ELSEVIER

Neurobiology of Aging 34 (2013) 128–136

NEUROBIOLOGY OF AGING

www.elsevier.com/locate/neuaging

Microglial activation in Alzheimer's disease: an (*R*)-[^{11}C]PK11195 positron emission tomography study

Alie Schuitemaker[a,b,*], Marc A. Kropholler[b], Ronald Boellaard[b], Wiesje M. van der Flier[a,c], Reina W. Kloet[b], Thalia F. van der Doef[b,e], Dirk L. Knol[c], Albert D. Windhorst[b], Gert Luurtsema[b], Frederik Barkhof[d], Cees Jonker[a], Adriaan A. Lammertsma[b], Philip Scheltens[a], Bart N.M. van Berckel[b]

[a] *Department of Neurology and Alzheimer Center, VU University Medical Center, Amsterdam, the Netherlands*
[b] *Department of Nuclear Medicine and PET Research, VU University Medical Center, Amsterdam, the Netherlands*
[c] *Department of Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, the Netherlands*
[d] *Department of Radiology, VU University Medical Center, Amsterdam, the Netherlands*
[e] *Department of Psychiatry, University Medical Center Utrecht, Utrecht, the Netherlands*

Received 15 May 2011; received in revised form 6 April 2012; accepted 30 April 2012

Abstract

Inflammatory mechanisms, like microglial activation, could be involved in the pathogenesis of Alzheimer's disease (AD). (*R*)-[^{11}C]PK11195 (1-(2-chlorophenyl)-*N*-methyl-*N*-1(1-methylpropyl)-3-isoquinolinecarboxamide), a positron emission tomography (PET) ligand, can be used to quantify microglial activation *in vivo*. The purpose of this study was to assess whether increased (*R*)-[^{11}C]PK11195 binding is present in AD and mild cognitive impairment (MCI), currently also known as "prodromal AD."

Methods: Nineteen patients with probable AD, 10 patients with prodromal AD (MCI), and 21 healthy control subjects were analyzed. Parametric images of binding potential (BP_{ND}) of (*R*)-[^{11}C]PK11195 scans were generated using receptor parametric mapping (RPM) with supervised cluster analysis. Differences between subject groups were tested using mixed model analysis, and associations between BP_{ND} and cognition were evaluated using Pearson correlation coefficients.

Results: Voxel-wise statistical parametric mapping (SPM) analysis showed small clusters of significantly increased (*R*)-[^{11}C]PK11195 BP_{ND} in occipital lobe in AD dementia patients compared with healthy control subjects. Regions of interest (ROI)-based analyses showed no differences, with large overlap between groups. There were no differences in (*R*)-[^{11}C]PK11195 BP_{ND} between clinically stable prodromal AD patients and those who progressed to dementia, and BP_{ND} did not correlate with cognitive function.

Conclusion: Microglial activation is a subtle phenomenon occurring in AD.

Keywords: Alzheimer's disease; Mild cognitive impairment; Microglial activation; PET

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder, clinically characterized by progressive cognitive decline and impaired execution of daily activities (McKhann et al., 1984). Patients with mild cognitive impairment (MCI) have documented memory impairment but are still able to perform daily activities in a normal manner. MCI is considered to be a transitional phase between normal aging and AD (Petersen et al., 1999). Subjects with MCI have an increased risk of developing clinical AD of about 12% per year compared with 1%–2% in the general population (Petersen, 2004). Recently, new criteria for the diagnosis of AD were proposed, which allows diagnosis related to neuropathological changes in AD, based on the use of biomarkers

* Corresponding author at: Department of Neurology, Zuwe Hofpoort ziekenhuis, PO Box 8000, 3440 JD Woerden, the Netherlands. Tel.: +31 348 427911.
E-mail address: ASchuitemaker@zuwehofpoort.nl (A. Schuitemaker).

0197-4580/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.neurobiolaging.2012.04.021

of AD (Dubois et al., 2010). According to this new classification, patients with MCI are considered to have "prodromal AD."

AD is characterized histopathologically by intracellular neurofibrillary tangles (NFT), extracellular deposits of amyloid in senile plaques, and diffuse loss of neurons (Braak and Braak, 1991). Although not a pathological hallmark specific to AD, activated microglia invariably are found in AD, and they may be present years before symptoms become apparent clinically (Petersen et al., 2006). Indeed, activated microglia could be an important therapeutic target, as microglial activation may be directly involved in the neurodegenerative process associated with AD (Yoshiyama et al., 2007).

Microglial activation can be quantified *in vivo* using positron emission tomography (PET) and (*R*)-[^{11}C]PK11195. (*R*)-[^{11}C]PK11195 (1-(2-chlorophenyl)-*N*-methyl-*N*-1(1-methylpropyl)-3-isoquinolinecarboxamide) is a highly specific ligand for the peripheral benzodiazepine-binding site (PBR). This site, also called the translocator protein (Papadopoulos et al., 2006), is expressed by cells of the mononuclear macrophage lineage and is markedly increased in activated microglia. Using (*R*)-[^{11}C]PK11195 and PET, microglial activation has already been demonstrated in several neurodegenerative diseases (Venneti et al., 2006). In AD, increased (*R*)-[^{11}C]PK11195 binding has been found in several brain areas (Cagnin et al., 2001; Yokokura et al., 2011). Recently, there have been two reports on (*R*)-[^{11}C]PK11195 binding in MCI (Okello et al., 2009; Wiley et al., 2009). In both studies, (*R*)-[^{11}C]PK11195 binding was assessed in two cohorts of MCI patients, being ^{11}C-labeled Pittsburgh compound B ([^{11}C]-PIB)-positive and -negative patients. These studies found either increased (Okello et al., 2009) or unchanged (Wiley et al., 2009) (*R*)-[^{11}C]PK11195 binding in MCI.

The purpose of the present study was to further investigate the extent and distribution of (*R*)-[^{11}C]PK11195 binding in larger cohorts of AD dementia and prodromal AD patients. A second aim was to establish whether presence of activated microglia in prodromal AD is associated with progression to AD dementia.

2. Methods

2.1. Subjects

Twenty patients with probable AD, 13 patients with MCI, and 21 healthy control subjects were included. Patients were recruited from the outpatient clinic of the Alzheimer center at the VU University Medical Center. All patients underwent standardized clinical assessment, including neurological and physical examinations, laboratory screening tests (including cerebrospinal fluid measures of amyloid β (Aβ), tau, and tau phosphorylated at threonine-181) (Bouwman et al., 2010), electroencephalogram (EEG), magnetic resonance imaging (MRI), and neuropsychological examination. Final diagnosis was established at a multidisciplinary consensus meeting. Diagnosis of probable AD was based on National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria (McKhann et al., 1984), and diagnosis of MCI on Petersen criteria (Petersen et al., 1999). Subjects underwent a standard battery of examinations, including history taking, medical and neurological examination, and neuropsychological examination, which consisted of the New York University Recall Test (NYU), Rey's Auditory Verbal Learning Test (RAVLT), Trail Making Test A and B, Fluency, Rey's complex figure, Boston Naming Test, and forward and backward condition of the Digit Span.

According to recently proposed criteria for prodromal AD (Dubois et al., 2010), MCI and AD patients were excluded from the analysis if there was no medial temporal lobe atrophy (MTA) or no abnormal cerebrospinal fluid profile (Bouwman et al., 2010) (one MCI patient). Consequently, MCI will be reported as prodromal AD. For clinical follow-up, prodromal AD patients visited the memory clinic annually. One patient progressed to dementia with Lewy bodies and was excluded from the analyses.

Control subjects without cognitive complaints were recruited by advertisement in local newspapers. All control subjects underwent the same diagnostic procedure (except EEG and lumbar puncture). Control subjects had to have age-corrected normal scores on neuropsychological assessments and a normal MRI (including MTA scores) (Bouwman et al., 2010), which was evaluated by a neuroradiologist.

Exclusion criteria for all subjects were known major psychiatric illness, previous head trauma with loss of consciousness of more than 1-hour duration, any significant metabolic disorder, and alcohol or substance abuse according to the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria (American Psychiatric Association, 2000). Intake of benzodiazepines, antipsychotic drugs, and non-steroidal anti-inflammatory drugs was not allowed because of possible interaction with (*R*)-[^{11}C]PK11195 binding. Written informed consent was obtained from all participants and in case of patients with AD also from a next of kin. The study protocol was approved by the Medical Ethics Review Committee of the VU University Medical Center.

2.2. MRI

All subjects had a structural MRI scan within 4 months of the PET procedure. MRI scans were acquired using a 1.0-T scanner (Magnetom IMPACT, Siemens Medical Solutions, Erlangen, Germany) and included a 3D heavily T1-weighted gradient echo sequence (magnetization prepared rapid acquisition gradient echo). Voxel size of the MRI images was $0.98 \times 0.98 \times 1.49$ mm^3. These scans