The Reality of Comorbidity: Depression and Drug Abuse

The comorbidity of drug abuse with depression is well established and has important therapeutic and prognostic implications. Although there is significant understanding of the environmental and neurobiological factors involved in depression and drug addiction considered separately, the mechanisms underlying comorbidity are not well understood. It is likely that the high prevalence of co-occurrence of these two disorders reflects, in part, overlapping environmental, genetic, and neurobiological factors (Figure 1). It is also possible that there will be differences in the neurobiology of comorbidity depending on the temporal course of its development (i.e., depression followed by drug abuse versus drug abuse followed by depression). It is possible that in the former, drugs are used in attempts to self-medicate the depressive state, whereas in the latter it is possible that early exposure to chronic drugs of abuse might lead to neurobiological changes that increase the risk of depression. Areas of overlap in depression and addiction will be discussed here to identify pertinent areas of research for understanding the neurobiology of their comorbidity.

Prevalence of Comorbid Mental and Drug-Abuse Disorders

The prevalence of drug abuse in mood disorders (other than alcohol and nicotine) is estimated to be 19.4% (lifetime prevalence), and the presence of drug abuse increases the risk for depression by a factor of almost 5 (odds ratio [OR] = 4.7) (Regier et al 1990). Within the subtypes of mood disorders, the comorbidity rates are highest for bipolar I (40.7%, OR = 11). For major depressive disorder (MDD), the prevalence estimates from the most recent national survey were 24% (Kessler et al 2003). The comorbidity with nicotine is even higher, and for MDD the prevalence is 38.2% (Zimmerman et al 2002).

For drug abusers (other than nicotine and alcohol), mood disorders were found to be 4.7 times more prevalent in drug-dependent subjects than in the entire population (Regier et al 1990). In cigarette smokers, the lifetime prevalence of MDD is also high and is estimated to range between 31% and 60% (Glassman et al 1988). It has been speculated that chronic cigarette smoking might trigger depression, and an epidemiologic study estimated that smokers have an almost twofold greater risk of becoming depressed than nonsmokers (OR = 1.9) (Breslau et al 1998). Also, smokers with MDD tend to have more severe levels of addiction to nicotine and worse outcomes on smoking cessation treatments than smokers without MDD (see review by Covey et al 1998).

Comorbidity of cannabis abuse and depression is also relatively common (Bovasso 2001). Similar to nicotine, it is speculated that cannabis abusers might be attempting to self-medicate their dysphoria. It is also possible that chronic cannabis abuse triggers depression. Indeed, a recent 15-year longitudinal study of a randomly sampled adult population showed that cannabis abuse preceded depressive symptoms and that subjects who abused cannabis were four times more likely to have depressive symptoms at follow-up than those who did not (Bovasso 2001).

Abuse of other drugs, including cocaine, sedative hypnotics, and opioids, is also greater in individuals with depression than in those without it, and those with the highest risk seem to be the ones with comorbid anxiety disorders (Goodwin et al 2002).

Developmental Factors

Substance abuse usually starts in adolescence, a period during which the brain is still undergoing significant developmental changes. The percentage of children exposed to a drug of abuse during adolescence is not negligible, as documented by data from the most recent Monitoring the Future study, which reported lifetime drug use rates in adolescents (children in the 8th, 10th, and 12th grade) of 37.4% for illegal substances and 40.9% for cigarettes (National Institute on Drug Abuse 2003). Although the effects of drugs of abuse during this stage of development have not been adequately investigated, for some drugs, such as nicotine, exposure during adolescence leads to greater neurobiological changes than exposures later in life. For example, epidemiologic studies have provided evidence of an increased likelihood for the development of nicotine addiction when cigarette smoking starts early during adolescence (Kandel and Chen 2000). Similarly, in rats, exposure to nicotine during the period corresponding to adolescence results in upregulation of nicotine receptors and an enhancement of the reinforcing responses to nicotine when compared with animals exposed in the postadolescent period (Adriani et al 2003). A similar pattern might exist for other drugs.

Recent studies in rodents also provide preliminary evidence that early exposure to certain drugs can lead to neurobiological changes associated with depression. In these studies, chronic exposure to a stimulant drug during the period corresponding to childhood resulted in enhanced sensitivity in adulthood to stress, decreased sensitivity to natural reinforcers (model for anhedonia), and a decreased threshold for helplessness (model used to assess effectiveness of antidepressant medication) (Bolanos et al 2003; Carlezon et al 2003). Animal models of disorders in humans have some obvious weaknesses, however, and the disease-specific adaptation processes to drugs depend on this correspondence. These studies offer interesting preclinical data and highlight the need for studies in humans to investigate the consequences of early drug exposure on brain neurobiology and on vulnerability for future drug abuse and mood disorders.

Genetic Factors

Evidence from human studies (e.g., adoption and twin studies) and animal studies (e.g., uses of genetically altered strains of rodents, induced mutations in mice) affirms the prominent role that genetic factors play in substance abuse and depression vulnerability. Some estimates from epidemiologic studies indicate that at least 40% of the vulnerability for addiction is related to genetic factors, and for depression these estimates are between 24% and 58% (Uhl and Grow 2004). Although some progress has been made with genome scan methods to determine chromosomal regions linked to drugs of abuse and to depression, the specific genes associated with drug addiction and mood disorders alone (or in combination) remain to be identified. In studies of both disorders, either one or both forms of comorbidity discussed here (i.e., abuse preceding depression or depression preceding drug abuse) might produce heterogeneity of the phenotype that confounds the discovery of disorder-related genes. Genetic studies of more homogeneous groups, not of the pure disorders but instead of specific forms of typical

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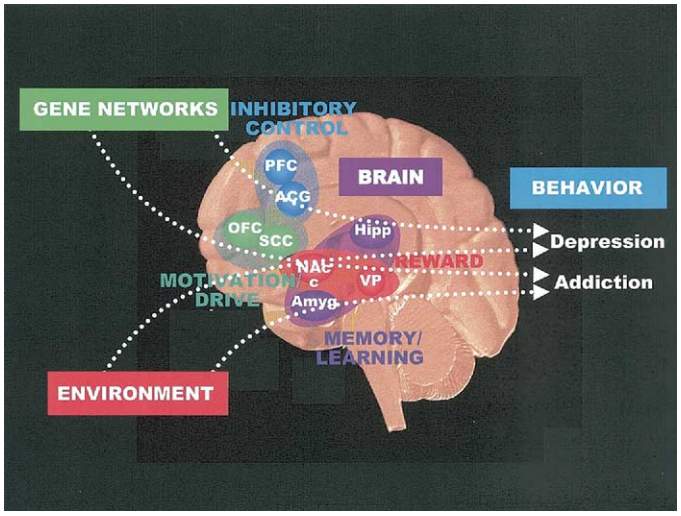

Figure 1. Diagram illustrating the complex interaction between genes, environment, and brain function that is likely to underlie the disrupted behavioral changes that occur in drug abuse and in depression. Overlapping environmental, genetic and/or neurobiological factors could account for the high degree of comorbidity between drug abuse and depression. Modified from Hamer (2002): Genetics. Rethinking behavior genetics. *Science* 298:71–72.

comorbid conditions, might define new phenotypes for investigation in genetic studies of drug abuse and depression.

It is also very likely that genetics play a prominent role in vulnerability to drug abuse and mood disorders due to gene–environmental interactions. Indeed, the important role that environmental factors have in modulating vulnerability as well as their interactions with genetic variants has been specifically demonstrated for depression (Caspi et al 2003). The specific consideration of two forms of comorbid drug abuse and depression suggest different environmental conditions that might be relevant (i.e., impoverished environments, such as in prison settings, that might make drug-stimuli particularly salient, or unavoidable, chronically stressful environments that might evoke depression). Also, changing the availability or acceptance of different drugs of abuse, such as nicotine and OxyContin, might create environmental conditions under which genetic vulnerabilities are unmasked.

Environmental Factors

Environmental variables that have been associated with substance abuse and depression show significant overlap (i.e., family disruption, poor parental monitoring, and low social class of rearing; Kendler et al 2003), and thus this overlap could contribute to comorbidity. In particular, stress, both acute and chronic, has been linked with both disorders. Because chronic stress is a common element in the environmental variables associated with both drug abuse and depression, it might account for some of their comorbidity. Acute stress is also linked to episodes of depression and to relapse in drug abuse. Moreover, disruption of different stress-mediated pathways has been documented for depression (the hypothalamic–pituitary–adrenal axis) and for chronic drug abuse (amygdala) that might converge to increase the comorbidity of these two conditions (see the review by Markou et al 1998). In fact, disruption of corticotropin-releasing factor in the amygdala has been postulated to underlie the anxiogenic and aversive consequences experienced during drug withdrawal (Koob 1999).

Pharmacologic Factors

Norepinephrine and serotonin are the neurotransmitters traditionally associated with the pharmacologic effects of antidepressant drugs, whereas dopamine (DA) is traditionally associated with the effects of drugs of abuse; however, the role of DA in depression has also been recognized (Di Chiara et al 1999; Willner 1983), and some antidepressants target the DA system (e.g., bupropion). Drugs of abuse are believed to exert their reinforcing effects by increasing DA in limbic regions, including nucleus accumbens (NAc) (Koob and Bloom 1988). In humans, the large and rapid increases in striatal DA (including NAc) induced by acute administration of drugs of abuse are associated with subjective reports of "high," euphoria, and mood elevation (see review by Volkow et al 2004). Dopamine increases in NAc also occur, although in less magnitude and duration, in response to natural reinforcers (i.e., food and gender) and other salient events (i.e., novel or unexpected stimuli) (see review by Horvitz 2000). These DA increases, whether induced by a drug or a natural stimulus, are linked to the motivational value of the stimulus and its ability to induce conditioned responses. Because drugs of abuse, by increasing DA, would enhance the salience of stimuli, one could postulate that this could temporarily ameliorate the amotivation and anhedonia in depression and could contribute to drug use in depressed patients. Similarly, disturbances in DA brain function in drug abusers could underlie the anhedonia and dysphoria that characterize drug withdrawal, which, in turn, could contribute to relapse as a means to ameliorate that aversive state (Markou et al 1998). Indeed, "depressive mood" during acute nicotine withdrawal is a significant predictor for smoking relapse (Killen et al 2003).

Although almost all drugs of abuse increase DA in NAc, this does not explain why the comorbidity of drug abuse and depression is higher for some of the drugs than for others. For nicotine, it is likely that the high prevalence of MDD with smoking, when compared with that of other drugs of abuse, reflects, in part, the fact that nicotine, by being legal, is much more available than illegal drugs. It is also likely, however, that the unique pharmacologic properties of nicotine contribute to the comorbidity. Indeed, preclinical and clinical studies have provided evidence that nicotine has antidepressant effects by mechanisms other than just DA increases (see review by Picciotto et al 2002). In addition, chronic cigarette smoking inhibits monoamine oxidase (MAO) A and MAO B in brain (Figure 2), which is an effect not linked to nicotine but that has been associated with antidepressant effects (see review by Fowler et al 2003). There are currently no data to assess whether the level of brain MAO inhibition observed in smokers is sufficient to have antidepressant effects. If the inhibition is sufficient, one could postulate that both the acute effects of nicotine as well as brain MAO inhibition by cigarette smoke could be factors that contribute to smoking in depressed patients. In this respect, it is interesting to note that smoking discontinuation in remitted patients can trigger a relapse to depression (Covey et al 1998).

Similarly, there are several lines of evidence that implicate the opiate system in the neurobiology of depression and in the therapeutic effects of antidepressant drugs (Vilpoux et al 2002). In rodents, chronic antidepressant treatment results in changes in the density of opiate receptors (Vilpoux et al 2002). Also, opiate analgesics, such as oxycodone and oxymorphone, have been

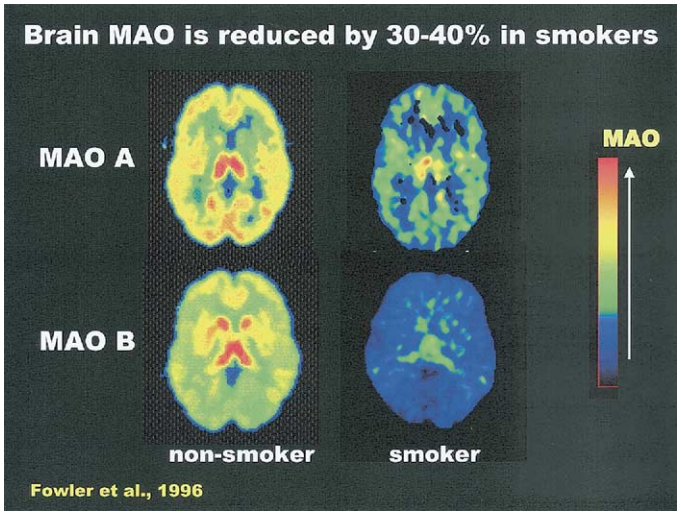

Figure 2. Brain images showing the concentration of monoamine oxidase (MAO) A and MAO B in a control subject and in a smoker. Cigarette smokers have significantly lower concentrations of MAO A and MAO B in brain than nonsmokers. Because drugs that inhibit these enzymes are effective antidepressants, this could contribute to smoking in depressed patients. Courtesy of Dr. Joanna Fowler, Brookhaven National Laboratory.

shown to improve mood in patients with refractory major depression (Stoll and Reuter 1999). Although it is recognized that comorbidity of depression with heroin is higher than in the general population, the information with opiate analgesics, the abuse of which has dramatically increased over the past few years (National Institute on Drug Abuse 2003; Substance Abuse and Mental Health Services Administration 2003), is much more limited.

The Neurobiology of Drug Use and Mood Disorders

Studies with neuroimaging technologies, such as positron emission tomography and magnetic resonance imaging, paired with behavioral measurement paradigms, have started to elucidate the neurochemical and functional brain changes that occur in response to drugs of abuse. These studies have shown a complex array of neural substrates involved in substance abuse disorders, including DA-related circuits that mediate saliency/reward, motivation/drive, conditioning/learning, and inhibitory control/disinhibition (Volkow et al 2003).

The addicted state, in striking contrast to the state of drug intoxication, is marked by significant decreases in DA brain function rather than increases. When drugs are used chronically, the repeated disturbance of the addict's DA system ultimately leads to decreases both in DA D2 receptors and in DA cell activity, and these adaptations persist long after the addict has discontinued drug use. These decreases in DA function are associated with dysfunction of prefrontal brain regions, including orbitofrontal cortex (involved in salience attribution) and cingulate gyrus (involved in inhibitory control and with mood regulation) (see review by Volkow et al 2003). The net result of these adaptations is a decreased sensitivity to natural reinforcers and other salient events, as well as a disruption of such frontal cortical functions as inhibitory control and salience attribution. In addition, imaging studies have implicated brain regions classically recognized to be involved with memory and conditioned learning (e.g., hippocampus, amygdala), mood regulation (e.g., ventral cingulate gyrus), and arousal (e.g., thalamus) in the acute responses to drugs of abuse (Li et al 1999; Volkow et al 1997, 2003) (Figure 1).

As is the case with drug abuse, it is likely that many brain regions mediate the diverse symptoms of depression. Human brain imaging studies have demonstrated changes in activity in numerous areas, including regions involved with mood regulation (e.g., ventral cingulate gyrus), cognitive operations (e.g., prefrontal cortex), memory (e.g., hippocampus), reward (e.g., ventral striatum), and arousal (e.g., thalamus) (Drevets 2001; Liotti and Mayberg 2001). Many of these brain regions have been implicated, as discussed above, in the acute response to drugs of abuse and in the adaptations that ensue after chronic drug administration. Moreover, changes in the brain's reward circuitry and in the amygdala have been implicated in inducing the negative emotional symptoms that often occur during early phases of withdrawal from many psychoactive drugs. Associations between self-reports of mood state and metabolism in limbic and paralimbic regions, identified to be abnormal in mood disorders, have also been correlated with mood abnormalities in abstinent methamphetamine abusers (London et al 2004).

Clinical Implications of Comorbidity

Comorbidity has implications for prevention, treatment, and disease progression. In one direction, because mood disorders increase the vulnerability for risk for drug abuse, diagnosis and treatment of depression could help prevent drug abuse. In the other direction, diagnosis and treatment of drug abuse might prevent later occurrence of depression.

Treatment of patients with comorbidity should include interventions for both disorders because lack of adequate treatment of one of the disorders might interfere with the recovery of the patient; however, treatment of the comorbid condition has its own special concerns. The potential for undesirable drug interactions should be considered, with respect both to drugs of abuse interfering with the effectiveness of antidepressants and to the increased risk for side effects of the antidepressants or enhanced toxicity of the drug of abuse. Also, as described above, comorbidity can exacerbate the severity of symptoms and affect response to treatment of either of the conditions.

Future Plans for Research in Comorbidity

Mechanisms Underlying Comorbidity

The National Institute on Drug Abuse (NIDA) and the National Institute of Mental Health (NIMH) have established priorities for genetic research to identify gene variations that increase vulnerability to mood and drug-abuse disorders or their comorbidity and to clarify how environmental factors can modulate gene expression and influence the development and course of either disorder separately or their comorbidity. Developmental brain studies will also be included to investigate the neurobiological and behavioral consequences of drug abuse through the various stages of development, the neurobiological circuits underlying drug addiction and mood disorders and their changes through development, and the modification of these circuits by environmental variables known to be involved in the occurrence of drug abuse and depression as a function of developmental stages.

More Effective Treatment Interventions for Comorbidity

Initiatives by NIDA and NIMH have been launched to accelerate drug discovery that include development of pharmacologic tools for basic and clinical research, discovery of new pharma-

cologic targets, and development and validation of models for evaluating novel therapeutics. Such investigations could pave the way for the development of new medication strategies to treat both conditions.

Services Research to Optimize the Prevention and Treatment of Comorbidity

The National Institute on Drug Abuse has developed strategies to meet the special challenges in service delivery that the prevention and treatment of comorbid mental and drug-abuse disorders require. For example, through the National Drug Abuse Treatment Clinical Trials Network, a NIDA-sponsored national research infrastructure for testing science-based treatments in community settings, NIDA is conducting trials to assess the impact of treating depression in drug abusers. Another example is the National Criminal Justice Drug Abuse Treatment Research System, which will allow investigation of interventions in the prison system, where rates of comorbidity between drug abuse and mental illness are at their highest.

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