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Letter to the Editor

Clinical Implications of Cocaine-Induced Cortical Depression

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Sir

(Trantham-Davidson and Lavin, 2004) found that the acute administration of cocaine decreased spontaneous firing and VTA-evoked responses in the prefrontal cortex (PFC), and compromised the membrane bistability of PFC pyramidal neurons. The authors previously reported similar findings after repeated cocaine administration, and should be commended for their pursuit of cocaine-induced neuroadaptations through *in vivo* single-cell recording studies. In other animal studies, chronic exposure to cocaine also produces dysfunctional morphological changes (Robinson *et al*, 2001) and reduced numbers (Lidow and Song, 2001) of PFC pyramidal neurons, which is consistent with reports (reviewed elsewhere) that cocaine-dependent patients have reductions in PFC metabolism and gray matter density, and perform poorly on standardized tests that assess frontal function (Dackis and O'Brien, 2003). While the authors reasonably concluded that electrophysiological alterations of pyramidal neurons might affect attention, working memory, and information processing, we believe that PFC dysfunction may also be a core component of cocaine addiction, and contribute to many baffling characteristics of addicted patients that were once thought to be purely psychological.

Denial, a hallmark of cocaine addiction, classically involves minimization, rationalization, and poor insight into cocaine-related hazards. These examples of nonadaptive executive function could stem from cocaine-induced PFC imbalances, as might problems with decision-making, impulse control, and motivation that are characteristic of cocaine-addicted patients. Also, it has been firmly established by a large number of controlled studies that regions of the PFC (especially the anterior cingulate cortex) are robustly activated during cue-induced cocaine craving. Remarkably, these hypermetabolic responses occur in regions that are hypometabolic at baseline, creating an enhanced 'delta' response that might underlie cue salience, an important yet poorly understood phenomenon that often leads to recidivism in the clinical arena. Pharmacological interventions that diminish the magnitude of this metabolic response, either by normalizing hypofrontality (eg glutamate-enhancing agents like modafinil) or dampening hypermetabolic responses to cocaine-conditioned cues (eg GABA-enhancing agents like topiramate or baclofen), are currently under intense investigation (Dackis, 2004). Human and animal studies also suggest that delta responses are important in cocaine reward. Patients with baseline negative affective symptoms (Newton *et al*, 2003), or baseline cocaine withdrawal (Sofuoglu *et al*, 2003), report enhanced cocaine-induced euphoria under controlled conditions. Additionally, cocaine reinstatement is obliterated in animals after baseline glutamate depletion has been pharmacologically normalized, diminishing the delta release (peak minus baseline) of glutamate after cocaine administration (Baker *et al*, 2003). Given these considerations, the evolving controversy over glutamate-enhancing *vs* GABA-enhancing agents for cocaine dependence could ultimately resolve in relative agreement.

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