Clinical Evaluation of PET Radiotracers

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Country

USA

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Clinical Evaluation of PET Radiotracers

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Alzheimer's disease & other dementias

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Research Abstract

1. We found that to measure translocator protein (TSPO) density in Alzheimers Disease (AD) and control subjects, a simple ratio method (standardized uptake value ratio, SUVR) can substitute for, and may even be more sensitive than, absolute quantitation. We also found that

TSPO binding increases with progression of AD but not in healthy aging, suggesting that inflammation increases in proportion to worsening of disease in AD. This work was performed under NCT00613119 and NCT00955422. 11C-PBR28 PET imaging was performed in 21 healthy controls, 11 individuals with mild cognitive impairment (MCI), and 25 AD patients. Group differences in 11C-PBR28 binding were compared using two methods: the gold standard method of calculating distribution volume (VT), using the two-tissue compartmental model with the arterial input function corrected for plasma free fraction of radiotracer and a ratio of brain uptake in target regions to that in cerebellum: SUVR. Using absolute quantitation, we confirmed that TSPO binding: 1) was greater in AD patients than healthy controls in expected temporo-parietal regions, and 2) was not significantly different among the three groups in cerebellum. Using the cerebellum as a pseudo-reference region, the SUVR method detected greater binding in AD patients than controls in the same regions as absolute quantification and in one additional region, suggesting that SUVR may have greater sensitivity. The results indicate that, to measure TSPO density in AD and control subjects, a simple ratio method (SUVR) can substitute for, and may even be more sensitive than, absolute quantitation. This method is expected to improve subject tolerability by allowing shorter scan time and not requiring arterial catheterization. It may also allow smaller sample sizes for comparable statistical significance because of the relatively low variability of the ratio values. We then sought to determine if TSPO binding increases with progression of AD and in healthy aging. Eleven patients with either AD or MCI and eight cognitively normal age-matched controls underwent 11C-PBR28 PET at baseline and after median follow-up of 2.7 years. Cerebellar gray matter was used as a pseudo-reference region. TSPO binding in temporo-parietal regions increased 4-6% per annum in patients, but did not increase in controls. Of great importance, the change in TSPO binding correlated with cognitive worsening on Clinical Dementia Rating scale Sum of Boxes and with reduced cortical volume. The annual rate of increased TSPO binding in temporo-parietal regions was about five-fold higher in patients with clinical progression (n = 9) compared to those who did not progress (n = 5). Taken together, these results suggest that TSPO may serve as a biomarker of Alzheimers progression and response to anti-inflammatory therapies. We extended this work in another study to determine whether patients with posterior cortical atrophy (PCA) demonstrate a pattern of binding to TSPO that is distinct from that in patients with amnestic AD. Towards that end, 11 PCA patients, 11 amnestic AD patients, and 15 age-matched controls underwent PET with 11C-PBR28 to measure TSPO and with 11C-Pittsburgh Compound B to measure fibrillar amyloid burden. PCA patients also underwent imaging with 18F-fluorodexoxyglucose (FDG) to measure cerebral glucose metabolism, and these results were compared to those from 15 age-matched historical controls. We found that PCA patients showed greater 11C-PBR28 binding than controls in occipital, posterior parietal, and temporal regions. In contrast, amnestic AD patients showed greater 11C-PBR28 binding in inferior and medial temporal cortex. Increased 11C-PBR28 binding overlapped with reduced cortical volume for both PCA and amnestic AD patients and with areas of reduced glucose metabolism in PCA patients. While both patient groups showed diffuse amyloid binding, PCA patients showed greater binding than amnestic AD patients in bilateral occipital cortex. Taken together, the results indicate that PCA and typical amnestic AD patients have distinct patterns of increased TSPO binding that mirrors cortical thickness loss and glucose hypometabolism. These results suggest that microglial activation is closely associated with neurodegeneration across different subtypes of AD. 2. Using 11C-(R)-rolipram, a phosphodiesterase type IV (PDE4) inhibitor, we found that two months of treatment with an SSRI increased (normalized) PDE4 binding in individuals with major depressive disorder (MDD). Work was performed under NCT00369798.

PDE4 is an important component of the cyclic adenosine monophosphate (cAMP) cascade, and studies suggest that it mediates the effects of several antidepressants. We previously confirmed in animals that increased 11C(R)-rolipram binding reflects the phosphorylated/active state of PDE4. Using this radioligand, we found that PDE4 binding was decreased in unmedicated patients with MDD, consistent with the cAMP theory of depression. To quantify the binding of 11C-(R)-rolipram as an indirect measure of this enzyme's activity in the brain of individuals with MDD, we performed 11C-(R)-rolipram brain PET scans in 28 moderately depressed MDD subjects and 25 age- and gender-matched healthy controls; roughly half of the patients were treatment-naive. We found that PDE4 levels were decreased in unmedicated individuals with MDD in vivo. In collaboration with Dr. Zarate (NIMH), we investigated cAMP cascade activity by using 11C-(R)-rolipram to image PDE4 in unmedicated MDD patients and after approximately eight weeks of treatment with a selective serotonin reuptake inhibitor (SSRI; mostly citalopram). 11C-(R)-rolipram PET scans were performed in 44 unmedicated patients during a major depressive episode and 35 healthy controls. Twenty-three of the 44 patients had a follow-up 11C-(R)-rolipram PET scan approximately eight weeks after treatment with an SSRI. Patients were moderately depressed (Montgomery-sberg Depression Rating Scale (MADRS) score=306) and about half were treatment-nave. 11C-(R)-Rolipram binding was measured using arterial sampling to correct for individual differences in radioligand metabolism. We found widespread, 20% reductions in 11C-(R)-rolipram binding in unmedicated MDD patients compared to controls across 10 large brain regions (p=0.001). SSRI treatment significantly increased rolipram binding (12%, P< 0.001) with significantly greater increases observed in older patients (P< 0.001). In contrast, 11 healthy controls who had a repeat scan without SSRI showed only small changes on repeat scans. Rolipram binding did not correlate with severity of baseline symptoms, and increased rolipram binding during treatment did not correlate with symptom improvement. Taken together, the results indicate that, consistent with the results of basic studies, PDE4 is decreased in unmedicated MDD patients and increased after SSRI treatment. Thus, the results suggest that the cAMP cascade, as indirectly measured with PDE4 binding, is downregulated in unmedicated patients with MDD, and that antidepressant treatment normalizes this 11C-(R)-rolipram downregulation.The lack of correlation between PDE4 binding and depressive symptoms could reflect the heterogeneity of the disease and/or the heterogeneity of the target, given that PDE4 has four subtypes. These results suggest that PDE4 inhibitors, which increase cAMP cascade activity, may have antidepressant effects.

Lay Summary
Further information available at:

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2016

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