Pharmacological MRI with continuous ASL in conscious rats: characterizing the relationship between CBF response to CNS compounds and plasma concentration levels

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INTRODUCTION:

Pharmacological functional MRI (phMRI) has been used to assess drug effects in the central nervous system (CNS), however little has been done to characterize the relationship between the phMRI pharmacodynamic (PD) response and plasma concentration (pharmacokinetics, PK) of the compound being evaluated. This study aimed at exploring PK/PD relationships of phMRI response to two CNS acting compounds in conscious rats, donepezil and lorazepam using arterial spin labeling (ASL) measurements of cerebral blood flow (CBF).

METHODS:

All animal procedures were reviewed and approved by Merck's IACUC. Scanning was conducted on a Bruker Biospec 7T/30. For conscious animal imaging, Sprague Dawley rats (280-310g) underwent daily one hour conditioning sessions to restrain and recorded scanner noise for 3 consecutive days prior to the day of imaging (King et al 2005; Welsh et al 2009). All scans were conducted using an Insight Neuroimaging resonator with a surface receive coil. Continuous ASL technique was used to obtain quantifiable parametric maps of CBF (TR/TE=3036/18.65ms; 2mm coronal slices, 64x64 matrix; 30x30 mm FOV). Six consecutive coronal slices were scanned so that most of the forebrain was sampled. Two compounds were tested that have known and different mechanisms of action, namely donepezil, an acetylcholinesterase inhibitor used to treat Alzheimer's disease, and lorazepam, a short-acting benzodiazepine used to treat anxiety. Animals were catheterized for I.V. infusion of active compound and control vehicle solutions. Two CBF measurements were taken immediately prior to infusion and 4 measurements were taken during a 30 minute infusion period. A terminal blood sample was drawn ~15 min after the infusion period, and plasma concentration of active compound was measured. Multiple doses of both compounds were administered to different rats. The phMRI PD response was expressed as either the absolute cortical CBF, i.e. the average across the 4 measurements during infusion (absCBF), or its difference relative to cortical CBF at pre-infusion period (deltaCBF). PK/PD relationship was explored by non-linear fitting of a Hill function to the PD measures and their respective PK data. From the fitting we computed amplitude of maximal response (amplitude), half-maximal effective concentration (EC50), and the Hill coefficient. Confidence intervals (CI) were computed for each parameter estimate and results obtained with either PD measurement were compared.

RESULTS and CONCLUSION:

Figure 1 shows PK/PD relationship data for donepezil and lorazepam for both cortical absCBF and deltaCBF and the respective fitted Hill functions. The Hill function accounts for a significant amount of the variance for both cortical absCBF and deltaCBF (as indicated by the significant R^2). Table 1 includes the parameter estimates and respective CIs. Although the amplitude is different for absCBF and deltaCBF, there is no significant difference between EC50 parameter estimates obtained from each PD measure. Interestingly, EC50's for both donepezil and lorazepam are in agreement with plasma concentrations previously shown to produce behavioral and biochemical activity in rats (Lister et al 1983; Kosasa et al 2000) suggesting that the CBF response is predictive of efficacy for CNS compounds. Overall, these results provide insight into CBF PK/PD relationships for two CNS compounds with different mechanisms of action. They also suggest potential use of conscious rat ASL as a platform providing translational biomarkers for CNS compound dose selection. Further confirmatory investigation, including verification of human translation, is needed.

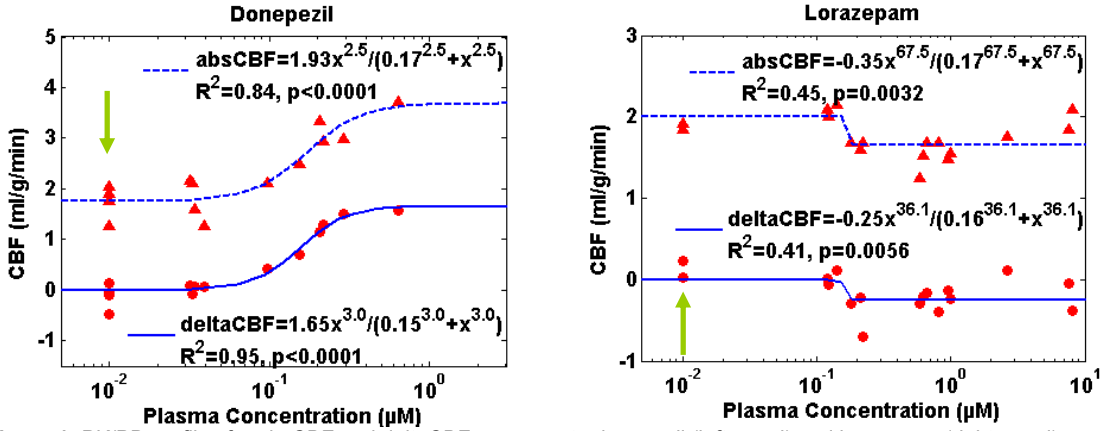

Figure 1: PK/PD profiles for absCBF and deltaCBF response to donepezil (left panel) and lorazepam (right panel). Triangle and circles depict individual absCBF and deltaCBF measurements, respectively. Dashed and solid lines are the fitted Hill function curves for absCBF and deltaCBF. Note similar profile between each compounds absCBF and deltaCBF, as well as the similar EC50. For display purposes CBF response to vehicle is shown at plasma concentration 10^{-2} μM (green arrow).

	Amplitude (ml/g/min)				EC50 (μM)			
	Abs		Delta		Abs		Delta	
	estimate	C.I.	estimate	C.I.	estimate	C.I.	estimate	C.I.
Donepezil	1.93	[1.63, 2.24]	1.65	[1.55, 1.76]	0.17	[0.14, 0.20]	0.15	[0.14, 0.17]
Lorazepam	-0.35	[-0.41, -0.29]	-0.25	[-0.28, -0.22]	0.17	[0.16, 0.19]	0.16	[0.03, 0.29]

Table 1: Parameter estimates for Hill function fits for absCBF and deltaCBF PD measures for Donepezil and Lorazepam.

REFERENCES: King et al, J Neurosci Meth,148:154 (2005); Welsh et al ISMRM (2009); Lister et al, Psychopharmacology, 81:292 (1983); Kosasa et al, Eur. J. Pharmacol, 389:173 (2000).