Modeling Dopamine Dynamics using Combined Microdialysis and MRI Measurements.

B. G. Jenkins[1], J-K. Choi[1], A. Hamamci[1], J. B. Mandeville[1], B. R. Rosen[1], and Y-C. I. Chen[1]
[1]AA Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Charlestown, MA, United States

Introduction – Dopamine dynamics are assessed invasively using microdialysis or cyclic voltammetry. Recent work indicates the coupling between dopamine (DA) release and a resultant hemodynamic change can be mediated through dopamine receptors on the vasculature and astrocytes (1). Thus, the possibility exists of modeling dopamine release and uptake using MRI hemodynamic data. We explore the possibilities and limits of this propostion in rats and monkeys.

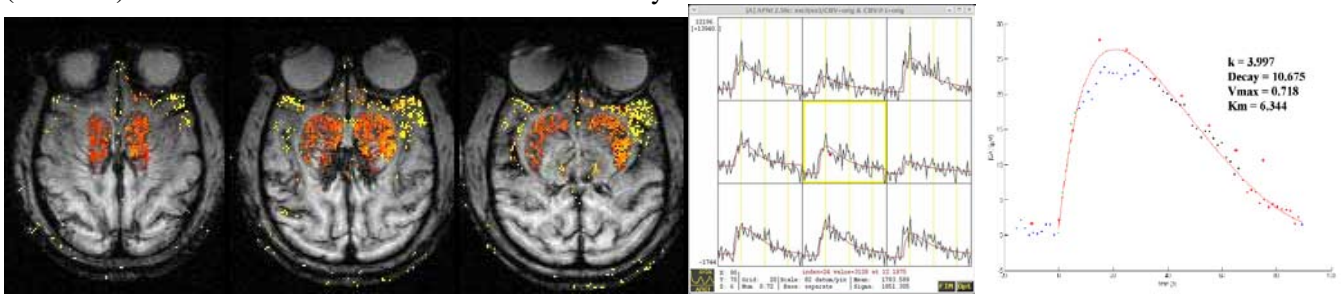
Methods – Data were collected using microdialysis in rats injected with either amphetamine or the DAT blocker CFT as described in (1). MRI measurements of relative cerebral blood volume (rCBV) were made as described previously (1). Dopamine release was modeled as Drug => Dopamine => CBV. Thus, an increase in DA can directly lead to an increase in CBV : $dCBV/dt = KdC_{DA}/dt$ [1] where C_{DA} is the DA concentration, and K is the coupling constant (in a given brain region) relating the amount of DA to the percent rCBV change. The C_{DA} is a balance between (R(t) for release as a function of time) and reuptake (U(t)) as : $dCDA/dt = R(t) - U(t)$ [2]. We modeled amphetamine effects as a single exponential process with release proportional to concentration and the DA uptake as a Michaelis-Menten form often used for invasive techniques (2). The amphetamine concentration time course is modeled as a single exponential decay: $[Amp] = [Amp]_0 e^{-t/\tau}$ [3] So, the resultant model is: $\frac{d[DA]}{dt} = k[Amp]_0 e^{-t/\tau} - \frac{V_{\max}[DA]}{K_m + [DA]}$ [4].

A similar model can be developed for dopamine transporter blockers such as cocaine or methylphenidate.

We resampled rCBV data at time intervals of [DA] measured by microdyalisis and fit to obtain the coupling constant. By integrating the model using a Runge-Kutta 4th order algorithm and nonlinear least squares fit we can determine values for the time constants, Vmax and Km for DA uptake. The tool was incorporated as a plugin to AFNI (NIH) such that maps of DA uptake constants could be made.

Results – At the doses of drugs used (0.75-3 mg/kg) the correlation between rCBV and DA was linear for amphetamine (DA releaser) and CFT (DAT blocker). The coupling constants for CFT and amphetamine were similar 0.55-0.75 (CBV(%)/DA(uM)) and showed greater variance between animal than between drug. Sinulations show that the model is quite sensitive to Vmax, but not to Km. This is because at high DA concentrations the DAT is saturated and uptake is dependent on Vmax. For rats average values were (n=10; 2.5 mg/kg amp; dorsal caudate/putamen): Km = 6.3 ± 3.0 uM Vmax = 3.5 ± 2.8 uM/s. Scmitz et al. (3), using amperometry for amphetamine infused into CPu, determined : Km = 3.0 uM and Vmax = 3 uM/sec. Data from before amphetamine yield values Vmax = 2-5 uM/s Km = 0.15-0.8 uM (2,3).

In monkeys we obtained average values (n=4; 2.5 mg/kg amp; dorsalateral putamen) of Km = 7.2 ± 4.6 uM; Vmax = 3.2 ± 2.8 uM/s From Cragg et al. (4) Vmax = 2.5-7 uM/sec (region and drug dependent) Km= 0.21 uM (assumed). Shown below are data from rats and monkeys.



(A) (B) (C)

Figure 1 – A: Map of Vmax in a monkey showing the strong localization in the striatum. The bright yellow pixels are artifacts. Bscreenshot of the fits from the AFNI plugin C: Fit of rCBV data converted to DA (uM) from rat striatum. The microdialysis points are the red stars, the CBV/DA in blue. The fitted parameters are shown on the figure.

Discussion – These results suggest that parameters relevant to DA release and uptake can potentially be measured non-invasively using MRI. The data are subject to numerous caveats but provide fruitful grounds for further investigation.

References – 1) Choi et al. (2006) *NeuroImage* **30**:700-712; 2) Wu et al. (2001) *J. Neurosci. Meth.* **112:**119-133; 3) Schmitz et al.(2001) *J. Neurosci.* **21:**5916-5924; 4) Cragg et al. (2000) *J. Neurosci*. **20**:8209-8217.