ELSEVIER

RESPONSE

In their letter, Lee, Ellinwood, and King suggest that the decrease in extracellular (dialysate) dopamine (DA) in the dorsolateral caudate nucleus that we (Paulson and Robinson 1996) recently found in association with amphetamine withdrawal may be, "secondary to supersensitivity of soma/dendritic and terminal dopamine autoreceptors." In support of this they cite a number of papers reporting that a week following the discontinuation of continuous treatment with amphetamine or cocaine, there is evidence for DA autoreceptor supersensitivity. It is, of course, an empirical question whether the neuroadaptations reported by Lee and his colleagues are responsible for the amphetamine withdrawal–related changes in extracellular DA we reported. We suggest, however, that one should generalize between these studies only with extreme caution and that, indeed, it may be inappropriate to do so. In all the studies cited by Lee and his colleagues that found evidence for DA autoreceptor supersensitivity animals received amphetamine or cocaine continuously through subcutaneously placed osmotic minipumps. In the amphetamine studies, animals received 4.8 to 5.0 mg per day infused continuously for 7 days. This dosing regimen has been shown to be neurotoxic, leading to striatal DA depletion (Ricaurte et al. 1984; Lee and Ellinwood 1989), presumably due to a loss of striatal DA terminals (Ellison et al. 1978; Ricaurte et al. 1984). For example, Ricaurte et al. (1984) reported that the continuous administration of 4 mg per day of d-amphetamine for only 3 days was sufficient to produce amphetamine neurotoxicity. In contrast, the intermittent dosing regimen used by Paulson and Robinson (1996) is not neurotoxic (Robinson and Camp 1987; Paulson et al. 1991).

There is a large literature indicating that the effects of continuous treatment with amphetamine or cocaine are very different from the effects of repeated intermittent treatment with these same agents (for reviews see Post 1980; Ellison and Eison 1983; Robinson and Becker 1986). As put by Ellison and Eison (1983), "Continuous amphetamines have effects on brain neurochemistry which are distinctively different from those following repeated injections" (p. 757). Consistent with this, Lee and his colleagues have reported that, "the continuous administration of cocaine produces findings consistent with D_2 autoreceptor supersensitivity," whereas "intermittent cocaine administration did not produce evidence of D_2-autoreceptor supersensitivity" (King et al. 1994, p. 743). The absence of DA autoreceptor supersensitivity following intermittent treatment with psychostimulants, which produces behavioral sensitization, is in agreement with the literature on the topic reviewed by White and Wolf (1991).

In reviewing the literature on the nature of the neuroadaptations produced by repeated amphetamine treatment Robinson and Becker (1986) suggested that one reason the literature on the topic appeared "contradictory and confusing" in the mid-1980s was because at that time little attention was paid to the differences between continuous treatment regimens that are potentially neurotoxic (as well as high-dose neurotoxic regimens) and the intermittent nonneurotoxic treatment regimens associated with behavioral sensitization. Today this view is generally accepted. That is, the neuroadaptations produced by continuous amphetamine administration and other neurotoxic regimens may not shed light on the nature of the neuroadaptations produced by intermittent (nonneurotoxic) amphetamine treatment regimens. For this reason, we suggest that it is not appropriate to generalize freely across studies using these very different drug treatment regimens.

Terry E. Robinson, Ph.D.
Pamela E. Paulson, Ph.D.
Department of Psychology
The University of Michigan

REFERENCES

Ellison GD, Eison MS (1983): Continuous amphetamine intoxication: An animal model of the acute psychotic episode. Psychol Med 13:751–761

Ellison G, Eison MS, Huberman HS, Daniel F (1978): Long-term changes in dopaminergic innervation of caudate nucleus after continuous amphetamine administration. Science 201:276–278

King GR, Ellinwood EH Jr, Silvia C, Joyner CM, Xue Z, Caron MG, Lee TH (1994): Withdrawal from continuous or intermittent cocaine administration: Changes in D_2 receptor function. J Pharmacol Exp Ther 269:743–749

Lee TH, Ellinwood EH Jr (1989): Time-dependent changes in the sensitivity of dopamine neurons to low doses of apomorphine following amphetamine infusion. Brain Res 483:17–29

NEUROPSYCHOPHARMACOLOGY 1997–VOL. 16, NO. 4

Published by Elsevier Science Inc.
655 Avenue of the Americas, New York, NY 10010

0893-133X/97/$17.00
PII S0893-133X(96)00167-4

Paulson PE, Camp DM, Robinson TE (1991): The time course of transient behavioral depression and persistent behavioral sensitization in relation to regional brain monoamine concentrations during amphetamine withdrawal in rats. Psychopharmacology 103:480–492

Paulson PE, Robinson TE (1996): Regional differences in the effects of amphetamine withdrawal on dopamine dynamics in the striatum: Analysis of circadian patterns using automated on-line microdialysis. Neuropsychopharmacology 14:325–337

Post R (1980): Intermittent versus continuous stimulation: Effect of time interval on the development of sensitization or tolerance. Life Sci 26:1275–1282

Ricaurte GA, Seiden LS, Schuster CR (1984): Further evidence that amphetamines produce long-lasting dopamine neurochemical deficits by destroying dopamine nerve fibers. Brain Res 303:359–364

Robinson TE, Becker JB (1986): Enduring changes in brain and behavior produced by chronic amphetamine administration: A review and evaluation of animal models of amphetamine psychosis. Brain Res Rev 11:157–198

Robinson TE, Camp DM (1987): Long-lasting effects of escalating doses of d-amphetamine on brain monoamines, amphetamine-induced stereotyped behavior and spontaneous nocturnal locomotion. Pharmacol Biochem Behav 26:821–827

White FJ, Wolf ME (1991): Psychomotor stimulants. In Pratt J (ed), The Biological Bases of Drug Tolerance and Dependence, New York, Academic Press, pp 153–197