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Animal Modeling and Neurocircuitry of Dual Diagnosis

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Abstract

Dual diagnosis is a problem of tremendous depth and scope, spanning many classes of mental disorders and addictive drugs. Animal models of psychiatric disorders studied in addiction paradigms suggest a unitary nature of mental illness and addiction vulnerability both on the neurocircuit and clinical-behavioral levels. These models provide platforms for exploring the interactive roles of biological, environmental and developmental factors on neurocircuits commonly involved in psychiatric and addiction diseases. While suggestive of the artifice of segregated research, training, and clinical cultures between psychiatric and addiction fields, this research may lead to more parsimonious, integrative and preventative treatments for dual diagnosis.

Keywords

Dual diagnosis; mental illness; schizophrenia; addiction; animal models; nucleus accumbens; hippocampus; dopamine; glutamate

INTRODUCTION

Dual Diagnosis: From Clinical Epidemiology to Basic Neuroscience

Substance Use Disorders (SUDs) occur at rates greater than in the general population across most major psychiatric disorders including schizophrenia, bipolar and unipolar depression, post-traumatic stress disorder, and antisocial and borderline personality disorders (1–5). Moreover, increased rates are not drug specific. People suffering from SUDs involving tobacco, alcohol and illicit drugs are way above the general population in all these disorders. Together, these observations suggest that shared as well as divergent disease aspects of mental disorders may commonly predispose to SUDs, and that shared properties among these drugs (e.g., their capacities to produce addiction), independent from their divergent properties (e.g., diverse and often opposing intoxicating/withdrawal effects), are important in understanding biological causality underlying dual diagnosis.

BASIC NEUROCIRCUITRY OF ADDICTIVE DISEASE

While differential intoxicating/withdrawal profiles of abused drugs are associated with their divergent effects on various brain regions and neurotransmitters (6), their shared reinforcing actions occur via mechanisms that are far more anatomically localized and neurochemically specific. The subcortical dopamine (DA) system, composed of neurons projecting from the midbrain ventral tegmental area (VTA) to the nucleus accumbens (NAc), plays a key role in natural motivation and operates as a common substrate upon which drugs act in addiction (7). Via numerous mechanisms at the level of the VTA and/or NAc, drugs most frequently abused in mental illnesses (and the general population), including nicotine, alcohol, amphetamine, cocaine, opiates and cannabis, all cause DA release into the NAc (8,9). Chronically, these drugs or their DA-related effects produce changes in NAc cellular protein expression, cellular

morphology, and functional alterations in local mechanisms of neuroplasticity underlying learning and memory (10–12). These changes likely comprise some of the chronic network adaptations underlying motivational sensitization whereby drug-seeking and taking become increasingly prioritized in the behavioral repertoire.

While these data describe addiction as a neurobiological process causing individuals to progress from substance use, to abuse, and then to dependence, we have no reason to assume this process is only applicable or specific to persons, (or animals) who are otherwise psychiatrically healthy. A similar process is likely to occur as a result of repeated addictive drug exposure in most if not all brains, whether psychiatrically healthy or ill. The key questions are whether particular brain conditions might accelerate this process, and if so, how?

Integrative Neurocircuitry of Mental Illness and Addiction Vulnerability

Psychological stress exacerbates psychiatric symptoms and accelerates drug use or relapse in patients with addictions. Accordingly, a growing literature describes how corticosteroids and other neurobiological mediators of stress impact brain regions implicated in addiction or mental illness (13). However, emerging data suggest this stress hormone connection is but the tip of the iceberg. Indeed, the major structures of the brain governing cognition, motivation, affect, and memory are so comprehensively interlinked that psychiatric and addictive disease processes are likely to be intimately bound together, and in many ways, indivisible (14).

In exploring this possibility, we have examined schizophrenia, as a prototypical dual diagnosis, in which SUD comorbidity is particularly high (15). Histopathological, neuroimaging and neurochemical correlates of schizophrenia have been incorporated into relatively sophisticated and comprehensive neurocircuit-based theories of its pathophysiology (16). Briefly, the preponderance of data regarding schizophrenia characterize it as: Neurodevelopmental syndrome entailing diffuse frontal cortical dysfunction and structural hippocampal abnormalities (17–19), associated with psychotic symptom exacerbation or reduction as a correlate of DA agonism or blockade, respectively, in the NAc (i.e., the dopamine hypothesis of schizophrenia) (20).

Against this background of schizophrenia research, basic science has revealed that inputs from a distributed network of cortical and temporal limbic regions including the prefrontal cortex (PFC), amygdala and hippocampus, play important roles in the motivational function of DA release in the NAc (Figure 1). Because the NAc and related striatal regions have direct influence on cortical and brainstem motor output centers, neuronal firing patterns across neuronal populations within these structures, most directly determine motivational states and behavioral output (21,22). The role of DA release in behavioral or motivational activation, then, is not simply about the amount of NAc-DA release as an isolated event, but is determined by the variable effects of DA release on neuronal firing rates across striatal neuronal populations (23). Critical to this determination is the ongoing activity of direct glutamatergic projections from the PFC, amygdala and hippocampus (24), which influence the firing rates of medium spiny NAc neurons in combination with DA release (21,23,25). Together, these data suggest that the effects of acute DA release into the NAc, whether endogenous or drug-induced, are determined by the functional integrity of distal PFC and temporal-limbic (amygdalar and hippocampal) regions. Since local neuroplastic events in the NAc, including long-term potentiation (LTP) and its variants, are contingent upon particular combinations of DA and glutamatergic discharge into this region (25,26), the functional integrity of the PFC, amygdala and hippocampus would also influence the long-term course of motivational or behavioral modifications attributed to repeated episodes of DA release (e.g., as in addictive drug abuse).

Animal and clinical data generally support the idea that various cortical and temporal limbic impairments can change drug-induced motivation and behavior. In adult rats, lesions to the

PfC, amygdala or hippocampus alter patterns of drug-induced behavioral sensitization (27), and motivational responding in self-administration (28,29). In humans, functional disturbances of the PfC are identified with abnormalities in volition, motivational planning, and impulsivity (30), as traits associated with increased SUD risk (31,32). Structural or functional abnormalities of the hippocampus are well documented in schizophrenia and most of the other major dually diagnosed disorders including major depression and bipolar disorder, post-traumatic stress disorder and borderline personality disorder (33–36).

ANIMAL MODELING DUAL DIAGNOSIS IN RATS WITH DEVELOPMENTAL HIPPOCAMPAL DAMAGE

Neonatal ventral hippocampal lesions (NVHL) in rats model multiple neurobiological and clinical features of schizophrenia (37). Excitotoxic ventral hippocampal injury in 7-day-old rats occurs at a time comparable with the second to third trimester of human brain development. Concurrently, hippocampal development may be especially sensitive to adverse genetic and environmental factors implicated in the pathogenesis of schizophrenia (38). Adult NVHL rats show atrophic changes in the ventral hippocampus and ventricular enlargement comparable with more subtle anatomical findings in human schizophrenia. They also demonstrate an array of behavioral abnormalities encompassing positive, cognitive and negative symptom domains of schizophrenia. In the positive domain, they show post-pubertal emergence of hyperlocomotive responses to stress, novelty, or drug-induced DA stimulation, modeling the typical post-adolescent-onset of psychosis (37). These symptoms are reduced by typical and atypical antipsychotics (39). In the cognitive and negative symptom domains, NVHL rats show sensory gating (prepulse inhibition) (40), working memory and latent inhibition deficits (41,42), and impaired social interaction (43–45). Neurobiologically, NVHLs produce biochemical and cellular changes in areas receiving ventral hippocampal input, including the PfC and NAc (46–50). The functional/developmental impact of NVHLs on these anterior cortico-striatal regions are reflected by changes in the firing responses of both NAc and PfC neurons provoked by VTA stimulation (51,52).

Studies on NVHL rats in paradigms measuring cognitive and motivational responses to addictive drugs were the first efforts to characterize a heuristically viable animal model of dual diagnosis schizophrenia. Using paradigms measuring spatial working memory of food reward in a radial arm maze, we found working memory deficits in NVHL rats that were not reversed by either nicotine or amphetamine (41). Subsequently, NVHL rats were examined in self-administration studies using paradigms modeling the progressive phases of human addiction (53). Here, NVHL rats showed enhanced rates of acquisition of lever pressing for food reward and delivery of intravenous cocaine. During acquisition and maintenance of cocaine self-administration, NVHL rats also showed increased binge-like patterns of drug intake. Thus, instrumental learning for both natural and drug rewards are enhanced in NVHL rats, even in the context of general cognitive deficits not relieved by addictive psychostimulants.

Next, NVHL and control rats were maintained on cocaine self-administration for approximately three weeks, leading to a total cumulative dose of cocaine that was not different between groups. Rats were then tested for persistence of lever pressing after cessation of cocaine delivery. NVHL rats showed increased lever pressing in extinction, and required a greater number of sessions to extinguish this drug-seeking compared with controls. After extinction of drug-seeking to the same level for both groups, rats were tested for the capacity of experimenter-delivered cocaine to re-instate drug-seeking behavior. Again, NVHL rats showed significantly greater drug-induced reinstatement of drug-seeking.

These extinction and reinstatement data demonstrated that chronic cocaine self-administration more robustly installs an addicted phenotype in NVHL rats compared with controls. To the

extent that NVHLs model schizophrenia, increased SUD comorbidity in this disorder reflects greater vulnerability to SUDs throughout several stages of the addictive process due to inherent neurocircuit dysfunction in the schizophrenic brain. Independent from drug intake, this could also manifest as other reward-related disturbances such as pathological water intoxication, inappropriate/compulsive masturbation and problem gambling (14,54).

Because impulsivity has been identified as a trait feature shared among patients with SUDs, and psychiatric disorders at risk for SUDs (31), we also investigated whether NVHL lesions produce impulsive approach to natural reward (55). Here, NVHL rats showed deficits in learning to respond to cues predictive of the presentation of water reward. However, they surmounted these deficits by utilizing an impulsive, non-cue-specific style of reward approach involving indiscriminant reward-seeking. Notably, their impulsive patterns were exacerbated by a prior history of cocaine exposure, while drug history had no effect on the performance of controls. These results may inform an ongoing debate about the causal association between impulsivity and SUDs in suggesting that both drug use and baseline impulsivity synergistically produce even greater impulsive phenotypes as an endophenotypic marker of the addiction process underway.

In ongoing studies designed to explore the neurobiological correlates of dual diagnosis, we have also examined NVHL rats in cocaine sensitization. Locomotor sensitization occurs when repeated doses of an addictive drug produces progressive increases in locomotor activity. This phenomenon has been suggested, on both neurobiological and phenomenological grounds, to be analogous with the process of drug-induced motivational sensitization as a core feature of the addiction process (56,57). In NVHL rats, daily cocaine injections (15 mg/kg i.p.) over 7 days produce abnormally elevated sensitization curves and some disruption of the incrementally increasing patterns of characteristic of controls. In addition, the capacity for prior drug experience to produce long-term increases in future drug responses are exacerbated in NVHL rats (58). These results parallel findings in rats with olfactory bulbectomy, which not only show neural changes in temporal-limbic circuits, and behavioral features of affective disorders, but also elevated psychostimulant sensitization curves (59) and self-administration (60). Taken together, these studies indicate that psychomotor responses to addictive drugs are involuntarily enhanced in animal models of psychiatric illness that involve differential forms of temporal-limbic circuit dysfunction, consistent with augmented progression of neuroplastic changes implicated in addictive disease.

SUMMARY

Varieties of mental illness, and schizophrenia in particular, may represent neurobiological conditions that produce psychiatric symptoms independent from drug exposure, but increased vulnerability to the addiction process with drug exposure. In this manner, increased SUD vulnerability is itself a primary disease symptom of the neurobiology of mental illness, emerging in parallel with, but not directly caused by the differential capacities of addictive drugs to enhance or reduce specific psychiatric symptoms. Thus far, animal studies confirm the unitary nature of the neurocircuits that govern both major psychiatric syndromes and enhanced addiction vulnerability. A key implication of this integrated neurocircuit theory is that many genetic and environmental risk factors for mental illness, SUDs, or dual diagnosis conditions could be identical. One factor (or certain sets of them) may predispose to common patterns of global neurocircuit dysfunction, which in turn predispose to mental illness, addictions, or very frequently, both. Given that both genetic and environmental stimuli sculpt the information processing, and learning attributes of neural networks commonly involved in mental illness and addictions, future investigations should explore the biological interactions of drug exposure and psychiatric disease processes in dual diagnosis neurocircuits. Further animal modeling of dual diagnosis may be vital to designing more parsimonious, preventative

and integrative treatments for dual diagnosis patients, while supplying the necessary scientific foundation for pushing systems of mental health care, education, and practice toward more integrated approaches for SUDs and mental illness.

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FIGURE 1.

Integrative Neurocircuitry of Dual Diagnosis

Note: The ventral portion of the striatum (nucleus accumbens) encodes information that guides the organization of motivated behavior via its connectivity with dorsal striatum and cortical and brainstem motor centers. Dopamine (thin dark arrows) released endogenously, or by action of addictive drugs, from the VTA into the nucleus accumbens, gates motivational information and facilitates neuroplastic changes. Glutamatergic axons (wide clear arrows) from the prefrontal cortex, amygdala and ventral hippocampus supply executive-decision making, affective and contextual memory information to the nucleus accumbens, and interact with dopamine efferents to influence motivational programming and adaptation. Compromise of these prefrontal or temporal limbic structures in schizophrenia and other psychiatric disorders may change short and long-term motivational implications of drug-induced dopamine release in the nucleus accumbens.