Biochemical Pharmacology 97 (2015) 566–575

Contents lists available at ScienceDirect

Biochemical Pharmacology

journal homepage: www.elsevier.com/locate/biochempharm

Review

Development of [^{18}F]ASEM, a specific radiotracer for quantification of the α7-nAChR with positron-emission tomography

Andrew G. Horti*

Department of Radiology, The Johns Hopkins School of Medicine, 600 North Wolfe Street, Baltimore, MD 21287-0816, USA

ARTICLE INFO

Article history:
Received 13 May 2015
Accepted 24 July 2015
Available online 29 July 2015

Keywords:
Positron emission tomography
PET
α7-nAChR
Alpha 7
Nicotinic receptor
[^{18}F]ASEM

ABSTRACT

The alpha-7 subtype of the nicotinic acetylcholine receptor (α7-nAChR) is fundamental to physiology; it mediates various brain functions and represents an important target for drug discovery. Exploration of the brain nicotinic acetylcholine receptors (nAChRs) using positron-emission tomography (PET) will make it possible to better understand the important role of this receptor and to study its involvement in schizophrenia, bipolar disorder, Alzheimer's and Parkinson's diseases, drug dependence, inflammation and many other disorders and simplify the development of nicotinic drugs for treatment of these disorders.

Until recently, PET imaging of α7-nAChRs has been impeded by the absence of good radiotracers. This review describes various endeavors to develop α7-nAChR PET tracers by several research groups including the author's group. Most initial PET tracers for imaging α7-nAChRs did not exhibit suitable imaging properties due to their low specific binding. Newly discovered [^{18}F]ASEM is the first highly specific α7-nAChR radioligand and in 2014 it was translated to human PET imaging.

Contents

1. Introduction

Nicotinic cholinergic receptors (nAChRs) are neurotransmitter-gated cationic channels that are present in the central nervous system (CNS), autonomic and sensory ganglia, and various non-neuronal cells. Two nAChR subtypes, α4β2- and α7-nAChR, are the most abundant nAChRs in the CNS [1].

* Corresponding author at: PET Center, Division of Nuclear Medicine, Radiology, Johns Hopkins Medicine, 600 North Wolfe Street, Nelson B1-122, Baltimore, MD 21287-0816, USA. Fax: +1 410 614 0111.
E-mail address: ahorti1@jhmi.edu (A.G. Horti).

http://dx.doi.org/10.1016/j.bcp.2015.07.030
0006-2952/

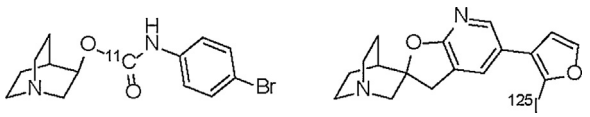

Fig. 1. First radioligands for emission tomography imaging of α7-nAChR [44,45].

The α7-nAChR subtype is highly expressed in the human brain and this subtype has been implicated in the pathophysiology of a variety of brain disorders and conditions including schizophrenia, Alzheimer's disease, bipolar disorder, traumatic brain injury, anxiety, depression, multiple sclerosis, inflammation, and drug addiction [1–10].

As was demonstrated in post-mortem studies, the density of α7-nAChRs in human brain tissue is significantly altered in many disorders:

Schizophrenia: In autoradiography and immunochemistry studies, Freedman et al. [11] and others [12–17] have demonstrated a significant post-mortem reduction (25–54%) of α7-nAChR binding or expression in the hippocampus and cortex of subjects with schizophrenia vs. controls.

Alzheimer's disease: A characteristic of Alzheimer's disease is degeneration of cholinergic neurons [18]. A number of reports have described a significant loss of α7-nAChRs in the cortex and hippocampus of patients with Alzheimer's disease [15,19] (see also review [20]).

Bipolar disorder: An autoradiography study using an α7-nAChR radiotracer demonstrated an increased binding in the hippocampus and perirhinal cortex in the brain slices of the subjects suffering from bipolar disorder [21].

Traumatic brain injury: Traumatic brain injury is a significant public health problem with almost 2 million documented cases per year in the USA, with a mortality of 20% [22,23]. Several reports found a significant reduction (30–70%, ex vivo or in vitro) of α7-nAChRs in animal models of traumatic brain injury [8,24–26], suggesting that alteration of the α7-nAChR is a crucial component of the biochemical perturbation caused by traumatic brain injury.

The difference in the denstity of α7-nAChRs in the brain between healthy subjects and patients suffering from various disorders was quantified in post-mortem studies, but it never was observed in the living human brain. Non-invasive quantification of α7-nAChRs in humans would provide a better understanding of their role in various CNS disorders and could also simplify the development of nicotinic drugs for treatment of these disorders [27–32].

PET provides the best opportunity for quantification of receptors in the human brain—better than any other clinical imaging modality [33,34]. However, since the invention of the PET technique in 1975 fewer than 40 of the existing receptors in the human brain have been imaged due to the lack of available PET radiotracers (see http://www.nimh.nih.gov/research-priorities/therapeutics/cns-radiotracer-table.shtml). Until recently, one of the major cerebral receptors lacking an appropriate PET radioligand for human imaging was α7-nAChR. The recently developed PET radioligand [^{18}F]ASEM has opened new avenues in noninvasive imaging of this receptor system in human subjects.

2. Initial PET radioligands for α7-nAChRs

In principle, a quality α7-nAChR radioligand for PET should exhibit the same set of characteristics as PET tracers for most other brain receptors: (1) a high specific and low non-specific binding in vivo; (2) high selectivity versus non-target binding sites; (3) reversible brain kinetics with good blood-brain barrier permeability; (4) radiochemistry that is suitable for short-lived isotopes; and (5) low radiation burden and toxicity. These general requirements for PET radiotracers have been summarized in many reviews [35–37].

While all general requirements must be met, the high specific binding is the most demanding property in the development of α7-nAChR radiotracers. Specific PET tracers for brain receptors are expected to obey the Eckelman's criterion that $B_{max}/K_D \geq 10$ (B_{max} = binding site density; K_D = binding affinity constant of the radiotracer) [38,39]. The concentration of the α7-nAChR binding sites in the primate brain is low (B_{max} = 5–15 fmol/mg protein or 1.5–12 fmol/mg tissue) [12,40,41]. Consequently, the expected binding affinity for a quality α7-nAChR PET radioligand must be in a sub-nanomolar range. This binding affinity requirement challenged the development of suitable α7-nAChR radioligands (see reviews [35,42,43]).

Investigators have been attempting to develop α7-nAChR radioligands for in vivo imaging since the pioneering work of the Dolle [44] (Orsay, France) and Pomper [45] (Baltimore, US) in 2001–2005. Both groups radiolabeled quinuclidine derivatives (Fig. 1) that were previously reported by AstraZeneca as potential α7-nAChR drugs. Unfortunately, these radiotracers did not exhibit a sufficient signal-to-noise ratio in lab animals and were not translated to humans.

In 2005–2010 many researchers, including our own group, worked on the development of a clinically viable α7-nAChR PET radioligand, and about two dozen α7-nAChR compounds were radiolabeled with [^{18}F] or [^{11}C]. As summarized in the recent reviews [35,46–48], those efforts did not lead to an α7-nAChR PET radioligand with sufficient in vivo specificity.

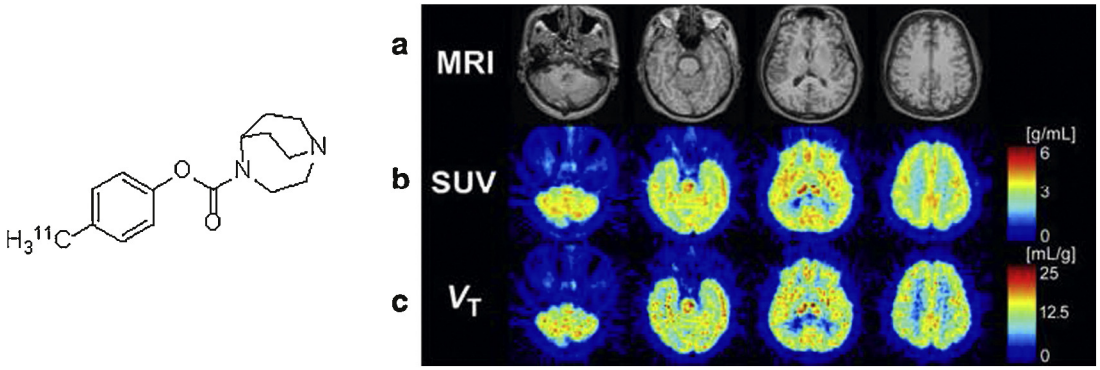

Fig. 2. Left: Structure of [^{11}C]CHIBA-1001. Right: PET images of human brain with [^{11}C]CHIBA-1001. Panel (a) magnetic resonance images (MRI) of the corresponding slices. Panel (b) Static images acquired from 0 to 90 min after injection of [^{11}C]CHIBA-1001 expressed as SUV. Panel (c) A parametric image for the total distribution volume of [^{11}C]CHIBA-1001 generated using Logan graphical analysis. The data from 30 to 90 min were applied to the Logan plot analysis. Reprinted from [49] with permission of Copyright Clearance Center's RightsLink service.