Measuring Agonist-induced μ-Opioid Receptor Desensitization in vivo with PET/MRI

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μ-Opioid receptor (MOR) agonists are the most effective analgesics for pain. However, the development of opioid tolerance results in less effective pain relief and prompts an increase in the dose needed over time. MOR agonists-induced receptor desensitization is a pivotal mechanism leading to opioid tolerance (1). Recent *in vitro* studies showed that desensitized MORs have an increased affinity for agonist binding (2). Therefore, it is anticipated that MOR agonists-induced desensitization and drug-radiotracer competition result in an increase and a decrease in PET binding potential signal, respectively. The purpose of this study is to measure and validate agonists-induced MOR desensitization *in vivo* using simultaneous PET/MRI.

Methods: PET/MRI images were acquired from four male macaques on a Siemens BrainPET scanner. A μ-opioid selective radiotracer, [^{11}C]carfentanil (~8 mCi; specific activity: ~3 mCi/nmol), was given as bolus-infusion for 100 min. PET data were binned into 1-min frames. Cerebral blood volume (CBV-fMRI) was measured following an iron oxide (10 ug/kg, i.v.) injection (3). Graded doses of an MOR agonist, morphine (baseline, 0.2, 0.5, and 1.0 mg/kg) and a biased MOR agonist, TRV130 (0.3 and 0.5 mg/kg), were given intravenously at 35 min post radiotracer administration. PET data was analyzed for binding potentials referenced to a non-displaceable compartment (BP_{ND}) using the simplified reference tissue model (4). A gamma-variant function was used to model the PET and fMRI temporal response to drug challenge.

Results: PET signal reached a steady-state with bolus/infusion of [^{11}C]carfentanil. Time activity curves (TACs) of the reference tissue are comparable between baseline and drug-challenging scans. Apparent *increases* in TACs in high-binding regions following morphine injection was observed, suggesting a potential increase in receptor affinity. Percent increases in BP_{ND} is ranging from ~25%-49%. We observed negative morphine-induced CBV changes as expected because MOR is inhibitory. Dose-dependent changes in BP_{ND} and CBV were found between 0.2 mg/kg and 0.5 mg/kg of morphine, but a dose of 0.5 mg/kg and 1.0 mg/kg caused similar BP_{ND} and CBV responses. In contrast, TRV130, a biased MOR agonist known not to desensitize MORs, caused drug-radiotracer competitions and resulting in a *reduction* in BP_{ND} (~22-40%).

Discussion and Conclusions: In this study, we demonstrated an increase in PET BP_{ND} potentially reflects morphine-induced MOR desensitization because an increased in PET BP_{ND} cannot be attributed to drug-radiotracer competition. [^{11}C]carfentanil is an agonist radiotracer, it is possible to detect a change in receptor affinity. On the other hand, TRV130, a novel MOR agonist that biased toward the G-protein (but not the beta-arrestin) pathway and dose not trigger receptor trafficking, caused robust reduction in [^{11}C]carfentanil binding. Additional experiments are ongoing to complete the dose-response study that will allow us to fit a PET/MRI model to quantitatively differentiate competition vs. desensitization.

References: (1) Williams JT, et al. Pharmacological Reviews. 2013. (2) Birdsong WT, et al. J Neurosci. 2013. (3) Mandeville JB. NeuroImage. 2012. (4) Lammertsma AA, et al. NeuroImage. 1996.

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