In vivo Evaluation of the Specificity of Novel Drugs Targeting Dopamine D3 receptors using MRI: Role of Positive and Negative Hemodynamic Indices

J-K. Choi1, J. B. Mandeville1, Y. I. Chen1, P. Grundt2, A. H. Newman3, and B. G. Jenkins1

1Radiology, Athinoula Martinos Center for Biomedical Imaging, Charlestown, MA, United States, 2Medical Chemistry, NIDA, Baltimore, MD, 3Medical Chemistry, NIDA, Baltimore, MD, United States

Introduction Dopamine receptors are divided into two families: D1 including D1 and D5 receptors and D2 including D2, D3 and D4 receptors. The role of the D3 receptor subtype in the brain and behavioral actions remains controversial. Further, synthesis of novel ligands targeting these receptors requires a means for assessing selectivity of the ligands in cases where radiolabels do not exist. We investigated the response to stimulation and inhibition of D3 receptors for existing and novel drugs using pharmacologic MRI (phMRI).

Methods Male Sprague-Dawley rats were scanned using phMRI and the IRON technique as described earlier (1). Tail vein was catheterized for both contrast agent (MION) and drug administration. Images were collected at 9.4T using a conventional gradient echo sequence with TR/TE of 500/7.6ms with in-plane spatial resolution of 0.2×0.2mm² and a 0.75mm slice thickness. Blood pressure was measured continuously. All images were registered onto a standard template for subsequent averaging across animals and maps of functional blood volume changes were obtained by converting signal intensity changes to ΔR2* on a pixel by pixel basis.

Results Administration of the highly selective D3 antagonist PG-10307 (2) induced positive cerebral blood volume (CBV) changes in brain regions corresponding to the distribution of D3 receptors (and associated circuitry) including nucleus accumbens (shell), antero-medial striatum, medial prefrontal cortex and thalamus (ΔCBV between 5–30%). There was pronounced activation in the hippocampus restricted to the subiculum - the output from the infralimbic cortex and dentate gyrus. Agonism of D3 receptors using 7-OH-DPAT produced negative CBV changes in D3 circuitry including nucleus accumbens, ventromedial hypothalamus and thalamus (between -10–20%). Brain regions not previously described as being part of D3 circuitry, such as interpeduncular region were also found. At high doses of 7-OH-DPAT, functional changes are differentiated across cortical lamina, with layer V-VI yielding positive CBV changes and layer IV yielding negative CBV changes, results consistent with differential D1 and D3 innervation in these layers respectively as seen using post mortem ligand binding and mRNA expression levels (3).

Discussion These results indicate the utility of in vivo, non-invasive imaging methods for the determination of the receptor selectivity of novel dopaminergic drugs – especially in the case of the D3 receptor where PET and SPECT ligands do not yet exist. Consistent with prior studies we found that D2/D3 agonists lead to decreased fCBV in rodents (4,5) and primates (6). The highly selective D3 antagonist studied led to increased fCBV in brain regions that are largely consistent with the limbic D3 circuitry. However one of the more exciting findings of this study - that is the ability to detect signals of opposite signs in the cortical layers using high doses (>1.5 mg/kg) of the D3 agonist 7-OH-DPAT. Using moderately high spatial resolution (0.21×0.21×0.75mm) we found that cortical layers V-VI showed positive fCBV changes consistent with D1 receptor expression while layers III-IV showed negative fCBV changes consistent with D3 receptor expressions as determined in histological data obtained by Guervich and Joyce (3). The signs of the hemodynamic changes are also completely consistent with assignment of a drug to having agonist or antagonist properties.

References