ELSEVIER

LETTER TO THE EDITOR

Cocaine Withdrawal and the Cerebral Influx of [^{18}F]fluoro-L-DOPA (FDOPA)

A recent article in *Neuropsychopharmacology* (Wu et al. 1997) reports the first attempt to assess with positron emission tomography (PET) the effects of chronic cocaine use on the cerebral influx of 6-[^{18}F]fluoro-L-DOPA (FDOPA), a tracer for DOPA decarboxylase in catecholamine fibers of living human brain. Other PET studies have probed the occupancy of dopamine uptake sites or post-synaptic receptors in cocaine users (Volkow et al. 1996, 1997). FDOPA/PET can, in principle, probe the metabolic state of dopamine neurons, but the interpretation of findings reported by Wu et al. is difficult.

The authors used a linear warping procedure to normalize each PET scan to a common coordinate system. The net plasma clearance of FDOPA (K_i) was then calculated on a pixel-by-pixel basis using a graphical analysis method first developed for in vivo assays of deoxyglucose metabolism by Gjedde (1982) and later generalized by Patlak et al. (1983) and Patlak and Blasberg (1985). In the specific application of this plot to the case of FDOPA (Gjedde 1988), the distribution volume of FDOPA observed in a region of interest is corrected for the presence of a brain-penetrating metabolite by subtracting the radioactivity concentration in a reference region assumed to be devoid of catecholamine fibers. The magnitude of K_i is then estimated from linear regression of this distribution volume as a function of the normalized and metabolite-corrected integral of FDOPA in arterial plasma (Martin et al. 1989). Wu et al. (1997) employ an ingenious method for defining contiguous regions in brain for statistical comparisons of K_i between subject groups, and for comparing effects of acute and chronic withdrawal from cocaine. However, it is not revealed how regions of interest (Figure 2) or reference regions in brain were delineated, nor is it explained how the HPLC fractionation of tracers in arterial plasma was accomplished. If the authors calculated the magnitude of K_i from the linear regression described above, it is distressing that the units (perhaps ml striatum^{-1} min^{-1}, or ml hg^{-1} min^{-1}) are misstated (as a rate constant, min^{-1}, Figure 3), or not stated at all (Table 1, Figure 2). The standard deviations of the mean estimates of K_i are high (>40%, Table 1) in comparison to reports from many laboratories (<20%, see Cumming and Gjedde 1998), casting some doubt on the claim of decreased FDOPA influx after extended abstinence from cocaine.

The authors review the literature describing the regulation of DOPA decarboxylase activity ex vivo and in vitro (see Neff and Hadjiconstantinou 1995), arguing that the enzyme might be regulated so as to influence the rate of trapping of DOPA decarboxylase substrates in living brain (Kish et al. 1995). Unfortunately, they have failed to cite independent discoveries of this idea (Gjedde et al. 1993; Opacky-Juffry and Brooks 1995), and the first demonstration by direct measurement of the phenomenon in living rat brain (Cumming et al. 1995).

The discussion contains several serious inaccuracies in the description of the implicit model underlying estimates of net plasma-brain clearance. Specifically, FDOPA is transferred across the capillary epithelium by facilitated diffusion followed by simple diffusion within brain, not active transport followed by perfusion within brain, as Wu et al. state. The irreversibility of the trapping of decarboxylated FDOPA metabolites was not demonstrated in the cited references (Patlak et al. 1983; Patlak and Blasberg, 1985; Martin et al. 1989). Indeed, the assumption of irreversible trapping of these metabolites is likely to be violated (Huang et al. 1991, see Cumming et al. 1998) during PET experiments lasting 120 min, as in the study under consideration. Furthermore, the rate of elimination of decarboxylated FDOPA metabolites from brain appears to be accelerated in patients with Parkinson's disease (Kuwabara et

NEUROPSYCHOPHARMACOLOGY 1999–VOL. 20, NO. 4

Published by Elsevier Science Inc.
655 Avenue of the Americas, New York, NY 10010
0893-133X/99/$–see front matter
PII S0893-133X(98)00096-7

al. 1993), and may conceivably also be abnormal during cocaine withdrawal, consequently altering the apparent magnitude of K_i calculated from linear regression. The interpretation of FDOPA/PET scans can be fraught with ambiguities. We feel that these ambiguities must be addressed more clearly in order to illuminate changes in dopamine metabolism underlying the pathophysiology of cocaine addiction.

Paul Cumming, Ph.D.
PET Centre
University of Aarhus
Aarhus, Denmark

Jakob Reith, M.D.
Dept. Neurophysiol
Glostrup County Hospital
Copenhagen, Denmark

Albert Gjedde, M.D., Ph.D.
PET Centre
University of Aarhus, Aarhus, Denmark

REFERENCES

Cumming P, Kuwabara H, Ase A, Gjedde A (1995): Regulation of DOPA decarboxylase activity in brain of living rat. J Neurochem 65:1381–1390

Cumming P, Gjedde A (1998): Compartmental analysis of DOPA decarboxylation in living brain from dynamic positron emission tomograms. Synapse 29:37–61

Gjedde A (1982): Calculation of glucose phosphorylation from brain uptake of glucose analogues in vivo: A re-examination. Brain Res Rev 4:237–274

Gjedde A (1988): Exchange diffusion of large neutral amino acids between blood and brain. In: Rakic L, Begley DJ, Davson H, Zlokovic BV, (eds), Peptide and Amino Acid Transport Mechanisms in the Central Nervous System. London: MacMillan, pp 209–217

Gjedde A, Léger G, Cumming P, Yasuhara Y, Evans AC, Guttman M, Kuwabara H (1993): Striatal L–DOPA decarboxylase activity in Parkinson's disease in vivo: Implications for the regulation of dopamine synthesis. J. Neurochem 61:1538–1541

Huang S-C, Yu D-C, Barrio JR, Grafton S, Melega WP, Hoffman JM, Satyamurthy N, Mazziotta JC, Phelps ME (1991): Kinetics and modeling of L-6-[^{18}F]fluoro-DOPA in human positron emission tomography studies. J Cereb Blood Flow Metab 11:898–913

Kish SJ, Zhong XH, Hornykiewicz O, Haycock JM (1995): Striatal 3,4-dihydroxyphenylalanine decarboxylase in aging: Disparity between post mortem and positron emission tomography studies. Ann Neurol 38:260–264

Kuwabara H, Cumming P, Léger G, Guttmann M, Diksic M, Evans AC, Gjedde A (1993): Dopamine turnover is increased in striatum of patients with Parkinson's disease. Brain 93, Sendai Japan, May 22–28

Martin WRW, Palmer MR, Patlak CS, Calne DB (1989): Nigrostriatal function in humans studied with positron emission tomography. Ann Neurol. 26:535–542

Neff NH, Hadjiconstantinou M (1995): Aromatic L-amino acid decarboxylase modulation and Parkinson's disease. Prog. Brain Res 106:91–97

Opacka-Juffry J, Brooks DJ (1995): L-Dihydroxyphenylalanine and its decarboxylase: New ideas on their neuroregulatory roles. Move Disord 10:241–249

Patlak CS, Blasberg RG, Fenstermacher JD (1983): Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. J Cereb Blood Flow Metab 3:1–7

Patlak CS, Blasberg RG (1985): Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. Generalizations. J Cereb Blood Flow Metab 5:584–590

Volkow ND, Wang GJ, Fowler JS, Logan J, Hitzemann R, Gatley SJ, MacGregor RR, Wolf AP (1996): Cocaine uptake is decreased in the brain of detoxified cocaine users. Neuropsychopharmacology 14:159–68

Volkow ND, Wang GJ, Fischmann MW, Foltin RW, Fowler JS, Abumrad NN, Vitkun S, Logan J, Gatley SJ, Pappas N, Hitzemann R, Shea CE (1997): Relationship between subjective effects of cocaine and dopamine transporter occupancy. Nature 386:827–830

Wu JC, Bell K, Najafi A, Widmark C, Keator D, Tang C, Klein E, Bunney BG, Fallon J, Bunney WE (1997): Decreasing striatal 6-FDOPA uptake with increasing duration of cocaine withdrawal. Neuropsychopharmacology 17:402–409