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Development of new radiopharmaceuticals for imaging monoamine oxidase B

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Abstract

Introduction: Imaging monoamine oxidase B (MAO-B) in the central nervous system with PET is an important goal for psychiatric studies. We here report an improved and automated radiosynthesis of *N*-(6-[^{18}F]-fluorohexyl)-*N*-methylpropargylamine ([^{18}F]FHMP; [^{18}F]-**1**), as well as the radiosynthesis of two new promising candidates for imaging cerebral MAO-B, namely, carbon-11-labeled 3-(4-[^{11}C]-methoxyphenyl)-6-methyl-2H-1-benzopyran-2-one ([^{11}C]-**2**) and *N*-((1H-pyrrol-2-yl)methyl)-*N*-[^{11}C]-methyl-1-phenylmethanamine ([^{11}C]-**3**).
Methods: Fluorine-18-labeled **1** was prepared via a tosyloxy precursor in 29%±5% uncorrected radiochemical yield, relative to [^{18}F]-fluoride. Both carbon-11-labeled compounds were prepared with [^{11}C]CH_3I using the "LOOP" method in 11% and 18% uncorrected radiochemical yields, respectively, relative to starting [^{11}C]CO_2. All radiotracers had specific activities >37 GBq/μmol and were >98% radiochemically pure at end of synthesis (<40 min). All radiotracers were evaluated by ex vivo biodistribution studies in conscious rodents.
Results: A major radioactive metabolite in the rodent brain was observed following administration of [^{18}F]-**1**. While [^{11}C]-**2** had moderate brain penetration and good clearance from normal brain tissue, distribution of radioactivity in brain was indicative of free and nonspecific binding. Good brain uptake was observed with [^{11}C]-**3** (0.8%–1.4% injected dose per gram at 5 min postinjection), binding appeared to be reversible and distribution conformed with regional distribution of MAO-B in the rat brain. Preinjection of **3** or L-deprenyl showed a modest reduction (up to 25%) of brain activity.
Conclusion: Carbon-11-labeled **3** was found to have the most favorable properties of the radiotracers evaluated; however, the signal-to-noise ratio was too low to warrant further in vivo imaging studies. Alternative radiotracers for imaging MAO-B are under development.

Keywords: Radiopharmaceuticals; Enzymes; Positron emission tomography; Monoamine oxidase B; Carbon-11; Fluorine-18

1. Introduction

Monoamine oxidase (MAO), a family of flavin-containing enzymes [1], is present in the outer mitochondrial membrane [2], although a small proportion is associated with the microsomal fraction [3]. These enzymes play a major role in the regulation of chemical neurotransmitters by catalyzing oxidative deamination of monoamine neurotransmitters, thereby controlling their availability and physiological activity [4]. As such, MAO is an important target for therapeutic drugs and toxic substances. It is involved in neurological disorders such as depression [5–7], Parkinson's disease [8,9] and Alzheimer's disease [10,11], as well as cigarette smoking [12,13].

The two isoenzymes, MAO-A and MAO-B, are gene products having different substrates and inhibitor specificities [4], and their ratios vary among organs and between species [14,15]. Monoamine oxidase A preferentially deaminates norepinephrine and serotonin and is selectively inhibited by clorgyline [16], while MAO-B preferentially oxidizes benzylamine and phenylethylamine and is selectively inhibited by L-deprenyl in human tissues (MAO-A, K_i=376 nM; MAO-B, K_i=16.8 nM) [6]. Both forms oxidize dopamine and dietary tyramine [17,18]. Positron emission tomography (PET) has been extensively used to image MAO-A binding with [^{11}C]-clorgyline [15,19], [^{11}C]-harmine

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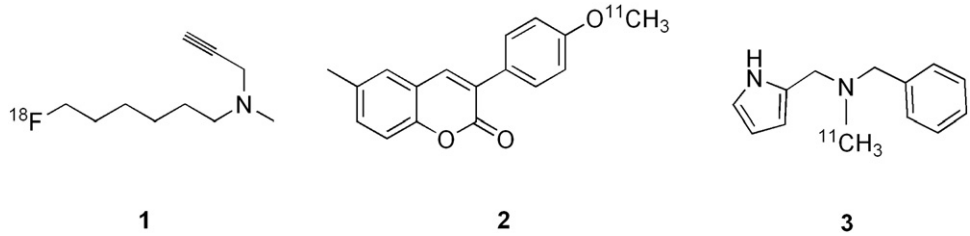

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Fig. 1. Lead compounds for imaging MAO-B with PET.

[7,20–22] and [^{11}C]-befloxatone [23]. Conversely, only [^{11}C]-L-deprenyl (and the deuterium-labeled [^{11}C]-L-deprenyl(-D_2)) has been applied for imaging MAO-B in the living human brain [19,24,25]. In addition, the challenge of kinetic modeling of MAO enzymes without a reference region, a major drawback of [^{11}C]-L-deprenyl and its deuterated analogue, is that both generate [^{11}C]-L-methamphetamine as a radioactive metabolite, a well-known brain-penetrating compound [26] that can confound imaging analysis [27].

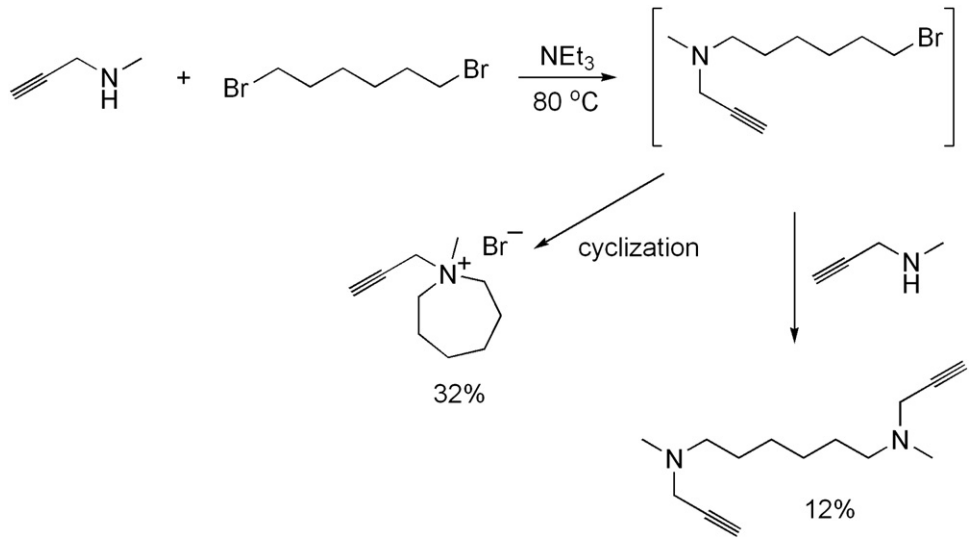
Many other radiotracers have been developed for imaging MAO-B (see Fowler et al. [28,29] for reviews). Of these radiotracers, analogues of Ro 19-6327 radiolabeled with [^{123}I]- (Ro 43-0463) or [^{18}F] [30,31], as well as [^{11}C]-DMPEA [32,33], have been evaluated in humans. While [^{123}I]-Ro 43-0463 and [^{11}C]-DMPEA had appropriate properties for SPECT or PET studies, respectively, the [^{18}F] derivative of Ro 19-6327 had limited brain uptake. Other radiotracers for this target have been evaluated in animal models: [^{11}C]-pargyline and [^{123}I]-2-iodopargyline [34,35], [^{18}F]-DL-4-fluorodeprenyl [36,37], [^{11}C]-MD-230254 [38], *N*-(6-[^{18}F]-fluorohexyl)-*N*-methylpropargylamine ([^{18}F]-FHMP) [39] and [^{11}C]-SL25.1188 [40,41]. Although [^{11}C]-MD-230254 and [^{11}C]-SL25.1188 show excellent promise, they are both prepared via [^{11}C]-phosgene [42], which requires an arduous synthesis (specialized apparatus, extensive upkeep, technical expertise and replacement of key components between production runs) and therefore is limited to only a few laboratories worldwide. Thus, there is still a demand for new radiotracers for imaging MAO-B that can be prepared rapidly and, if possible, in an automated, commercial, radiosynthetic device.

In this article, we report studies of [^{18}F]-FHMP ([^{18}F]-**1**) for imaging MAO-B, as well as the new radiotracers [^{11}C]-3-(4-methoxyphenyl)-6-methyl-2H-1-benzopyran-2-one, [^{11}C]-**2**, and *N*-[^{11}C]-methyl-*N*-(phenylmethyl)-1H-pyrrole-2-methanamine, [^{11}C]-**3** (Fig. 1), based on the promising in vitro binding assays of **2** [43,44] and **3** [45]. A new, automated synthesis of [^{18}F]-**1** is reported, as well as syntheses of [^{11}C]-**2** and [^{11}C]-**3** via "LOOP" methods [46,47]. All three compounds were evaluated ex vivo in rat brain and, where appropriate, metabolite analyses were conducted of both brain homogenates and plasma.

2. Results and Discussion

2.1. [^{18}F]-FHMP ([^{18}F]-1)

Based on extensive structure–activity relationships [48,49], Mukherjee et al. [39] showed [^{18}F]-**1** is approximately 200 times more selective for MAO-B over MAO-A



Scheme 1. Reaction of 1,6-dibromohexane with *N*-methylpropargylamine.