Commentary on "Neurochemical Predictors and Correlates of Vulnerability to Cocaine Use" by-King and Flowers

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SUMMARY

This proposed study concerns the neurochemical and behavioral factors that influence cocaine craving. The researchers hypothesize that heightened mesolimbic dopamine (DA) activity leads to cocaine craving and is associated with both histrionic behavior and increased sensitivity to the rewarding aspects of cocaine use. Finally, they hypothesize that heightened DA activity is reflected in increased motor activity. These points may be summarized as follows: Increased mesolimbic dopamine function is associated with increased cocaine craving, histrionic behavior, increased reward, and increased motor activity. Cocaine craving is associated with increased DA and homovanillic acid (HVA) in cerebro-spinal fluid (CSF), histrionic behavior, and increased motor activity. Increased DA and HVA in CSF is associated with increased motor activity.

The investigators therefore plan to determine whether levels of DA and HVA in CSF correlate with cocaine craving, whether histrionic traits as defined in the "Diagnostic and Statistical Manual of Mental Disorders" (3ded. rev.) (DSM-III-R) correlate with cocaine craving, whether increased motor activity correlates with cocaine craving, and whether CSF DA and HVA levels correlate with increased motor activity.

STRENGTHS OF THE PROPOSED RESEARCH

The authors of this proposal have made a series of bold hypotheses, and they are to be commended for the originality and novelty of their thinking, as well as for the thorough and logical way in which they support their arguments. The overarching idea—that individual differences in dopaminergic function are reflected not only in cocaine craving but also in personality traits and physiological measures—

integrates current thought on the neurobiology of reward, cocaine abuse, and personality. The strengths can be summarized as follows:

1. Individual differences in DA function are associated with assessment of cocaine craving, personality traits, and physiological measures.

2. Theoretical framework integrates thoughts on the neurobiology of reward, cocaine abuse, and personality.

3. Promising preliminary data are presented.

4. Methodology includes study of long-term inpatient substance abusers, which yields a better control of variables such as CSF measures.

The appeal of integrative biologically based approaches to psychiatric phenomena is readily understood. Several biological psychiatrists have criticized their field for its often limited approaches. The authors of this proposal, on the other hand, offer their hypotheses within a systematic and ambitious framework. They cite the work of Cloninger and Siever, both of whom have also made pioneering attempts to construct inte-grative approaches to the psychobiology of Axis I and II disorders.

WEAKNESSES OF THE PROPOSED RESEARCH

The appeal of the systematic and integrative biologically based approaches should be balanced by an acknowledgment of the difficulties faced. Approaches (such as the one taken in these proposed studies) that empha-size individual differences in a particular neurotransmitter run the risk of being overly reductionistic. Furthermore, approaches that situate unitary biological differences as the basis of a broad range of heterogenous behaviors (e.g., from cocaine use to extroversion) run the risk of ignoring a variety of other factors (biological and psychological) that may account for their expression. Weaknesses and potential difficulties with these studies are summarized as follows:

1. Single neurotransmitter approach is reductionistic.

2. Single biological difference is correlated with heterogeneous behavior (e.g., cocaine use with extroversion) that excludes multiple

factors and interactions, for example, between biological, psychological, and sociological domains.

3. Lumbar CSF levels of DA and HVA are measured, but the meso-limbic DA systems contribute only a small effect in the lumbar tap.

4. There is no indication of comparing ratios of CSF metabolites (e.g.,HVA and 5-hydroxyindole acetic acid (5-HIAA)).

5. Long-term cocaine use may modify DA uptake.

6. Cocaine craving measures need to be reliable.

7. Concept of cocaine craving attacks has not been generally accepted.

8. Sociopathy is not identical to histrionic behavior, but terms are used interchangeably.

9. Motor activity is not solely influenced by DA activity. For example, attention deficit-hyperactivity disorder (ADHD) may influence both motor activity and substance abuse.

10. Motor activity measures need to be valid and standardized (e.g.,-comparison between wrist monitor and nurse ratings).

Despite the difficulties, some of which are common for proposals of this type, it is clear that the authors have a track record of providing empirical validation of their theoretical claims. In particular, they have preliminary data on the correlation of CSF HVA and cocaine craving, of CSF HVA and histrionic traits, and of histrionic traits and motor activity. This lends support to the proposed studies. In fact, the authors acknowledge several methodological limitations to their proposal. First, lumbar CSF DA and HVA may not strongly reflect mesolimbic DA activity. Evidence is needed, therefore, to establish the extent to which the CSF measures reflect the intracerebral ones. CSF studies remain a valuable approach, yet they need to be understood in terms of the context of their total contribution.

The authors also acknowledge the limitations of focusing on a single neurotransmitter system, and they propose to measure monoamine metabolites other than those of DA. This is particularly timely in view of recent work suggesting that measuring patterns of CSF metabolites is more meaningful than focusing on any particular concentration

level (Potter and Manji 1993). It is also important in view of recent work emphasizing the involvement of the serotonin system in cocaine craving.

The effects of long-term cocaine use itself lead to difficulties in studying the DA system. Thus, long-term cocaine use could potentially modify the parameters of DA uptake. The authors plan to use statistical methods to minimize this effect. This is a difficult problem, and it would be helpful to know the extent of the difficulty from preliminary data.

Finally, measurements need to be selected for reliability and validity. In the measurement of cocaine craving, several groups have succeeded, but the reliability should be checked in the authors' laboratory using the same questions. Data on this would be necessary. Further details on cocaine craving attacks are needed. The issue of personality traits also needs clarification. For example, how do histrionic traits compare to antisocial personality disorder and other sociopathy? It is noted in the proposal that the histrionic factor is loaded primarily on histrionic, borderline, and dependent traits. Further, it is noted that CSF HVA is correlated with antisocial features in control samples. These personality and sociopathy connections to biological measures need support.

ALTERNATE STRATEGIES

Because of the theoretical and empirical concerns regarding the correlation between dopaminergic function and motor activity, it might be appropriate to consider the role of hyperactivity in this context. The relationship between attention deficit disorder (ADD) and dopaminergic function should be assessed, perhaps by administering Ward and colleagues' (1993) recent scale that measures childhood ADD in adult subjects. It has been found (Manuzza et al. 1991) that a subgroup of children with ADD become substance abusers. Finally, previous work has used nursing assessments as measures of motor activity; this might be supplementary or an alternative to wrist movement. Some alternate and additional ideas are summarized as follows:

1. Use DA challenges (e.g., apomorphine) to elucidate dopaminergic function instead of CSF levels.

2. Study serotonin function also, using both CSF metabolite measures (5-HIAA) and challenges (e.g., m-chlorophenylpiperazine (mCPP) or fenfluramine).

3. Assess ADD with the Wender scale for childhood ADD (Ward et al. 1993).

4. Obtain functional measures of DA with imaging positron emission tomography (PET).

5. Study homogenous personality-disordered patients such as those with borderline personality disorder or antisocial personality disorder.

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