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LETTER TO THE EDITORS

Paulson and Robinson (1996) have recently reported that, on days 3 and 7 after withdrawal from chronic, twice-a-day amphetamine pretreatment (escalating doses × 40 days), there was behavioral depression (nocturnal hypoactivity) associated with a significant decrease in dopamine and its metabolites in the dorsolateral caudate nucleus, but not in the nucleus accumbens. They point out that, with their microdialysis method, it is not possible to ascertain the exact nature of the neurobiological adaptations responsible for the decrease in the "nigrostriatal" terminal region. They list a number of possible mechanisms, including increased dopamine uptake and sensitivity of autoreceptor regulation of dopamine release. As to the changes in autoreceptor regulation, they state that the literature on stimulant withdrawal or sensitization-related changes in the release-modulating terminal autoreceptors is small and inconsistent. They state that it is not known whether there are changes in the substantia nigra somadendritic autoreceptors controlling firing rate.

We propose that the decreased concentrations of dopamine and its metabolites reported by Paulson and Robinson (1996) may be indeed secondary to the *supersensitivity* of soma/dendritic and terminal dopamine autoreceptors. Apomorphine supersensitivity of nigral dopamine neurons following withdrawal from a dosing regimen producing behavioral *tolerance* (continuous infusion) was reported in the 1980s (Ellinwood and Lee 1983; Lee and Ellinwood 1989). The dopamine neurons exhibited an initial subsensitivity to the impulse-inhibiting effect of apomorphine; this subsensitivity then progressed to the control level on day 2 and finally supersensitivity on day 7 of withdrawal. Utilizing L-dopa accumulation as an index of dopamine synthesis, the second study also found evidence of supersensitive terminal autoreceptors on day 7, as demonstrated by enhanced inhibition of dopamine synthesis by apomorphine (10-50 μg/kg SC). These *in vivo* results were extended in an *in vitro* study (Lee et al. 1993), that demonstrated that, even in the absence of striatonigral feedback, nigral dopamine neurons were supersensitive to bath-applied dopamine. This *in vitro* study provided a strong evidence for the original hypothesis (Ellinwood and Lee 1983) that soma/dendritic dopamine autoreceptors become supersensitive in a time-dependent manner during the first week of withdrawal. Paulson and Robinson (1996) have reported significant behavioral and biochemical changes as early as day 3; however this early appearance of apparent autoreceptor supersensitivity might be related to the much longer pretreatment than done in the earlier studies (i.e., 40 days vs. 7 days).

Very similar time-dependent changes in nigra dopamine neuron firing rate sensitivity to apomorphine (i.e., sub- followed by supersensitivity) also have been reported following withdrawal from 14-day continuous cocaine administration (Zhang et al. 1992), a dosing regimen that, again, consistently leads to behavioral tolerance (King et al. 1994). Furthermore, with fast-scan in vitro voltammetry, Jones et al. (1996) have also found that continuous cocaine infusion induces a supersensitivity of terminal autoreceptors regulating DA release on day 7. This voltammetry study, along with the earlier studies, support the hypothesis that the supersensitivity of soma/dendritic and terminal dopamine autoreceptors may be one of the mechanisms mediating the DA hypofunction reported by Paulson and Robinson (1996). In conclusion, there are several lines of evidence that indicate that alterations in autoreceptor control of dopamine impulse-flow and synthesis/release are closely related to significant decreases in dopamine and dopamine metabolites in the dorsolateral caudate nucleus.

Based on their negative findings in the nucleus accumbens, Paulson and Robinson (1996) have stated that: (1) there has been a great emphasis over the years on the role of the nucleus accumbens dopamine in mediating the affective and motivational states of psychomotor stimulant drugs and (2) perhaps it is time to reconsider the possibility that dopamine neurotransmission in the dorsal striatum may be involved in complex psychological functions as well. As stated (Lee et al. 1993), we completely agree with their statements. We also agree (Ellinwood and Lee 1983; Gawin and Ellinwood 1988) that examining changes on withdrawal days 3–7 might be fruitful in elucidating the mechanisms underlying the various behavioral deficits noted in *compulsive* stimulant abusers during withdrawal. The major research focus on the nucleus accumbens (vs. the dorsolateral striatum), on the one hand, and on behavioral *sensitization* (vs. *tolerance*), on the other, may have led to unintended neglect

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of important mechanisms, which may be associated with stimulant abuse.

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