AIMAGING α4β2 NICOTINIC ACETYLCHOLINE RECEPTORS WITH [^{18}F]NIFENE PET

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April 22, 2014

The nicotinic acetylcholine receptor (nAChR) system plays a major role in neuropathologies related to substance abuse, Alzheimer's disease, and other neuropsychiatric illnesses. Positron emission tomography (PET) imaging of the nAChR system noninvasively yields crucial neurochemical information concerning these disorders and can evaluate the efficacy of drugs interacting with nAChRs. The novel PET radioligand [^{18}F]nifene targets the α4β2 subtype of nAChRs. The overarching goal of this work was to characterize and develop [^{18}F]nifene in preclinical models to preliminarily assess its viability for human PET procedures.

The radiochemical procedure for [^{18}F]nifene production was refined. The kinetic profile of [^{18}F]nifene was characterized in rhesus monkeys with compartment modeling. Further kinetic analysis included measurements of receptor density (B_{max}) and *in vivo* radioligand-receptor affinity ($1/K_{Dapp}$). Experiments using [^{18}F]nifene to examine drug interactions at the α4β2 nAChR site were performed. These studies were conducted with lobeline, a smoking cessation drug, and the acetylcholinesterase inhibitors physostigmine and galanthamine, drugs of interest as treatments for the cognitive symptoms of Alzheimer's disease. The neurochemical effects of chronic alcohol exposure and healthy aging on the nAChR system were also assessed with [^{18}F]nifene in rhesus monkeys.

[^{18}F]Nifene in rhesus monkeys exhibited binding potentials of 1.5-2.0 in thalamic regions and 0.2-0.5 in extrathalamic areas. Fast transport rates across the blood brain barrier (K_1=0.9 min^{-1}), high *in vivo* affinity (K_{Dapp}=2.4 pmol/mL), and rapid specific binding kinetics (k_{off}>0.1 min^{-1}) characterized [^{18}F]nifene's kinetics. These fast properties allowed [^{18}F]nifene to accurately interrogate subtle drug interactions at α4β2 nAChRs, demonstrated by *in vivo* observations of perturbations to the [^{18}F]nifene time course following administration of lobeline, physostigmine, and galanthamine. Decreases in [^{18}F]nifene binding in frontal and insular cortex following alcohol exposure indicated [^{18}F]nifene's viability for interrogating nAChR physiology in a pathology-specific model. These findings establish [^{18}F]nifene as a vital tool for investigating α4β2 nAChR physiology and drug interactions with PET imaging.