007) ended their review with a discussion of the effects of clozapine on psychostimulant withdrawal. They presented data showing that subchronic (10-14 days) treatment with clozapine attenuated the reward-threshold elevating effects of withdrawal from nicotine. This result was in good agreement with reports from clinical studies that clozapine was effective in reducing smoking (see Coyle, 2006). The underlying mechanism of these intriguing effects of clozapine remains to be discovered.

CONCLUSIONS

Comorbidity of substance abuse and other psychiatric disorders is a complex phenomenon. In recent years studies of individual differences in early experience have revealed that these experiences influence susceptibility to drug taking in adulthood (Koehl *et al.*, 2001; 2002; Adriani *et al.*, 2006) and imaging studies implicate altered circuitry mediating self control in drug addiction (Baler and Volkow, 2006; Krystal *et al.*, 2006). These and related findings suggest that there are alterations in brain circuitry and/or neurotransmitter function that lead to a vulnerability to drug abuse.

Even in the absence of a specific vulnerability conferred by biological and/or environmental factors, people may have a natural tendency towards the consumption of abused substances. This is because most of those substances activate natural systems that are in place to signal biologically important events. In particular, dopaminergic systems projecting from the ventral midbrain to a number of telencephalic sites are activated by rewarding stimuli such as food, water, sex and social stimuli as well by most drugs of abuse (*e.g.*, Di Chiara, 1998). Drugs of abuse can be viewed as hijacking natural reward systems. Our biology is configured to predispose us towards primary stimuli that contribute to our survival and to learning to be attracted to secondary stimuli that signal those primary biologically important events. If stimuli such as drugs of abuse are encountered and those stimuli activate these natural reward systems, they subvert the natural function. Drugs of abuse satisfy a fundamental biological process by activating systems that signal that a biologically important event has occurred when in reality no such event has taken place. A substance that directly activates a system normally activated by biologically important events serves no physiological need. Thus, drugs of abuse, by hijacking natural reward systems, produce incentive conditioning (Beninger, 1983) and become ends in themselves although they fail to serve the needs of the individual using them.

Drug abuse that is comorbid with a psychiatric disorder cannot result solely from a natural tendency to consume substances that activate reward systems because the frequency of drug abuse in psychiatric populations including those with a diagnosis of schizophrenia or depression is several times higher than it is in the general population. This then frames the question of what are the underlying mechanisms mediating elevated drug use in psychiatric patients. We know that changes

in the brain, for example in glutamatergic neurotransmission, that result from the interplay of genes and environmental factors increase susceptibility to a number of psychiatric disorders. Do these same changes lead to an increased vulnerability to drug abuse? Coyle (2006) and Krystal *et al.* (2006) would argue that they do. Although our understanding of the mechanisms underlying susceptibility to schizophrenia, for example, is growing at a rapid pace, the evidence supporting the argument for a common mechanism with drug abuse is still quite weak. In the end, a better understanding of comorbid psychiatric disorders will come from improved understanding of nonpathological brain function. The extensive work now being done on the role of regions of the prefrontal cortex and its interconnecting circuits with other cortical and striatal structures in self-control and motivation for reward and punishment provides an excellent example. The continued efforts of basic and clinical scientists working side by side to further unravel the mysteries of brain function and its modulation by interacting genetic and environmental factors will lead to a better understanding of the mechanisms underlying comorbidly occurring drug abuse and other psychiatric disorders. This knowledge will bring about more rational treatment options.

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