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RESPONSE

Decreasing Striatal 6-FDOPA Uptake with Increasing Duration of Cocaine Withdrawal

I would like to reply to Cumming, Reith, and Gjedde regarding our study ("Decreasing Striatal 6-FDOPA Uptake with Increasing Duration of Cocaine Withdrawal") which is the first study to assess the effects of chronic cocaine use on the cerebral uptake of 6-[^{18}F]-fluoro-L-DOPA (FDOPA) which is a tracer for DOPA decarboxylase in catecholamine fibers of the living human brain (Wu et al. 1997).

We appreciate the correspondents' comment regarding the ingenuity of our method for defining contiguous regions for statistical comparisons of K. There were some requests for additional information regarding several points, which we provide in this response. First, there was a request for how the regions of interest and reference regions were delineated. The regions of interest were manually drawn from an averaged normal control striatal FDOPA image from a preliminary study. The reference regions were placed in the occipito-temporal junction, which has low cortical dopaminergic input.

Second, there was a request for an explanation of how the HPLC fractionation of the plasma samples was accomplished. The HLPC studies were performed with a computer controlled HPLC system (Waters Associate, Milford, MA) that included two 510 pumps, a U6K injector, a variable wave length UV detector operated at the 280 nm. A 3.9 $\times$ 150 mm μBondapak C18 column (Part number 86344) and an isocratic solvent (acetonitrile: 0.01 M phosphoric acid 2:98) running at 1.4 mL/min was used for this study. In this system 6-fluoro-L-dopa and 6-fluoro-3-O-methyl-L-dopa have retention times of 2.5 and 6.0 min.

The blood samples were centrifuged at 2000 rpm for 10 min and the plasma was separated. Each plasma sample (0.2 mL) was mixed with a solution of 1 M trifluoroacetic acid (0.2 mL). The mixture was centrifuged for 10 min at 2000 rpm. An aliquot (50 μL) of the supernatant was mixed with a solution (50 μL) containing authentic samples of 6-fluoro-L-dopa (0.1 mg/mL) and 6-fluoro-3-O-methyl-L-dopa (6F3OMD) (0.1 mg/mL). The final mixture was applied to HPLC. The fractions containing 6-fluoro-L-dopa (the peaks at 2.5 min) and 6 F3OMD (the peaks at 6.0 min) were collected in different test tubes for radioactivity measurements.

We thank the correspondents for pointing out a typographical error in the units which should be stated as ml striatum^{-1} min^{-1} (Figure 3). Although the standard deviation of the K_i is >40% (Table 1), the results were statistically significant by ANOVA (see Results, p. 406) indicating that middle abstinence cocaine subjects (abstinence days 11–30) had significantly lower FDOPA uptake than either early abstinence cocaine subjects (abstinence days 1–10) or normal controls.

We regret not citing all the possible manuscripts pertinent to the topic as mentioned by the correspondents. The correspondents also raised several issues regarding the description of the implicit model underlying estimates of net plasma-brain clearance. We agree that an accurate description of FDOPA's transfer across the capillary epithelium is by facilitated diffusion followed by simple diffusion. Concern over the irreversibility of decarboxylated FDOPA being trapped was raised (Cumming and Gjedde 1998). We note that the citation by Huang et al. 1991 notes that the estimated k_4 value is not very large and does not cause a large deviation from a straight line in the Patlak plot. Furthermore, even if the k_4 value were larger, there would have to be a significant difference between the middle cocaine abstinence subjects, the early cocaine abstinence subjects and normal controls to account for the differences reported. There is no evidence that middle cocaine abstinence subjects would have a different rate of elimination from normal controls or early abstinence cocaine subjects. Given the relatively small size of k_4, we feel that this consideration would not materially affect our conclusion that middle abstinence cocaine subjects have significantly lower FDOPA uptake than either early abstinence cocaine subjects or normal controls. Neverthe-

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less, it is important to test other cocaine subjects to see if our finding can be replicated.

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REFERENCES

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

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

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