PET assay of extrastriatal dopamine D2/D3 receptors

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Extrastriatal dopamine D_2 /D_3 receptors have been implicated in a variety of cognitive and psychiatric disorders. ^{18} F-Fallypride and ^{11} C-FLB457 are commonly used PET radioligands for studying extrastriatal dopamine D_2 /D_3 receptors, but differences in their *in vivo* kinetics may affect sensitivity for measuring subtle changes in receptor binding. Focusing on regions of low receptor density, experiments were performed to compare of the properties of ^{18} F/^{11} C-fallypride and ^{11} C-FLB457 in the rhesus monkey. Multiple-injection (MI) experiments were used to provide a full characterization of the *in vivo* kinetic of both tracers, showing that ^{11} C-FLB457 has a greater free space distribution volume than ^{18} F-fallypride (V_{ND} = 3.0 vs 0.9, respectively) and that ^{11} C-FLB457 has a three-fold higher affinity for D_2 /D_3 receptors (K_{Dapp} 0.13, FLB457; K_{Dapp} =0.39, fallypride). To investigate the sensitivity of both radioligands to changes in D_2 /D_3 receptor density after drug intervention, we performed both receptor-blocking and dopamine depletion studies using ^{11} C-fallypride and ^{11} C-FLB457. D_2 /D_3 receptor blocking studies with haloperidol show that both ^{11} C-FLB457 and ^{11} C-fallypride give similar measures of occupancy for the same drug dosage. Neither tracer was sensitive to changes after dopamine depletion with AMPT due to the bias introduced by using reference region methods. We also investigated the utility of using ^{18} F-fallypride for measuring changes in D_2 /D_3 binding due to deep brain stimulation (DBS) of the bed nucleus of the stria terminalis. These experiments measured large changes during scans acquired while the stimulators were on, and only small differences in scans where the stimulators were turned off, demonstrating that the use of high-affinity radioligands has great potential for advancing the understanding of the neurochemical changes induced by DBS. Taken as a whole, the experiments performed provide an evaluation of the differences between fallypride and FLB457, assessing their strengths and weaknesses for various imaging applications. This work provides a template for evaluating new tracers used for extrastriatal D_2 /D_3 assay.