Radiopharmaceuticals

4

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4.1 Introduction

Radiotracers and radiopharmaceuticals for Nuclear Medicine imaging with applications in neurology have been implemented for more than 50 years, based on the research efforts of scientists in the academic world, hospitals, and industry. The first described imaging applications in humans were pioneered in the early 1950s in the USA for the detection of intracranial lesions and for the assessment of regional cerebral blood flow. Images were obtained using conventional gamma cameras, after administering inert radioactive gases by inhalation or radioactive metal complexes by injection. These agents were not aimed to detect any specific mechanism or molecular target, but they were used in the research setting for describing pathophysiological processes.

The strong efforts in radiochemistry, in addition to the technological improvements of the tomographic detection systems, contributed to enforce the interest for this emerging technique, and the first studies in a clinical setting were reported during the 1960–1970s. The potential impact to patient care boosted the need of new and more specific radiotracers. Thus, the development of new tracers for neuroimaging applications turned from using radioactive salts and known chelating agents to the modern concept of molecular neuroimaging. This latter model is based on the specific interaction between the imaging agent and the molecular structure or cellular process of interest, such as receptors, enzymes, transporters, or metabolic pathways. The emitting radionuclides contained within the agent provide a signal that can create an image if associated with the proper imaging system. After four decades of hard work in radiochemistry, hundreds of radiotracers containing different single photon and positron emitter nuclides have been developed and applied to the most common imaging modalities for the evaluation of brain function, accomplishing clinical and investigational requirements (Table 4.1). A number of them have been approved by authorities and are currently used in Nuclear Medicine departments by physicians for specific applications, showing a potential impact for direct patient care. The major clinical areas of application include cerebrovascular diseases, movement disorders, dementia, epilepsy, and brain tumors. Neuroimaging radiotracers are also employed for the study of other mental disorders such as schizophrenia, addiction, depression, and anxiety.

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Table 4.1 Early PET and SPECT human brain studies

Date	PET	SPECT
1955		[^{85}Kr]Gas
1963		[^{133}Xe]Gas
1964		[^{99m}]TcO_4^-
1965	[^{68}Ga]EDTA	
1967	[^{15}O]Oxygen	
1969	[^{15}O]Water	
1975		[^{123}I]Iodoantipyrine
1976	[^{11}C]Methionine	
1977	[^{18}F]FDG [^{11}C]Tryptophan [^{11}C]Valine	
1981		N-isopropyl-[^{123}I] Iodoamphetamine ([^{123}I]IMP)
1983	N-[^{11}C]Methylspiperone [^{18}F]FDOPA	[^{123}I]IQNB
1984	[^{18}F]Cyclofoxy	
1985	[^{11}C]Raclopride [^{11}C]Carfentanil [^{11}C]Flumazenil	[^{99m}Tc]HMPAO
>1985	Many	Many

Unexpectedly, the expanded range of radiotracers hasn't been followed by a parallel introduction of radiopharmaceuticals, as tools for answering clinical needs. During the last decade, radiotracers in order to get approval for clinical use or marketing authorization have been facing implemented radiopharmaceutical requirements, similar to those that are broadly applied to all drugs. In particular, the increased awareness for the quality and safety of radiopharmaceuticals and the need for confirmation that the diagnostic agent has to provide clinically useful information contributed to make a widespread use of new agents very challenging.

Last but not least, the use of SPECT and PET neuroimaging is not restricted to the clinical or investigational field in the hospital Nuclear Medicine departments. During the last decades, this imaging technique has gained attention in neuroscience for the excellent capability to gain insight into disease mechanisms, describing the kinetics of the radiotracers and measuring target reserves, such as enzymes or receptors. For this reason, the standard methodology developed to study normal and pathological processes has been extended to support drug discovery in the universities and in the pharmaceutical industry. Neuroimaging with carbon-11 and fluorine-18 PET radiotracers has become a routine procedure for the development of biomarkers for novel central nervous system therapeutics. Using a PET-specific radiotracer identical to a drug candidate, brain penetration and target occupancy measurements can be defined. The drug interaction with a specific brain target can also be studied by competition, if a suitable radiopharmaceutical for the same target is available. Such information may have a substantial impact in a go/no-go decision on a set of drug candidates before first-in human studies and furthermore may produce a significant effect on the overall pipeline cost for drug development.

4.2 Brain SPECT and PET Radiotracers: A Journey More than 50 Years Long

From a historical perspective, the use of radiotracers for brain scanning began in the early 1950s for the localization and identification of tumor damage by Sweet and Brownell [1–3].

Several compounds incorporating radionuclides were synthesized in order to obtain stable agents with a low toxicity profile. Among these, the most satisfactory have been the positron emitters arsenic-74 as arsenate, copper-64 as versenate, and mercury-203 as neohydrin [4, 5]. These scanning agents were not required to have any specific interaction; they were able to permeate across the disrupted blood–brain barrier (BBB), thus allowing a rudimental detection of the membrane integrity and the lesion extensions with camera-type systems. Despite the raising interest for the methodology, these long half-life radionuclides displayed suboptimal characteristics for a clinical use. A few years later, driven by favorable nuclear properties, a radionuclide generator, and known chemistry, the researcher's attention shifted to the development of a suitable agent containing gallium-68 [6]. As a consequence of the available "ready to use" ^{68}Ga-EDTA (ethylenediaminetetraacetic acid) milked from the generator, and the introduction of new positron scintillator cameras [7, 8], hundreds of patients were investigated during the 1960s [9, 10]. Unfortunately, the enthusiastic consensus for gallium-68 imaging faded away during the 1970s, mainly because of the restricted use of first-generation ^{68}Ge/^{68}Ga generators and the parallel development of new emerging radionuclide tracers, such us single-photon emitters technetium-99m/iodine-123 and the positron emitting carbon-11/fluorine-18.

Since the dramatic change that occurred at Brookhaven National Laboratory in the late 1950s for the availability of ^{99}Mo/^{99m} Tc generators, the radiometal technetium-99m opened a new era in Nuclear Medicine as well as in early neuroimaging [11]. The ideal nuclear properties, the easy availability from a generator, and the flexible chemistry facilitated the introduction of this emerging radionuclide that is, at present, the most employed for Nuclear Medicine procedures worldwide. The first agents ^{99m}Tc-pertechnetate and ^{99m}Tc-DTPA (diethylenetriaminopentaacetic acid), as well as other gamma emitters radiotracers thallium-201 and gallium-67 citrate, were evaluated for pathologies with altered BBB due to tumors or traumas [12–14]. However, all these radiotracers had the relevant constraint that they could be employed in neurological disease just for the evaluation of an altered BBB.

In the late 1950s, a few years later from the initial brain tumor scanning, Munck and Lassen pioneered the assessment of cerebral blood flow (CBF) by using inert radioactive gases, thus providing the basis for regional CBF functional imaging. Evaluation in human brains was performed by administrating trace amounts of krypton-85 by inhalation or intravenous injection in saline solution [15, 16]. In the original methodology, blood samples were collected from bilateral jugular veins and counted, reflecting the global blood flow and oxygen use. The further advance was the measurement of the regional cerebral perfusion achieved by placing detectors on the patient's scalp, to determine radiotracer accumulation and clearance on a regional basis, thus opening the way for a more modern concept of CBF scanning using a noninvasive approach [17, 18].

In the 1960s, major improvements occurred using molecular [^{15}O]oxygen for regional oxygen extraction and perfusion assessments, also taking advantage of the increased performances of imaging systems due to the introduction of first-generation Anger cameras [19]. Ter-Pogossian and Brownell evaluated the radiotracer kinetics after a single breath by means of a pair of detectors. However, the first results were not satisfactory because of the difficult interpretation of the collected data [20, 21]. Some years later, radioactivity administration was modified by using continuous [^{15}O]oxygen inhalation, producing a "steady-state" brain distribution dependent on perfusion and oxygen extraction, as well as the physical decay of the radioisotope [22]. Nevertheless, this technique suffered for some important disadvantages such as a constant delivery of the radioactive gas and a long-time scan during which, it is assumed, no change in physiological status occurs. A more practical and suitable method for imaging was then introduced using an intravenous injection of [^{15}O]oxygen water instead of a labeled gas [23], becoming a standard procedure for rCBF assessment with PET. These methods have been used in clinical

settings since the 1980s in several clinical conditions including strokes, brain tumors, and Parkinson's disease [24–26]. Despite the fact that the early evaluations were much more qualitative than quantitative, these methodologies represent a milestone for neuroimaging because of the direct impact on patient healthcare.

An alternative to PET radiopharmaceuticals for the rCBF measurement was developed during the 1980s by the parallel and successfully investigational studies with iodine-123 and technetium-99m. These efforts resulted in the development of perfusion agents able to overpass the normal BBB, such as [^{123}I]iodoantipyrine, [^{123}I]IMP (l-3-[^{123}I]-iodo-α-methyl-tyrosine), [^{99m}Tc]HMPAO ([^{99m}Tc]exametazime), and [^{99m}Tc]ECD ([^{99m}Tc]bicisate). Most of them have reached an established clinical use for the evaluation of various neurological diseases such as dementia, Alzheimer's disease, epilepsy, stroke, and Parkinson's disease [27–30].

A fundamental advance for Nuclear Medicine applications was the application of fluoro-18-deoxyglucose ([^{18}F]FDG) to image cerebral glucose metabolism in 1976, destined to become the most important PET tracer to this day with indications for tumors and for identification of foci of epileptic seizures [31, 32]. [^{18}F]FDG, a glucose analog, is able to delineate the glucose metabolism, which is very active in the normal brain and often hyperreactive in tumors.

The promising results using a radiotracer able to interact with substrates, in addition to the early quantitative imaging applications, confirmed the full potential of this emerging technique in describing molecular processes on human brain in health and disease. A general enthusiasm and great expectation for the future were soon satisfied by a rapid increase in the development of new radioactive molecules, typically including the positron emitters carbon-11 and fluorine-18 and single-photon emitters iodine-123 and technetium-99m. The new generation of radiotracers were designed for displaying affinity for receptors, enzymes, or other biological structures thus defined as radioligands, for interacting with specific metabolic pathways or for reproducing the chemical structures of drugs incorporating a radionuclide with identical characteristics or with minimal modifications or at least retaining the key biochemistry. Among the expanded range of imaging molecules, the first widespread applications included the regional amino acid metabolism using native amino acids or derivatives labeled with carbon-11, like [^{11}C]methionine, leucine, and unnatural amino acids [33–35]. A few years later, fluorine-18 dihydroxyphenylalanine ([^{18}F]FDOPA), a dopamine synthesis pathway analog, and N-[^{11}C]methylspiperone, a radioligand for dopamine/serotonin receptors, were used to assess for the first time the neurotransmission function in humans [36, 37]. The mid- to late 1980s were characterized by a continuous introduction of new radioligands with major advances for the quantification of dopamine receptor subtypes ([^{11}C]raclopride, [^{11}C]Schering-23390), dopamine transporters ([^{11}C]nomifensine), central benzodiazepine receptors ([^{11}C]flumazenil), peripheral benzodiazepine receptors ([^{11}C]PK11195), opioid receptor agonists and antagonists ([^{11}C]carfentanil and [^{11}C]diprenorphine) [38–44], as well as for the enzyme monoamine oxidase type B ([^{11}C]deprenyl) [45]. A new field of research appeared to be very auspicious for more specific and useful clinical applications with PET chemistry imposing a dominate role in neuroimaging.

Radiotracer expansion certainly benefitted from an increased understanding of both physiological and pathological molecular processes, but the great effort of chemists, pharmacists, biologists, physicists, and physicians was key to the progress. The influx of scientists from various fields allowed the discovery and validation of new radiopharmaceuticals to achieve a vast array of targeted radiotracers. This great evolution was also facilitated by the increased availability of supporting technologies and infrastructures such as generators, cyclotrons, SPECT and PET scanners, and chemistry laboratories. In addition, the notable improvements in radiochemistry, mainly in labeling strategies for rapidly labeling molecules with high specific activity starting from the most popular short-life PET radionuclides, have boosted the design of new radiotracers claiming the important role this discipline is playing in this field.

During the 1990s, a progressive investigation focused on the improvement of the existing imaging, as well as in modulating and delineating neurotransmission systems other than dopaminergic and serotoninergic. [^{11}C]WAY-100635, [^{11}C]MDL-100907, and [^{11}C]McNeil-5652 were introduced, respectively, for a more selective evaluation of serotonin receptor subtypes 1a/2a distribution and for the SERT/5-HTT transporters [46–48]. Novel [^{11}C]NNC112, [^{11}C]FBL457, and [^{11}C]-β-CIT displayed high affinities, respectively, for dopamine receptor subtypes 1 and 2/3 and for dopamine transporters [49–51]. Beyond the dopaminergic/serotoninergic systems, new imaging agents were aimed at exploring acetylcholinesterase enzyme ([^{11}C]MP4A and [^{11}C]PMP) and nicotinic receptor reserves (2-[^{18}F]F-A85380), as well as vesicular monoamine transporter type 2 ([^{11}C]DTBZ) and ATP-binding cassette (ABC) transporters like P-glycoprotein ([^{11}C]verapamil) [52–56].

For many years, the development of target-specific agents has been strongly dominated by PET chemistry, given the relatively easy replacement of a carbon, an oxygen or nitrogen with a radioisotope conserving the original chemical structures. However, the major worldwide diffusion of SPECT scanners promoted the investigation for the development of agents containing a suitable single-photon emitter radionuclide. A number of radioiodinated tracers which bind CNS receptors were synthesized and introduced successfully as alternatives to PET tracers in clinical settings. Iodinated derivatives displayed excellent properties for the quantitative evaluation of the muscarinic ([^{123}I]IQNB, [^{123}I]iododexetimide), dopamine ([^{123}I]IBZM and [^{123}I]epidepride), and benzodiazepine ([^{123}I]iomazenil and [^{123}I]NNC-13-8241) receptor reserves and for dopamine/serotonin transporter function ([^{123}I]-β-CIT) [57–63]. Because of the intrinsic difficulties to incorporate a radiometal such as technetium-99m into small molecules, able to pass the normal BBB and conserving the affinity for a specific target, investigational studies were not as consistent as for the main PET tracers in neurology. The synthesis and evaluation of the first [^{99m}Tc]-labeled tropane analogs that display selective dopamine transporter binding were reported in 1996 and 1997 (TRODAT-1 and technepine), and [^{99m}Tc]TRODAT-1 has succeeded in entering evaluation for clinical approval a few years later [64–66].

From 2000 to the present, the range of radiotracers for studying biochemical and pathophysiological molecular mechanisms has been expanding continuously. New targets of interest for neurological applications have been explored, among which are norepinephrine transporters ([^{11}C]methyl reboxetine), neurokinin-1 ([^{18}F]SPA-RQ) and cannabinoid-1 ([^{18}F]MK-9470) receptors and Alzheimer-related proteins (beta-amyloid with [^{11}C]PiB (Pittsburgh compound B) and related fluorine analogs, and more recently tau protein and alpha-synuclein with [^{18}F]THK5105) [67–71]. The concomitant advances in PET technology and the scanner proliferation in industrialized countries corroborated to establish the role of imaging in both research and clinical settings to improve our understanding in diagnoses, monitoring disease progression, and the response to treatment.

Unfortunately, relatively few radiotracers have been translated into the clinical setting, due to high requirements and complex procedures for getting the approval from authorities and, not least, because of the high costs of the required infrastructures. In addition, the utility of carbon-11, incorporated in most of the developed compounds, is limited by its short radioactive half-life, and for this reason, its on-site production and use are essential. On the contrary, fluorine-18 radiotracers may be produced and distributed to local hospitals, making use of this technology more widely accessible. A notable and successful example on the evolution for a specific clinical need, although uncommon, is represented by the radiopharmaceuticals employed in amyloid PET imaging. The first published experimental data using a carbon-11 compound ([^{11}C]PiB) with affinity for amyloid plaques has been followed by the development and commercialization of fluorine-18 analogs ([^{18}F]florbetapir, [^{18}F]florbetaben, and [^{18}F]flutemetamol) in less than 10 years [72].

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