Nuclear Medicine Imaging Tracers for Neurology

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Philip H. Elsinga

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P. H. Elsinga (✉)
Department of Nuclear Medicine and Molecular Imaging, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
e-mail: p.h.elsinga@umcg.nl

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Abstract

Tracers to investigate neurological disorders with positron emission tomography (PET) or single-photon emission computed tomography (SPECT) have found many applications. Several molecular targets can be studied in the human brain in vivo, both in health and disease. Initially, most attention was given to tracers for translocator protein (TSPO), deposition of beta-amyloid, and the dopaminergic system. Many clinical studies have been published with application of a variety of tracers for these targets. During the past few years, more tracers have reached the stage of human studies such as imaging agents for tau protein, P2X7 receptor, SV2A receptor, and the cholinergic system. Other targets of interest that have been studied in man to a lesser extent are *N*-methyl-D-aspartic acid (NMDA), serotonergic, adenosine, gamma-aminobutyric acid (GABA), sigma, opioid, and metabotropic glutamate subtype 5 (mGlu5) receptors. In addition, several transporter systems have received a great deal of attention. Many tracers for new molecular targets are under development and may open new horizons in the future. Most PET tracers for the brain were initially labeled with ^{11}C but were later replaced by ^{18}F-labeled analogs, since this radionuclide enables longer scanning protocols, dissemination to other hospitals, and commercialization. This initial chapter will highlight PET tracers that have already reached the state of human application.

1.1 Introduction

This chapter describes positron emission tomography (PET) and single-photon emission computed tomography (SPECT) tracers that have been validated in humans and are applied in clinical studies. Many other tracers with potentially improved properties are currently under preclinical evaluation. In Table 1.1, an overview is given of molecular targets and processes associated with neurological diseases and available tracers for nuclear medicine imaging in humans.

An ideal nuclear medicine imaging tracer for brain imaging should satisfy the following requirements:

- Simple automated synthesis procedure suitable for reliable and robust production and low radiation burden for personnel. For clinical studies, GMP compliance is a prerequisite.
- Appropriate molar activity which should be sufficiently high, so that tracer binding is minimally affected by nonradioactive counterparts. Especially for

Table 1.1 Overview of nuclear medicine tracers and their application in clinical studies

Target	Related disease	Tracers (human application)	Binding mechanism
TSPO	MS, AD, stroke, PD, HD, schizophrenia	[^{11}C]PK11195, DAA and PBR derivatives, [^{18}F]GE180	Antagonist
GABA	Stroke	[^{11}C]/[^{18}F]Flumazenil	Antagonist
Dopaminergic system	PD, HD, tardive dyskinesia, schizophrenia, autism, ADHD, drug abuse, depression	[^{18}F]FDOPA, [^{11}C] SCH23390	Vesicular storage D_1 antagonist
		[^{11}C]Raclopride, [^{123}I] IBZM	D_2 antagonist
		[^{11}C]PHNO	D_2 agonist
		[^{18}F]FP-CIT, [^{18}F] FE-PE2I [^{99m}Tc]TRODAT-1, [^{123}I]PE2I, [^{123}I]-β-CIT	Dopamine transporter
ß-Amyloid	AD, MCI	[^{11}C]PIB	Staining agent
		[^{18}F]Florbetaben/ florbetapir	
NMDA	Schizophrenia	[^{11}C]GSK-931145 [^{18}F]GE179	Antagonist
P-Glycoprotein	Neurodegeneration	[^{11}C]Verapamil, [^{11}C] dLop, [^{11}C]metoclopramide	Substrate
Cholinergic system	AD, PD, HD, schizophrenia	[^{11}C]MP4A [^{18}F]FEOBV	Acetylcholinesterase inhibitor VAChT ligand
		[^{18}F]FP-TZTP [^{18}F]ASEM, [^{11}C] CHIBA-1001 [^{18}F]A-85360, [^{18}F] flubatine	M_2 antagonist α_7-nAChR ligands $\alpha_4\beta_2$-nAChR ligands
mGlu-5	Depression, anxiety, schizophrenia, PD	[^{11}C]ABP688, [^{18}F] PSS232 [^{18}F]FPEB	Antagonist
VMAT2	PD, AD, HD	[^{11}C]DTPZ, [^{18}F] AV-133 [^{18}F]FP-DTBZ	
Adenosine receptor	PD, AD, epilepsy, sleep, neuroinflammation	[^{11}C]MPDX, [^{11}C] preladenant	A_1 antagonist A_{2a} antagonist
		[^{11}C]TSMX	A_{2a} antagonist
P2X7 Serotonergic system	Neuroinflammation Depression, anxiety, OCD, schizophrenia	[^{18}F]JNJ-64413739 [^{11}C]JNJ54173717 [^{11}C]DASB	Antagonist Serotonin transporter ligand
		[^{11}C]WAY100635, [^{18}F]MPPF	5-HT_{1A} antagonist
		[^{11}C]Cimbi-36	5-HT_{2A} agonist

(continued)

Table 1.1 (continued)

Target	Related disease	Tracers (human application)	Binding mechanism
Norephedrine	Depression	[^{11}C] Methylreboxetine	NE transporter ligand
Opioid receptors	Analgesia, shock, appetite, thermoregulation	[^{11}C]Carfentanil	Mu opioid receptor antagonist
Monoamine oxidase	Neurodegenerative and inflammatory processes	[^{11}C]Deprenyl	MAO inhibitor
Energy	Neurodegenerative and inflammatory processes	[^{18}F]FDG	Glucose consumption
Neuronal activity SV2A Sigma	Neurodegenerative and inflammatory processes AD AD	[^{15}O]Water [^{11}C]/[^{18}F]UCB-J [^{11}C]SA4503, [^{18}F] fluspidine	Blood flow Synaptic density Ligands
Tau protein	AD	[^{18}F]THK523, [^{18}F] AV1541	Staining agent
Phosphodies-terase-PDE-4 Phosphodies-terase-PDE-10	Depression Neurodegeneration	[^{11}C]Rolipram [^{11}C]IMA107, [^{11}C] Lu AE92680, [^{18}F] MNI589	Breakdown of cAMP
Demyelinization	Multiple sclerosis	[^{11}C]MeDAS	Staining agent
Cannabinoid R2	Neuroinflammation	[^{11}C]NE40	Antagonist

targets with low densities, high specific radioactivity is an important issue. In addition some compounds (e.g., opioid ligands) are pharmacologically active at very small concentrations, resulting in a need for ultra-high molar activities.

- Log*P* between 1.5 and 4 in order to passively cross the blood–brain barrier, enabling high accumulation of target bound radioactivity.
- High affinity (i.e., a low value for K_D, resulting in a high binding potential B_{max}/K_D) to achieve sufficient target-bound radioactivity and high specificity so that the measured radioactive signal represents binding to the target of interest.
- Metabolic stability to ensure that measured radioactivity represents binding of the administered tracer and not binding of a metabolite. Metabolites should not enter the brain.
- Low affinity for *P*-glycoprotein since *P*-glycoprotein can transport tracers out of the brain resulting in low brain uptake.
- Appropriate radionuclide: the radioactive half-life should match the rate of the physiological process of interest.

So to summarize: Radioactivity accumulation should represent target density or functionality, enabling the acquisition of quantitative data (Elsinga 2002). Since the ideal tracer does not exist, PET data should be interpreted with care. The following text discusses tracers for the human brain, arranged by molecular target.

1.2 Glucose Consumption

The most generally applied tracer in PET is 2-[^{18}F]fluoro-2-desoxyglucose (FDG). In neurology, FDG is used for quantifying the regional cerebral glucose consumption rate. In several neurological diseases (dementia, PD, AD, stroke), glucose consumption is reduced in specific brain regions, indicating impaired functionality of these areas. Many recent studies with FDG focus on quantification, differential diagnosis, pattern recognition (Nobili et al. 2018; Kogan et al. 2019), and on dual modality imaging (PET and MRI) aiming to increase its clinical utility. Numerous articles including review papers on the use of FDG have appeared in the literature. In many cases, FDG is applied in combination with tracers for other targets, as described in Chap. 1 (Demetriades 2002; Mielke and Heis 1998). In addition, several chapters in this volume will address the use of FDG-PET imaging.

1.3 Translocator Protein TSPO

Microglia act as resident macrophages in the brain governing the immune response. Activated microglia cells are associated with neuroinflammation, which plays an important role in the onset of neurodegenerative disease. TSPO, formerly known as the peripheral benzodiazepine receptor (PBR), is overexpressed by activated microglia (Politis et al. 2012). Several PET tracers for TSPO have been developed. (*R*)-[^{11}C]PK11195 [1-(2-chlorophenyl)-*N*-methyl-*N*-(1-methylpropyl)-3-isoquinoline carboxamide] was the first non-benzodiazepine and selective TSPO ligand (Hashimoto et al. 1989). The compound has nanomolar affinity for TSPO (Chauveau et al. 2008). This PET tracer is widely applied in TSPO PET imaging. (*R*)-[^{11}C]PK11195 has been used in many studies of the human CNS, including studies in multiple sclerosis, Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis, Huntington's disease, HIV, herpes encephalitis, and schizophrenia. Although (*R*)-[^{11}C]PK11195 shows increased brain uptake in several neurodegenerative disorders, the ligand has several disadvantages. The sensitivity is low, and it is difficult to quantify small changes in TSPO expression. (*R*)-[^{11}C]PK11195 displays a low brain penetration, high plasma protein binding, and high nonspecific binding because of its high lipophilicity. This results in a low signal-to-noise ratio. The lack of sensitivity and specificity of (*R*)-[^{11}C]PK11195 has hampered development of a standard method for quantitative data analysis. (*R*)-[^{11}C]PK11195 PET has been used mainly for assessing microglia/macrophage activation in various neurodegenerative disorders, as an indication of neuronal and tissue damage. A (metabolite-corrected) plasma input with a reversible two-tissue compartment model was shown to be the best approach for analyzing (*R*)-[^{11}C]PK11195 kinetics in brain. Because of the disadvantages of (*R*)-[^{11}C]PK11195, second- and third-generation TSPO tracers have been developed that should additionally distinguish TSPO polymorphism. Most of these new TSPO tracers are still in the early stage of investigation. Preclinical research efforts are aimed to resolve the following issues: (1) metabolic stability of the tracer, (2) adequate binding

potential (BP), (3) appropriate kinetics of the ligand receptor interaction, and (4) suitable quantification methods (Narayanaswami et al. 2018; Best et al. 2019).

Radioligands such as [^{11}C]PBR28, [^{11}C]DAA1106, [^{18}F]FEDAA1106, and [^{18}F]PBR111 have been developed to image TSPO in vivo (Dollé et al. 2009; de Vries et al. 2006). Published data using the second-generation tracers [^{11}C]DAA1106 and [^{18}F]FEDAA1106 in humans are promising, as they showed significantly higher brain uptake than [^{11}C]PK11195. Furthermore, increased [^{11}C]DAA1106 binding was reported in AD patients (Yasuno et al. 2008). A study using [^{11}C]PBR28 found focal increases of radiotracer binding in the brain of multiple sclerosis patients. In addition, third-generation TSPO-tracers such as [^{18}F]GE180 have been developed. [^{18}F]GE180 was studied in a head-to-head comparison with [^{11}C]PBR28 (Zanotti-Fregonara et al. 2018). It was concluded that kinetic modeling for [^{18}F]GE180 was more challenging than that for [^{11}C]PBR28 because of poor brain penetration.

1.4 GABA Receptor

The development of epilepsy has been associated with the impairment of gamma-aminobutyric acid (GABA) neurotransmission in the brain. The high-affinity ligand [^{11}C]flumazenil has been used widely for the investigation of GABA receptors (Hammers 2004) and was labeled in various positions (Halldin et al. 1988). [^{11}C]Flumazenil is available commercially in the United States and has been approved by the Food and Drug Administration (FDA) for use in various clinical trials. Using [^{11}C]flumazenil with PET in patients with acute hemispheric ischemic stroke, it was shown that this tracer can distinguish between irreversibly damaged and viable neuronal tissue during early onset of the disease. With [^{11}C]flumazenil, a reduction in the number of GABA/central benzodiazepine receptors was observed in the hippocampus of patients with mesial temporal lobe epilepsy, caused by unilateral hippocampal sclerosis. [^{11}C]Flumazenil has also been used to estimate the synaptic density of benzodiazepine receptors in persons who became blind. Compared with sighted controls, a significantly lower benzodiazepine receptor density was reported in the cerebellum of the blind subjects. In recent years, the ^{18}F-analog [^{18}F]flumazenil has become available (Hodolic et al. 2016). As flumazenil contains already a fluorine atom, [^{11}C]flumazenil and [^{18}F]flumazenil are chemically and pharmacologically identical, but with ^{18}F prolonged scanning protocols are possible. However, the synthesis of [^{18}F]flumazenil proceeds with low radiochemical yields, which has hampered widespread acceptance of [^{18}F]flumazenil (Zhang et al. 2019).

1.5 Dopaminergic System

The dopaminergic system plays a major role in neurological and psychiatric disorders such as PD, Huntington's disease, tardive dyskinesia, and schizophrenia. The neurotransmitter dopamine plays an important role in the control of movement, cognition, and emotion. Changed levels of dopamine also play a role in various

neuropsychiatric disorders, such as autism, attention deficit hyperactivity disorder, and drug abuse. Knowledge on altered dopamine synthesis and dopamine receptor densities is important for understanding the mechanisms underlying the pathogenesis and therapy of these diseases (Elsinga et al. 2006).

PET and SPECT tracers have been developed to measure presynaptic dopamine synthesis and transport. For measuring dopamine synthesis, the most commonly used tracer is 6-[^{18}F]FDOPA, whereas for dopamine transport, several radiolabeled tropane analogs are used in the clinic. Postsynaptically, dopamine exerts actions through several dopamine receptor subtypes. The dopamine receptor family consists of five subtypes D_1–D_5. In order to investigate the role of each receptor subtype, selective and high-affinity PET radioligands are required. To a lesser extent, work has been published related to radioiodinated tracers for SPECT. For the dopamine D_1 and D_2/D_3 subtypes, the most commonly used ligands are [^{11}C]SCH23390 (Kosaka et al. 2010) and [^{11}C]raclopride. [^{18}F]Fallypride is suitable for the investigation of extrapyramidal D_2 receptors. For SPECT studies of D_2/D_3 receptors, [^{123}I]IBZM is commercially available. For the other subtypes, no suitable radioligands have been developed (Tissingh et al. 1997).

6-[^{18}F]Fluoro-L-DOPA (FDOPA) is used to evaluate the central dopaminergic function of presynaptic neurons (Eidelberg et al. 1990; Sioka et al. 2010). Uptake of FDOPA is an indicator of DOPA transport into the neurons, its decarboxylation by amino acid decarboxylase (AADC) to 6-[^{18}F]fluorodopamine, and the capacity for dopamine storage, mainly in the striatum. 6-[^{18}F]Fluorodopamine can be converted by catechol-*O*-methyltransferase (COMT) to 3-*O*-methyl-6-[^{18}F]fluoro-L-DOPA, which is uniformly distributed throughout the brain. 6-[^{18}F]Fluorodopamine is also metabolized via monoamine oxidase to 6-[^{18}F]fluoro-3,4-dihydroxyphenylacetic acid and subsequently by COMT to yield 6-[^{18}F]fluorochomovanillic acid. In clinical studies, AADC is commonly inhibited with carbidopa. As a result of this inhibition of peripheral AADC, the delivery of FDOPA to the brain is increased.

The first FDOPA PET study of human brain was reported in 1983, showing increased accumulation of radioactivity in the striatum. In patients with established bilateral PD, FDOPA PET showed influx constant reductions in the caudate, putamen, striatal nigra, and midbrain. The decline with age in FDOPA uptake was more rapid in PD than in normal subjects. FDOPA PET is a good tool to monitor the progression of PD and the impact of therapies. The availability of FDOPA has improved since several robust nucleophilic [^{18}F]fluorination methods have become available (Zarrad et al. 2017; Tredwell et al. 2014).

1.5.1 Dopamine Transporter (DAT)

DAT is another important target for investigation of presynaptic dopaminergic function (Brooks 2010). The function of DAT is critical for the effects of antidepressant drugs. The use of DAT ligands has a practical benefit. In 6-[^{18}F]FDOPA PET, for example, medication with L-DOPA or other drugs is usually stopped before the PET scan, and patients sometimes receive inhibitors for AADC and COMT to reduce the

peripheral metabolism of the tracer. Usually, these pretreatments are not needed for PET scans with DAT tracers. Of course, effects of other medication on DAT images should be taken into account.

Several PET ligands of different chemical classes have been investigated to study DAT. The first reported tracers were [^{11}C]nomifensine and [^{18}F]GBR13119 followed by [^{11}C]*d-threo*-methylphenidate. Later, tropane analogs have been developed. [^{11}C]-β-CFT and [^{11}C]-β-CIT showed high affinity and were metabolically stable. The major drawback of [^{11}C]-β-CIT was its low selectivity toward DAT, although [^{123}I]-β-CIT (DaTSCAN, developed in the early 1990s, Innis et al. 1991) is clinically being used as a SPECT tracer (Nocker et al. 2012). [^{123}I]-β-CIT is commercially available. A significant correlation of the striatal uptake of [^{123}I]-ß-CIT with the severity and duration of PD has been reported. [^{123}I]-β-CIT scan is a useful tool in daily clinical practice to confirm diagnosis of PD and to differentiate PD from other diseases. [^{123}I]-β-CIT SPECT can contribute to treatment selection and can be used to monitor the effectiveness of therapies. In later years, an [^{18}F]analog of β-CIT has been developed. [^{18}F]FP-CIT PET images of striatal uptake were superior to those of [^{123}I]-β-CIT obtained with SPECT. Plasma analysis using [^{18}F]FP-CIT indicated the presence of only one minor metabolite. [^{18}F]FP-CIT (Hong et al. 2018; Yoo et al. 2018) has become an equally useful tracer in clinical practice as [^{123}I]-β-CIT (Sihver et al. 2007, see also Chap. 32 in this volume).

In order to circumvent the disadvantages, i.e., the limited availability, of cyclotron-produced radionuclides, ^{99m}Tc-labeled DAT tracers were developed (Kung et al. 1996). These tracers contain neutral lipophilic complexes that contain *N*-(alkylthiolate)tropane, aminobis(ethylthiolate), and a complex of ^{99m}Tc. [^{99m}Tc]TRODAT-1 belongs to this group (Chen et al. 2013). Using [^{99m}Tc]TRODAT-1 scintigraphy, the loss of DAT in PD patients could be measured very accurately. [^{99m}Tc]TRODAT-1 has been successfully applied to correlate striatal DAT expression with therapeutic results in patients with attention deficit hyperactivity disorder (ADHD). Patients with elevated striatal DAT responded better to methylphenidate therapy than those with lower DAT levels. On the basis of these results, the possible use of DAT measurements to predict a response to methylphenidate therapy was suggested. As a follow-up result, the decrease of DAT levels in ADHD patients who underwent methylphenidate therapy (measured with SPECT and [^{99m}Tc]TRODAT-1) correlated with an improvement in clinical symptoms. Caution has to be exercised in the interpretation of [^{99m}Tc]TRODAT-1 scans, since the uptake of this tracer is affected by age and sex (Mozley et al. 2001). [^{99m}Tc]TRODAT-1 is still used on regular basis, and several publications on PD in combination with this SPECT-tracer have appeared.

Other tropane tracers have been used as a biomarker for the integrity of presynaptic dopaminergic nerve cells in patients with movement disorders. ^{123}I-labeled *N*-(3-iodoprop-2*E*-enyl)-2-β-carbomethoxy-3β-(4-methylphenyl) nortropane, or PE2I, has about tenfold higher in vitro selectivity for the DAT over the serotonin transporter (SERT) compared to DaTSCAN (Ziebell 2011). Furthermore, [^{123}I]PE2I has faster kinetics than [^{123}I]-β-CIT. Because of its rapid kinetics, [^{123}I]PE2I binding to the DAT can be quantified with kinetic or graphical analysis. Since [^{123}I]PE2I is a

selective radioligand with optimal kinetic properties for accurate quantification of DAT availability in the striatum, it is currently considered the best radioligand for DAT imaging in the human brain with SPECT. More recently, ^{11}C-methyl and ^{18}F-fluoroethyl analogs of PE2I have been developed for human use. Studies in nonhuman primates concluded that the kinetics and metabolic behavior of [^{18}F]FE-PE2I were more favorable than those of [^{11}C]PE2I. All studies indicated highest tracer uptake in the striatum. [^{11}C]PE2I has been used in several human PET studies comparing controls with myoclonic epilepsy or with addicted counterparts. Application of various kinetic modeling procedures demonstrated a higher DAT activity in controls. The radioactive half-life of ^{11}C-PE2I may be too short for proper estimation of the striatal distribution volume, and [^{18}F]FE-PE2I may be better in this respect (Seki et al. 2010). Thus, [^{18}F]FE-PE2I is now more frequently used in human PET studies (Jakobson Mo et al. 2018).

1.5.2 D_1 Receptor

Two PET ligands, [^{11}C]NNC112 and [^{11}C]SCH23390, have been applied for human studies of the dopamine D_1 receptor (Catafau et al. 2010; Farde et al. 1987). In a PET study of D_1 receptor distribution in human brain, [^{11}C]NNC112 showed major localization of radioactivity in the striatum and neocortex. The striatum/cerebellum and neocortex/cerebellum ratios were 3.8 and 1.8, respectively. In a study in patients with schizophrenia in comparison with normal subjects, it was shown that the binding potential of [^{11}C]NNC112 was significantly elevated in the dorsolateral prefrontal cortex of patients with schizophrenia compared with healthy controls (Abi-Dargham et al. 2002). In recent years no new studies have been published with this radiotracer.

Other PET studies of D_1 receptor distribution in human brain employed [^{11}C]SCH23390, which accumulated mainly in striatum. [^{11}C]SCH23390 is currently the most common PET-tracer for D_1 receptors. Striatum-to-cerebellum ratios and kinetic constants are commonly used as parameters for quantitative imaging. PET scans of schizophrenic patients were similar to those obtained in healthy control subjects (Karlsson et al. 2002). With [^{11}C]SCH23390, it was possible to assess dopamine receptor occupancies in the striatum of patients treated with antipsychotics. Binding potential of the D_1 receptors in the striatum and frontal cortex decreased with age. There was no gender difference in D_1 binding potentials. In a study in patients with Huntington's disease, significant reductions of both the D_1 ([^{11}C]SCH23390) and D_2 ([^{11}C]raclopride) binding potentials in the striatum were shown. A comparative study using [^{11}C]NNC112 and [^{11}C]SCH23390 was performed in patients with schizophrenia and age-matched controls. The D_1 binding potential of both tracers in the frontal cortex, anterior cingulate, temporal cortex, and striatum of the schizophrenia patients was significantly lower than those of controls (Kosaka et al. 2010). Recent publications with [^{11}C]SCH23390 are relating D_1R availability to pathology (Plavén-Sigray et al. 2018; Stenkrona et al. 2019). Inconsistent results between groups have been discussed in literature and might by due to demographic factors.

1.5.3 D_2 Receptor

The D_2 receptor in the striatum has been one of the major targets of PET imaging. [^{11}C]*N*-methylspiperone, an analog of butyrophenone neuroleptics, was one of the first radioligands. Compared to [^{11}C]*N*-methylspiperone which also has affinity for the 5-HT_2 receptor, [^{11}C]raclopride has a higher selectivity for D_2 receptors. [^{11}C]Raclopride binds reversibly to D_2 receptors, which is an ideal property for estimation of B_{max} (Sioka et al. 2010; Elsinga et al. 2006). For this reason, [^{11}C]raclopride has been widely used as a D_2 receptor ligand. Several lines of evidence have indicated that [^{11}C]raclopride binding is reduced when the synaptic concentration of endogenous dopamine is increased. For the measurement of extrastriatal D_2 receptors that are expressed in much lower densities than D_2R in the striatum, ligands with very high affinity are required, in order to achieve sufficient binding to D_2 receptor. For this purpose, [^{11}C]FLB457 was developed (Narendran et al. 2011a). Another high-affinity benzamide, [^{18}F]fallypride, was also developed for this purpose. The longer half-life of this ^{18}F-labeled ligand enabled quantification of D_2 receptors in the caudate and putamen, using a prolonged scan protocol lasting 2 or 3 h (Millet et al. 2012). Both high-affinity tracers have also been used to measure dopamine release after administration of amphetamine. It should be noted that compounds within the benzamide class, such as raclopride and FLB457, do not only bind to D_2 receptors but also bind to D_3 receptors. The development of a D2-selective PET tracer has remained a challenge.

[^{123}I]IBZM (Kung et al. 1990) is a commercially available SPECT tracer for D_2/D_3 receptors. Comparative studies have reported a good correlation of the regional cerebral distribution of [^{123}I]IBZM and [^{11}C]raclopride. Calculated values for receptor density or receptor occupancy of the two tracers show systematic differences, which can be attributed to either the analysis method or the imaging modality (Catafau et al. 2009). In recent years, [^{123}I]IBZM has not been reported anymore in research articles.

1.5.4 D_2/D_3 Agonists

The use of agonists as imaging tracers may offer several advantages because they are supposed to bind only to the high-affinity state of the receptor, whereas antagonist tracers bind to both the high- and low-affinity binding sites. (−)-[^{11}C]-*N*-propylnorapomorphine (Narendran et al. 2011b) and (+)-[^{11}C]PHNO (4-propyl-9-hydroxynaphthoxazine) (Willeit et al. 2006) are successful D_2 receptor ligands. After exerting effects on second messenger systems, agonists will dissociate because of a conformational change of the receptor protein, back to the low-affinity state. In comparison to antagonists, receptor binding of radiolabeled agonists is expected to be more sensitive to changes in endogenous dopamine levels that compete with injected radioligands for binding to the receptor. As has been discussed in the section on dopamine synthesis and transport, the level of extracellular dopamine is an important parameter in neurological and psychiatric diseases.

It was shown that the binding of (−)[^{11}C]-*N*-propylnorapomorphine was indeed more sensitive to alterations in endogenous dopamine levels than [^{11}C]raclopride. This agonist tracer has not been used anymore in recent years and has been replaced by (+)-[^{11}C]PHNO. Its structure is based on naphtoxazine. (+)-[^{11}C]PHNO has been evaluated in several animal species and in humans. PHNO displayed higher binding potential values compared to [^{11}C]-*N*-propylnorapomorphine. The affinity of (+)-[^{11}C]PHNO for D_3 receptors is higher than for D_2 receptors. (+)-[^{11}C]PHNO has shown to be useful for evaluation of new drugs, estimation of receptor occupancy, and assessment of levels of extracellular dopamine under pathological conditions (Graff-Guerrero et al. 2008).

1.6 Beta-Amyloid Deposition

Many advances have been made to understand the neuropathological processes in AD. The accumulation of beta-amyloid is a primary event leading to the formation of neurofibrillary tangles and loss of synapses and neurons (Huang and Mucke 2012). The first clinically useful tracer for beta-amyloid imaging was ^{11}C-labeled Pittsburgh compound B (PIB) (Klunk et al. 2004). PIB is an analog of thioflavin T that binds to fibrillar beta-amyloid deposits with high sensitivity and specificity. PIB binds to both extracellular amyloid plaques and vascular amyloid deposits. At tracer dosages, PIB does not bind to neurofibrillary tangles or Lewy bodies (Zhang et al. 2012).

To improve the accessibility of beta-amyloid imaging, a second generation of ^{18}F-amyloid tracers was developed. Four ^{18}F-amyloid imaging agents are in advanced stages of development: flutemetamol, a 3′-fluoro analog of PIB (Thurfjell et al. 2012); florbetapir, a styrylpyridine derivative (Doraiswamy et al. 2012); FDDNP, a naphthol analog (Ossenkoppele et al. 2012); and florbetaben, a derivative of stilbene (Barthel and Sabri 2011). With the exception of FDDNP, these tracers show comparable results to PIB in clinical populations, although their nonspecific binding in white matter appears to be higher.

2-(1-(6-[(2-[^{18}F]Fluoroethyl)(methyl)amino]-2-naphthyl)ethylidene)malononitrile ([^{18}F]FDDNP) showed higher binding in AD than in the healthy brain. Despite its slow clearance kinetics, [^{18}F]FDDNP is used for the detection of neurofibrillary tangles and beta-amyloid plaques in patients with AD. In a comparative study between [^{11}C]PIB and [^{18}F]FDDNP, [^{11}C]PIB showed higher binding in patients with AD than in controls and patients with mild cognitive impairment (MCI). [^{18}F]FDDNP uptake was higher in brains of AD patients than in healthy controls, but MCI could not be distinguished from AD or from controls. Differences in binding potentials between patients with AD, or MCI, and healthy controls were more pronounced for PIB.

[^{18}F]florbetaben, [^{18}F]florbetapir, and [^{18}F]flutemetamol are clinically approved. They show very high sensitivity and specificity to detect beta-amyloid plaques. All three PET tracers are licensed to pharmaceutical industry. The clinical value of these tracers and the role of beta-amyloid in AD in particular are still under debate (Sala-Llonch et al. 2019; Palermo et al. 2019; Paghera et al. 2019).

With newly developed technology to get antibodies in the brain using transferrin as a vector, specific bifunctional transferrin beta-amyloid ^{124}I-labeled constructs were developed that specifically target the soluble neurotoxic beta-amyloid aggregates rather than insoluble fibrils. The expression of these soluble oligomers correlates better with disease severity than the insoluble plaques. The method has not yet been tested in humans (Sehlin and Syvänen 2019).

1.7 NMDA Receptor, Glycine Transport

Glycine acts as a neurotransmitter and is a modulator of the neuroexcitatory activity of the *N*-methyl-D-aspartate (NMDA) receptor. Impaired function of the NMDA receptor is responsible for cognitive dysfunction in patients suffering from neuropsychiatric diseases, like schizophrenia (Zorumski and Izumi 2012). Specific transporters are responsible for the uptake of glycine into the brain. The high-affinity transporters, GlyT-1 and GlyT-2, terminate the activity of glycine on the NMDA receptor in the synapse. GlyT-1 has been shown to maintain low levels of glycine at the synapse. Inhibition of GlyT-1 would increase glycine concentrations around the synapse, resulting in enhanced activity of the NMDA receptor. Several imaging agents for GlyT-1, such as [^{18}F]-2,4-dichloro-*N*-((1-(propylsulphonyl)-4-(6-fluoropyridine-2-yl)piperidine-4-yl)methyl)benzamide ([^{18}F]MK-6577 and [^{11}C]GSK931145, have been developed. Although the tracer is slowly metabolized, [^{11}C]GSK931145 has been successfully evaluated for the visualization of GlyT-1a in the human brain (Gunn et al. 2011). [^{18}F]GE-179 was developed as a next-generation NMDA antagonist and displayed a low nanomolar affinity of 2.4 nM. The tracer showed favorable kinetic properties. First human studies showed reproducible brain uptake (McGinnity et al. 2014). With [^{18}F]GE-179 it was possible to measure increased uptake around epileptic foci as a result of enhanced NMDA activation (McGinnity et al. 2015). A fully automated GMP-compliant synthesis method has been published (Yue et al. 2019).

1.8 P-Glycoprotein

Permeability of the blood–brain barrier (BBB) is an important factor in the maintenance of cerebral homeostasis (Bartels 2011). The BBB only allows entry of lipophilic compounds with low molecular weights by passive diffusion. In addition, the barrier contains transporters such as P-glycoprotein (P-gp), multidrug resistance-associated protein (MRP), and organic anion-transporting polypeptides (OATPs). The action of these carrier systems results in rapid efflux of harmful compounds from the central nervous system (CNS). P-gp is the most studied efflux transporter. PET studies related to P-gp were aimed at (1) direct evaluation of the effect of P-gp modulators on the cerebral uptake of therapeutic drugs, (2) assessment of mechanisms underlying drug resistance in epilepsy, (3) examination of the role of the BBB

in the pathophysiology of neurodegenerative and affective disorders, and (4) exploration of the relationship between polymorphisms of transporter genes and the pharmacokinetics of test compounds within the CNS (Colabufo et al. 2010; Elsinga et al. 2005).

Several radiotracers have been prepared to study P-glycoprotein function in vivo with PET, whereas some other PET tracers unintendedly proved to be P-gp substrates. These include alkaloids ([^{11}C]colchicine), anticancer drugs ([^{11}C]daunorubicin, [^{18}F]paclitaxel, [^{11}C]tariquidar, [^{11}C]elacridar), calcium antagonists ([^{11}C]-*R*-(+)-verapamil), ß-adrenoceptor antagonists ((*S*)-[^{11}C]carazolol, [^{18}F]-(*S*)-1′-fluorocarazolol, [^{11}C]carvedilol), serotonin 5-HT$_{1A}$ receptor antagonists ([^{18}F]MPPF), opioid receptor antagonists ([^{11}C]loperamide, [^{11}C]carfentanil), and various ^{64}Cu-labeled copper complexes. (*R*)-[^{11}C]verapamil is by far the most investigated PET tracer for P-gp. The tracer has been administered to healthy volunteers, and blocking studies with the immunosuppressant agent cyclosporin A were carried out. The results indicated that P-gp activity at the human BBB can be measured despite the high lipophilicity of (*R*)-[^{11}C]verapamil. Using tracer distribution volume as parameter, (*R*)-[^{11}C]verapamil uptake in the midbrain was significantly increased (18%) in Parkinson's disease patients compared with healthy controls. This suggests a decrease in P-gp activity at the BBB of PD patients (Bartels et al. 2010). (*R*)-[^{11}C]Verapamil has been further investigated in epileptic patients (Shin et al. 2016), and the effect of age on P-gp function/expression was investigated (Bauer et al. 2009). A drawback of [^{11}C]verapamil is its metabolic instability. Therefore deuterated [^{18}F]fluoroverapamil derivatives have been synthesized and preclinically evaluated. [^{18}F]d7-verapamil was shown to be the most stable verapamil derivative, maintaining its affinity for P-gp (Raaphorst et al. 2018).

Loperamide is an opiate agonist and a substrate for P-gp at the BBB. [^{11}C]Loperamide ([^{11}C]Lop) has been applied for studying P-gp function and multidrug resistance in tumors and normal tissues noninvasively. However, demethylation of [^{11}C]Lop to [*N*-methyl-^{11}C]-*N*-desmethyl-loperamide ([^{11}C]dLop) hampers its use as PET tracer for P-gp function since [^{11}C]dLop is also a good substrate for P-gp. Therefore, [^{11}C]dLop has been studied as a PET tracer for studying P-gp function (Seneca et al. 2009). In a study with healthy volunteers, there was minimal brain uptake of [^{11}C]dLop. There were five hydrophilic radiometabolites. Because of much lower nonspecific binding, [^{11}C]dLop is preferred over [^{11}C]verapamil. Surprisingly, the usability of [^{11}C]dLop has not been further investigated in recent years.

During a search for ^{18}F-labeled Pgp-substrates, [^{18}F]MC225 was identified as a promising tracer with improved metabolic stability compared to [^{11}C]verapamil and an increased basal uptake, as it is a weak P-gp substrate. This may enable not only assessment of decreased but also increased function/expression of P-glycoprotein (Savolainen et al. 2017). Another weak P-gp substrate, [^{11}C]metoclopramide, has already been evaluated in primates and humans. The relative importance of both the influx hindrance and the efflux enhancement components of P-glycoprotein was reported (Tournier et al. 2019).

1.9 Cholinergic System

Acetylcholine is an endogenous neurotransmitter at cholinergic synapses and acts on nicotinic and muscarinic receptors to mediate functions, such as attention, memory, cognition, and consciousness. Degeneration of cholinergic neurons has been observed in several neurodegenerative diseases, such as AD and PD (van Waarde et al. 2011). Acetylcholinesterase (AChE) is the enzyme that terminates cholinergic actions by the rapid hydrolysis of acetylcholine to choline and acetate. AChE has been a target for radioligand development as well as drug development because its levels decrease in AD. Radiolabeled AChE inhibitors and substrates have been developed for mapping AChE in vivo in brain. For measurements of AChE activity, various labeled esters of 1-methyl-4-hydroxypiperidine have been developed (Irie et al. 1996). *N*-[^{11}C]methylpiperidin-4-yl acetate ([^{11}C]MP4A) has a tertiary amine structure that makes it lipophilic, and therefore, the tracer can passively cross the BBB. [^{11}C]MP4A is specifically hydrolyzed by AChE. The hydrophilic metabolite, *N*-[^{11}C]methylpiperidinol ([^{11}C]MP4OH), is trapped in the brain. [^{11}C]MP4A has been tested as PET tracer for the AChE activity in patients with AD and PD (Shinotoh et al. 2004). For kinetic analysis, usually a three-compartment model is used to measure AChE. The parameter k_3 reflecting hydrolysis of the tracer is altered in disease. In a study of patients with AD, cortical regions displayed a reduced k_3 value compared with controls. The reduction in k_3 was both regionally and individually heterogeneous. In another study with patients with PD and ten Parkinson's patients with associated dementia (PDD) compared with age-matched controls, the cortical k_3 values for [^{11}C]MP4A were strongly reduced in PDD and slightly decreased in PD compared with controls. The PDD group had lower parietal k_3 values for [^{11}C]MP4A than patients with Parkinson's disease.

In contrast to AChE which acts both pre- and post-synaptically, the vesicular acetylcholine transporter (VAChT) is a glycoprotein regulating the accumulation of acetylcholine only into the presynaptic vesicles of cholinergic neurons. The cholinergic innervation is decreased at early stages of AD and PD. Therefore, VAChT is considered as a significant diagnostic target and an indicator for cholinergic neuronal integrity and function. A large number of vesamicol derivatives have been tested for their affinity to VAChT. [^{18}F]fluoroethyl benzovesamicol (FEOBV) emerged as a promising PET tracer for VAChT imaging. The compound has high affinity for VAChT and negligible affinity to sigma receptors. Most vesamicol derivatives have affinity for both VAChT and sigma receptors. FEOBV has been successfully used in human PET studies. These can involve short static scans made 3 h post-injection, with white matter as a reference region to estimate regional gray matter VAChT binding (Petrou et al. 2014). Binding data with respect to AD and PD have been published, showing a decreased uptake of [^{18}F]FEOBV in gray matter in patients compared to healthy control subjects (Aghourian et al. 2017).

Neuronal $\alpha_4\beta_2$ nicotinic cholinergic receptors (nAChRs) are part of a heterogeneous family of ligand-gated ion channels expressed in the central nervous system. Their activation by acetylcholine and nicotine causes a rapid increase in cellular permeability to ions, such as Na^+ and Ca^{2+}. nAChR dysfunction is implicated in

diseases such as schizophrenia, Huntington's disease, AD, and PD. nAChRs also play a significant role in nicotine addiction (Palma et al. 2012). 3-[2(*S*)-2-Azetidinylmethoxy]pyridine (A-85380) is a highly potent and selective $\alpha_4\beta_2$ nAChR agonist with subnanomolar affinity. 6-[^{18}F]Fluoro-A-85380 and 2-[^{18}F]fluoro-A-85380 have been studied for $\alpha_4\beta_2$ nAChR imaging in the brain. A-85380 has also been labeled as 5-[^{123}I]iodo-A-85380 for SPECT. These compounds displayed slow kinetics. Next-generation PET tracers based on the (homo)epibatidine scaffold, [^{18}F]flubatine, [^{18}F]AZAN, and [^{18}F]XTRA, were reported to have faster kinetics enabling scanning times of 90 min, or less. Most effort was put in the further development of [^{18}F]flutabine as a clinical tool to study the human brain (Sabri et al. 2015; Sabri et al. 2018). Recently, [^{18}F]XTRA and [^{18}F]nifene have shown to be also promising for human studies (Coughlin et al. 2018; Mukherjee et al. 2018). Kinetic modeling and dosimetry studies have been published.

The α_7 subtype of nAChR also plays a role in neurodegeneration. It has been suggested that this subtype mediates the phosphorylation of tau protein and also modulates immunological processes. The agonist 4-[^{11}C]Methylphenyl-1,4-diazabicyclo[3.2.2]nonane-4-carboxylate ([^{11}C]CHIBA-1001), a 4-methyl-substituted derivative of SSR180711, has been developed as a PET agent for the study of α_7-nAChR (Sakata et al. 2011) and was successfully evaluated to determine receptor occupancy by tropisetron (Ishikawa et al. 2011). [^{18}F]ASEM has been investigated in patients with schizophrenia (Wong et al. 2018). The data suggest decreased distribution volume in cingulate cortex, frontal cortex, and hippocampus in schizophrenic patients compared to healthy controls.

Muscarinic cholinergic M_2 subtype-selective tracers have been developed since this subtype is lost in the cerebral cortex in AD. M_2-selective PET tracers would offer the possibility to quantify such losses. Most tracers for cholinergic receptors have not demonstrated subtype selectivity. Tracers that are subtype selective in vitro typically do not cross the BBB. 3-((3-(3-Fluoropropyl)thio)-1,2,5-thiadiazol-4-yl)-1,2,5,6-tetrahydro-1-methylpyridine (FP-TZTP), a muscarinic agonist based on a series of non-fluorinated analogs, has been radiolabeled with ^{18}F ([^{18}F]FP-TZTP). [^{18}F]FP-TZTP was found to be a promising imaging agent for the M_2 receptor (Podruchny et al. 2003). In human studies, an age-related increase in M_2 receptor binding potential was found in healthy control subjects, using [^{18}F]FP-TZTP and PET. No recent studies on M_2 receptors have been reported.

1.10 Metabotropic Glutamate-5 Receptor

Glutamate is an important excitatory neurotransmitter at neuronal synapses in the brain. Glutamate produces its excitatory effects by acting on cell-surface ionotropic or metabotropic glutamate receptors (mGluRs). Of the eight subtypes, mGluR5 is usually found with moderate to high density in postsynaptic neurons of the frontal cortex, caudate, putamen, nucleus accumbens, olfactory tubercle, and hippocampus, whereas the density in the cerebellum is low (Homayoun and Moghaddam 2010). Dysfunction of mGluR5 is implicated in a variety of diseases of the CNS,

including anxiety, depression, schizophrenia, PD, drug addiction, and withdrawal. Radiolabeled analogs of 2-methyl-6-(phenylethynyl)-pyridine (MPEP) have been developed as potent, highly selective PET tracers for mGluR5. A drawback is their high lipophilicity, lack of mGluR subtype selectivity, and unfavorable brain accumulation kinetics. As a second-generation tracer for mGluR5, 3-(6-methyl-pyridin-2-ylethynyl)-cyclohex-2-enone-*O*-[^{11}C]-methyl-oxime ([^{11}C]ABP688) was evaluated. This tracer showed high and specific radioactivity uptake in rodent and human brain (DeLorenzo et al. 2011). [^{11}C]ABP688 has been used in several studies to investigate changes of mGlu-5 binding in depression, alcohol abuse, schizophrenia, and epilepsy. Except from alcohol abuse, the distribution volume was reduced in all cases. As a follow-up, 3-(pyridin-2-ylethynyl)-cyclohex-2-enone-*O*-(3-(2-[^{18}F]fluoroethoxy)propyl-oxime ([^{18}F]PSS232) was developed to enable prolonged study protocols. First-in-man studies showed that its brain uptake corresponds to known mGlu-5 distribution and can be quantified using a two-tissue compartment model. Because reference tissue models are available, no arterial sampling is needed, making this PET tracer very promising for clinical application (Warnock et al. 2018).

[^{18}F]FPEB was published at the same time and was synthesized by direct [^{18}F]fluorination and removal of the ylide functionality (Stephenson et al. 2015). [^{18}F]FPEB proved to be a weak P-glycoprotein substrate (Jung et al. 2019). Using this tracer, mGlu5 receptors were shown to be upregulated in PD patients compared to controls. An upregulation of mGlu5 receptors was also detected in postcentral gyrus and cerebellum of male subjects with autism. Other human studies with this tracer were related to alcohol abuse and reward (Leurquin-Sterk et al. 2018).

1.11 Vesicular Monoamine Transporter

The vesicular monoamine transporter (VMAT2) is present in monoaminergic neurons of the brain and is responsible for transporting neurotransmitters (dopamine, norepinephrine, and serotonin) into the neuron and storing them in vesicles for synaptic release. Decreases in the VMAT2 level are implicated in movement disorders, such as PD, AD, and Huntington's disease (Brooks et al. 2003). VMAT2 has been studied with PET using [^{11}C]dihydrotetrabenazine (2-hydroxy-3-isobutyl-9-[^{11}C]methoxy-10-methoxy-1,2,3,4,6,7,-hexahydro-11b*H*-benzo[α]-quinolizine) ([^{11}C]DTBZ) (Koeppe et al. 1996). Binding of DTBZ to the vesicular monoamine transporter is stereospecific. The (+)-enantiomer showed a high-affinity in vitro binding to the VMAT2 in rat striatum, whereas the (−)-enantiomer was inactive. [^{11}C]DTBZ has been applied for investigation of VMAT2 in the human brain with PET (Koeppe et al. 2008). In normal subjects and PD patients, a decrease of the distribution volume of [^{11}C]DTBZ was found in the putamen with increasing age. Parkinson patients displayed a significant reduction in distribution volume in the putamen and in the caudate nucleus. Later studies revealed a significant correlation of [^{11}C]DTBZ binding reduction with severity of the loss of motor functions. In addition, it was shown that PET with (+)[^{11}C]DTBZ can differentiate Lewy body

dementia from AD. The trend that is observed for several targets in this chapter also holds true for DTBZ, namely, that a promising ^{18}F-analog has become available: the [^{18}F]fluoropropyl derivative [^{18}F]FP-DTBZ, also called [^{18}F]AV-133 (florbenazine). Its synthesis was already published in 2010. Also for this PET tracer the (+)-enantiomer proved to be active (Naganawa et al. 2018). A human study concerning VMAT2 in LBD and AD has been published, showing lowered VMAT2 densities (Villemagne et al. 2012). In recent years several studies were conducted in PD patients, which also examined the link of PD with obstipation.

1.12 Adenosine Receptors

Adenosine is an endogenous modulator of a variety of physiological functions in the CNS. During the last two decades, the receptor subtypes A_1R and $A_{2A}R$ have been extensively studied. There is growing evidence that these adenosine receptor subtypes could be promising therapeutic targets for neurodegenerative diseases such as AD and PD and for other neurological pathologies such as epilepsy, ischemic brain disorders, or sleep disorders.

Several PET tracers for the adenosine receptor have been reported (Ishiwata et al. 2007). A_1 receptors have been studied using [1-methyl-^{11}C]-8-dicyclopropylmethyl-1-methyl-3-propylxanthine (MPDX). [^{11}C]MPDX PET studies in healthy volunteers showed the highest binding potential in striatum followed by the thalamus. Also, Logan plot analysis with arterial input was applied. The distribution pattern of [^{11}C]MPDX in the brain was different from that of blood flow as measured by [^{15}O]water (Fukumitsu et al. 2008).

For A_{2a} receptors, PET tracers for human use have also been developed. The distribution in brain of [^{11}C]KF18446 is in agreement with the distribution of $A_{2A}R$ known from postmortem studies in humans as well as in rodents and monkeys. A two-tissue, three-compartment model was used to measure the distribution of $A_{2A}R$ in the brain using metabolite-corrected arterial input function.

Furthermore, Mishina reported differences of $A_{2A}R$ and D_2R expression in the striata of drug-naive PD patients and those with dyskinesia and alterations of these receptor systems after antiparkinsonian therapy. The binding potential of striatal $A_{2A}R$ was measured using PET and [7-methyl-^{11}C]-(*E*)-8-(3,4,5-trimethoxystyryl)-1,3,7-trimethylxanthine ([^{11}C]TMSX) in drug-naive patients with PD, seven PD patients with mild dyskinesia, and six elderly control subjects (Mishina et al. 2011). The binding potential of [^{11}C]TMSX was increased in the putamen of PD patients with dyskinesia. $A_{2A}R$ were asymmetrically downregulated in the putamen in drug-naive patients with PD, and this asymmetric regulation of $A_{2A}Rs$ seems to compensate for the decrease in dopamine. Their study also showed that $A_{2A}Rs$ were increased in human putamen after antiparkinsonian therapy. [^{11}C]Preladenant was developed as a PET tracer based on the non-xanthine SCH442416 scaffold (Zhou et al. 2014). After successful evaluation in rats and primates, human studies were conducted in healthy subjects (for initial validation) and in PD patients for investigation of A_{2a} receptor occupancy by the drug

istradefylline (Ishibashi et al. 2018). Binding potentials were calculated from computed *k*-values, derived from a SRTM2 fit.

A few ^{18}F-tracers for $A_{2A}R$ have been developed, based on the non-xanthine scaffold SCH442416 (Khanapur et al. 2017). Also, [^{18}F]CPFPX was developed as a radiofluorinated xanthine for the A_1 receptor (Nabbi-Schroeter et al. 2018). All these ^{18}F-fluorinated analogs look promising. [^{18}F]CPFPX has reached the stage of human studies and was successfully employed to measure A_1 receptor occupancies in the human brain (Elmenhorst et al. 2012).

1.13 Serotonergic System

Serotonin (5-hydroxytryptamine, 5-HT) has diverse physiological roles as a neurotransmitter in the central nervous system. It is also a regulator of smooth muscle function and platelet aggregation. The brain 5-HT system has been implicated in several neuropsychiatric disorders, including major depression, anxiety, obsessive–compulsive disorder, and schizophrenia.

1.13.1 Serotonin Transporter

The transmission of serotonin is controlled in part by the serotonin transporter (SERT), which regulates the concentration of free and active 5-HT in the synaptic cleft (Jayanthi and Ramamoorthy 2005). Trans-1,2,3,5,6,10-β-Hexahydro-6-[4-([^{11}C]methylthio)phenyl[pyrrolo-[2,1-a]isoquinoline ([^{11}C]McN5652) binds selectively to the SERT, and the regional distribution of its binding in humans correlates well with the known distribution of the SERT. The drawback of [^{11}C]McN5652 is its high nonspecific binding and slow release from specific binding sites. [^{11}C]-*N*,*N*-Dimethyl-2-(2-amino-4-cyanophenylthio)benzylamine ([^{11}C]DASB) was found to be a promising tracer for SERT imaging (Houle et al. 2000). It displays nanomolar affinity for SERT and has 1000-fold greater affinity for SERT over dopamine transporter and norepinephrine transporter. Several human PET studies with [^{11}C]DASB have been performed (Turkheimer et al. 2012). The highest uptake was in the midbrain, thalamus, hypothalamus, and striatum, reaching a maximum at 30–40 min. After blocking with citalopram, an 80% reduction in specific binding of [^{11}C]DASB in SERT-rich regions was measured. The metabolism of [^{11}C]DASB was rapid, with about 50% of the intact compound remaining in plasma at 20 min after injection. No difference in regional SERT binding potential was found between depressed patients and normal subjects. However, in patients with major depression and with even more negativistic dysfunctional attitudes, a higher SERT binding potential was measured, which led to low extracellular 5-HT. It is concluded that [^{11}C]DASB is a useful tool for antidepressant development, PET studies in obsessive–compulsive disorder (Lee et al. 2018), and alcoholism.

4-[^{18}F]F-ADAM (*N*-((*E*)-4-[^{18}F]Fluorobut-2-*en*-1-yl)-2β-carbomethoxy-3β-(4′-fluoro phenyl)nortropane) turned out to be the most suitable SERT tracer out of a

series of ^{18}F-analogs. The tracer has been used in human studies. Most optimal scanning time was 120–140 min after injection. Subjects with depression had lower SERT availability than controls (Yeh et al. 2015).

1.13.2 5-HT Receptor Ligands

Effects of 5-HT are also mediated by receptors (5-HT$_1$ to 5-HT$_7$). 5-HT$_{1A}$ receptors function both as presynaptic autoreceptors in the raphe nuclei and as postsynaptic receptors in the terminal fields. The 5-HT$_{1A}$ receptor is involved in modulation of emotion and is implicated in the pathogenesis of anxiety, depression, hallucinogenic behavior, motion sickness, dementia, schizophrenia, and eating disorders. Many psychiatric drugs modulate serotonergic transmission or specifically target the 5-HT$_{1A}$ receptors. Various compounds have been developed for quantification of these receptors (Passchier and van Waarde 2001). [^{11}C]WAY100635 was developed as a highly selective, silent antagonist at both pre- and postsynaptic sites (Pike et al. 1995; Takano et al. 2011). Analogs of WAY100635 bearing bulkier cycloalkylcarbonyl groups appear to be more resistant to amide hydrolysis. However, the increased lipophilicity also reduces receptor affinity. Major problem of the WAY family is the often troublesome radiochemical synthesis. In parallel to evaluation of the WAY100635 compound, a series of arylpiperazine benzamido derivatives was synthesized that selectively bind to 5-HT$_{1A}$ receptors. Studies showed that benzoyl substituents affected the inhibition constant (K_i) of the compound. A fluoro analog, *p*-[^{18}F]MPPF, displayed a high binding affinity to 5-HT$_{1A}$ receptors (Shiue et al. 1997; Aznavour and Zimmer 2007). A large number of human studies have been performed both with [^{11}C]WAY100635 and [^{18}F]MPPF under various pathophysiological conditions. The number of PET studies with these tracers is continuously growing, and no important improvements regarding tracer development have been made.

The 5-HT$_{2A}$ receptor modulates cortical GABAergic, glutamatergic, and dopaminergic neurotransmission. An adequate balance of 5-HT$_{2A}$ receptor activity at inhibitory and excitatory neurons is needed for normal neuronal functioning. The 5-HT$_{2A}$ receptor has been implicated in various physiological functions and pathological conditions, including schizophrenia, major depression, anxiety, and sleep disorders. Various 5-HT$_{2A}$ receptor tracers have been proposed as PET radiopharmaceutical for 5-HT$_{2A}$ receptor quantification, most notably [^{11}C]*N*-methylspiperone, [^{18}F]altanserin, [^{18}F]setoperone, and [^{11}C]MDL 100,907). [^{11}C]MDL 100,907 appeared to be the most promising 5-HT$_{2A}$ tracer (Lundkvist et al. 1996) because of its high brain uptake with high target-to-nontarget contrast, prototypical 5-HT$_{2A}$ receptor selectivity, and absence of blood–brain barrier penetrating radiolabeled metabolites interfering with 5-HT$_{2A}$ receptor quantification (Talbot et al. 2012). Despite these results, [^{11}C]MDL 100,907 has become obsolete. [^{11}C]Cimbi-36, the first agonist PET tracer for 5-HT$_{2A}$ receptors, proved to be more useful for in vivo measurements of serotonin release as its binding is more sensitive to endogenous serotonin levels compared to antagonists. It should be noted that [^{11}C]Cimbi-36 is

metabolized by ^{11}C-demethylation. The small molecule radiolabeled metabolites display non-displaceable binding. [^{11}C]Cimbi-36 has been applied in human PET studies (da Cunha-Bang et al. 2019).

1.14 Nonadrenergic System

Many diseases affect the sympathetic nervous system, and imaging of pathological changes of noradrenergic neurotransmission has been an important area of PET research. Most postganglionic sympathetic neurons in the autonomic nervous system release the neurotransmitter norepinephrine (NE), which stimulates adrenergic receptors in various organs. The NET is a transmembrane protein located in the adrenergic nerve terminals that is responsible for active reuptake (uptake 1) of NE released from neurons. NE is stored in neuronal vesicles and is released upon stimulation. Brain norepinephrine transporters (NETs) are involved in various neurological and psychiatric disorders, including depression, attention deficit hyperactivity disorder, drug addiction, and eating disorders. NETs are also the site of action of many antidepressant drugs in the brain. Several radiolabeled NET inhibitors, for example, [^{11}C]desipramine, have been tested as radiopharmaceuticals for PET imaging, but they showed high nonspecific binding. Reboxetine ((*RS*)-2-[(*RS*)-2-ethoxyphenoxy)benzyl]morpholine) is a specific NET inhibitor with a high affinity and selectivity. It has been developed for the treatment of depressive illness. Among the different reboxetine derivatives that have been tested, (*S*,*S*)-methylreboxetine is considered a promising PET ligand. [^{11}C]Methylreboxetine ([^{11}C]MRB, [^{11}C]MeNER) has been tested in man for the investigation of cocaine addiction (Ding et al. 2010). The results suggest that (a) brain NET concentration declines with age in healthy controls and (b) there is a significant upregulation of NET in thalamus and dorsomedial thalamic nucleus in cocaine-addicted individuals. No new PET tracers for NETs have been developed during the last few years.

1.15 Opioid Receptors

Opioids such as morphine are commonly used analgesics in clinical practice (Waldhoer et al. 2004). Three opioid receptors that mediate opioid effects have been identified: δ (enkephalin preferring), κ (dynorphin preferring), and μ (morphine and ß-endorphin preferring). The opioid receptors play an important role in the regulation of analgesia, shock, appetite, thermoregulation, and cardiovascular, mental, and endocrine function. The μ opioid receptors are the major receptors to mediate the analgesic effects of opioids, although δ and κ receptors are also important in antinociception. Opioids have been found to protect cells in the heart and brain from ischemic injury via the δ receptors. On the other hand, κ antagonists prevent neurodegeneration. The κ opioid receptors have been implicated in several brain disorders, including drug abuse, epilepsy, Tourette's syndrome, and AD. Diprenorphine is a highly potent and non-subtype-selective opioid receptor antagonist with

subnanomolar affinity (Koepp and Duncan 2000). Diprenorphine has been labeled as [6-*O-methyl-11C*]diprenorphine ([^{11}C]DPN). PET studies have been reported in human brain using high and low specific activity [^{11}C]DPN. After pretreatment with 1 mg/kg naloxone, the uptake of [^{11}C]DPN was reduced to background levels throughout the brain. [^{11}C]DPN PET has been applied to study endogenous opiate response to pain in patients with rheumatoid arthritis. There were significant increases in [^{11}C]DPN binding in association with a reduction in pain in most areas of the brain. Also, decreases in [^{11}C]DPN binding in various cortical areas and the thalamus in patients with poststroke pain were found. These findings suggest that there are substantial increases in opioid receptor occupancy by endogenous opioid peptides during pain.

Research on κ opioid receptors has shifted to the use of agonist tracers and ^{18}F-analogs of antagonists (Li et al. 2018). [^{11}C]LY2795050 has been applied as a promising tracer for κ opioid receptor imaging and has been tested in human studies (test-retest reproducibility, blocking with LY2456302, receptor occupancy studies) (Naganawa et al. 2016).

[^{11}C]carfentanil is the tracer of choice for μ opioid receptors at this moment. Its first application goes back to the 1980s. The tracer is mainly taken up in cortical regions and thalamus. Bound [^{11}C]carfentanil can be displaced by other antagonists; thus the tracer can be used to determine μ opioid receptor occupancy and availability. Also studies related to addiction and reward were successful (Nummenmaa et al. 2018). As carfentanil is a very potent drug, the administered dose should be kept very low (<1 μg), in order to avoid any pharmacological effect. For human PET studies, [^{11}C]carfentanil should be prepared with ultrahigh specific radioactivity.

1.16 Monoamine Oxidase

Monoamine oxidase (MAO) is a mitochondrial enzyme which inactivates dopamine, noradrenaline, and serotonin in the brain. Two isoforms (A and B) of the enzyme have been identified. MAO-A preferentially oxidizes serotonin and noradrenaline, whereas MAO-B preferentially oxidizes phenethylamine. MAO-B is highly abundant in astrocytes. Astrocyte activity and thus the activity of MAO-B are upregulated in neuroinflammatory and neurodegenerative processes including PD and AD. Dopamine is a substrate for both enzymes. MAO-A is mainly involved in depression and anxiety, whereas MAO-B is involved in neurodegenerative diseases.

To measure MAO-A activity, the MAO-A inhibitor [^{11}C]harmine was developed for PET studies of MAO-A distribution and concentration in the brain of patients with psychiatric and neurological disorders or with neuroendocrine tumors. It was shown that tumors in patients with midgut carcinoids and endocrine pancreatic tumors could be visualized with [^{11}C]harmine (Sacher et al. 2012). [^{11}C]-L-deprenyl, an irreversible inhibitor, has been developed for measurement of MAO-B activity (Fowler et al. 1987). It was found that [^{11}C]-L-deprenyl uptake was increased in hippocampus, temporal lobes, and white matter of AD patients. The same has been found in patients with amyotrophic lateral sclerosis (ALS). This increased uptake

has been ascribed to an increased presence of activated astrocytes. Astrocytosis measured with deuterated [^{11}C]-L-deprenyl in MCI patients can be considered as an early phenomenon of AD (Carter et al. 2012). A carbamate-based reversible MAO-B inhibitor, [^{11}C]SL251188, was synthesized by ^{11}C-carbonylation and showed favorable results in nonhuman primates. First-in-man studies have been performed in controls and patients with depression. Preclinical studies on ^{18}F-fluorinated deprenyl analogs are also underway, but these compounds are degraded to brain-penetrating radioactive metabolites, as is [^{11}C]-L-deprenyl (Nag et al. 2016).

1.17 SV2A Receptors

In recent years, the synaptic vesicle glycoprotein 2A (SV2A) has been proposed as indicator for the disruption and alteration of synapses, which is associated with several brain diseases. The SV2A protein plays an important role in proper functioning of the nervous system. A few PET tracers developed by UCB S.A. were used in human studies: [^{11}C]UCB-J and [^{18}F]UCB-H. Both compounds are very similar but have either a [^{18}F]fluoro or a [^{11}C]methyl substituent on the pyridine ring. These compounds bind with nanomolar affinity to the SV2A protein. The biodistribution of the UCB-based PET tracers is uniform throughout the healthy brain. In 2015, a first-in-man study with [^{18}F]UCB-H was published, and its biodistribution and radiation dosimetry were determined (Bretin et al. 2015). Slightly later, also [^{11}C]UCB-J was tested in humans. A comparative study showed that [^{11}C]UCB-J has a higher binding potential than [^{18}F]UCB-H (Mercier et al. 2017). Finally [^{18}F]UCB-J, having the same methyl group but a ^{18}F substitution on the trifluorophenyl ring, showed the same excellent imaging properties than [^{11}C]UCB-J and could benefit from the longer half-life and lower positron energy of ^{18}F. For both [^{11}C] and [^{18}F]UCB-J, there are still some radiochemical challenges: the reliability and yield of the synthesis should be increased. One study was published in which 10 AD patients and 11 healthy controls were compared. Hippocampal SV2A binding was significantly reduced in the AD brain (Chen et al. 2018).

1.18 Sigma Receptors

Sigma receptors are categorized in the sigma-1 and sigma-2 subtypes. Sigma-1 receptors are abundantly expressed in the brain. These receptors are located in the cell membrane and the mitochondria-associated membrane of the endoplasmic reticulum of neurons, where they are playing a role in regulation of ion channels and neurotransmitter receptors. Therefore sigma-1 receptors are recognized as potentially interesting targets for imaging and therapy in brain disorders. One of the first sigma-1 PET tracers was [^{11}C]SA4503, which could be easily prepared by ^{11}C-methylation. [^{11}C]SA4503 showed a decreased uptake in frontal, temporal, and occipital lobes, cerebellum, and thalamus of patients with early AD (Mishina et al. 2008). The tracer has also been applied in PET studies to determine the receptor

occupancy of atypical antipsychotics. More recently, (*S*)-[^{18}F]fluspidine has been investigated for imaging of sigma-1 receptors in humans (Ludwig et al. 2019). Its radiosynthesis proceeds through a one-step ^{18}F-fluorination, in high radiochemical yields. This PET tracer displayed <5% plasma metabolites in healthy volunteers. Application of (*S*)-[^{18}F]fluspidine in patients with CNS disorders is still pending.

1.19 Tau Protein Deposition

Tau proteins stabilize microtubuli which play a fundamental role in neuronal activity. Similar to deposition of beta-amyloid, deposition of tau protein in the form of neurofibrillary tangles is also associated with neurodegeneration and cognitive impairment. These tangles already form before disease becomes manifest. Tau protein can aggregate in different ways, which affects the selectivity of PET tracers. Six isoforms of tau occur, with either three (3*R*) or four repeats (4*R*) of the microtubules. Different isoforms can cause the same tauopathy. Besides accumulation of tau protein in AD brain and dementia variants, this accumulation is also observed in other tauopathies including Pick's disease, PSP, and chronic traumatic encephalopathy. Several PET tracers have been developed for tau imaging. As both tau aggregates and beta-amyloid contain beta sheets, it has been challenging to develop selective PET tracers. Furthermore densities for tau aggregates are up to ten times lower than for beta-amyloid. The so-called first-generation tau tracer [^{18}F]AV-1451 (T807; flortaucipir) shows about 25-fold affinity for tau over beta-amyloid and is very specific and sensitive for the AD type of tau protein (Saint-Aubert et al. 2017). This tracer is currently in use at many PET sites because of its favorable kinetics and uptake pattern, which has been confirmed by Braak staining. [^{18}F]AV-1451 mainly binds to paired helical filaments (PHF)-tau which are characteristic lesions in AD brain. The ultimate value in clinical decision-making using [^{18}F]AV-1451 is still not clear, more research is needed to validate [^{18}F]AV-1451 (Wang and Edison 2019).

Second-generation PET tau tracers have been developed aiming at a more accurate staging of AD, less non-specific binding, and improvement of binding selectivity. The chemical structures are based on the same scaffolds as the first-generation tracers, therefore their binding sites are similar, but they display less non-specific binding. This generation includes [^{18}F]MK-6240, APN-1607([^{18}F]PM-PBB3), [^{18}F]GTP1, and [^{18}F]PI-2620. These tracers have been used in human PET studies comparing healthy subjects with AD patients. Different PET tracers have affinity for specific types of tau proteins. Binding differences between tau tracers could thus be used for the differential diagnosis of tauopathies.

1.20 Phosphodiesterase

Phosphodiesterase 10A is an enzyme responsible for the breakdown of cAMP and cGMP, which are important second messengers involved in the regulation of cellular functions through effectors. PDE10A affects the signaling of G-coupled

receptors, such as dopamine receptors, besides many other physiological processes. Within the brain, PDE10A is mainly localized in striatum. PDE10A inhibitors were developed as potential therapeutic agents in neurodegenerative diseases. Based on these inhibitors, several tracers were prepared to study PDE10A with PET. Some of these have reached the stage of human PET studies and were used to quantify PDE10A in healthy subjects and in different patient populations. Data acquired in healthy volunteers suggest that [^{11}C]IMA107, [^{11}C]Lu AE92686, and [^{18}F]MNI589 are the most promising tracers for PDE10A, with the lowest nonspecific binding. Based on the application and logistics of the scan, one might either prefer an ^{11}C- or a ^{18}F-tracer. The tracers showed a loss of PDE10A activity in the caudate and putamen of patients with PD or schizophrenia (Boscutti et al. 2019).

PDE4 is another isozyme involved in the breakdown of cAMP and implied in similar pathology as PDE10A. However, PDE4 is expressed in other parts of the brain, such as cortical regions related to working memory. For imaging of PDE4 with PET, (*R*)-[^{11}C]rolipram is the only radiotracer that has been used in human studies. Originally the tracer was developed for cardiac studies, but more recently it has also been applied for the brain. In a study where subjects received SSRI medication and were scanned with [^{11}C]rolipram, it was found that PDE4 inhibitors have antidepressant effects (Fujita et al. 2017). In another PET study, loss of PDE4 in cortical areas was found in PD patients (Niccolini et al. 2017).

1.21 P2X7 Receptor

The purinergic P2X7 receptor is an ion channel which is mainly present on activated microglia and therefore an important target in neurodegeneration and neuroinflammation, like TSPO. Stimulation of these receptors results in release of proinflammatory cytokines. Several preclinical experiments have demonstrated the role of P2X7 receptors in amyloid plaque formation, cognition, neuron loss, and motor coordination. Antagonism of P2X7 is in many cases neuroprotective. PET imaging of P2X7 receptors can be of great value to obtain more knowledge on neurodegeneration and to monitor treatment.

[^{11}C]JNJ54173717 is a tracer showing nanomolar affinity for human P2X7 (K_d 1.6 nM), good brain penetration, and low nonspecific binding in rats and primates. The tracer has recently been applied to quantify P2X7 receptors in humans (Van Weehaeghe et al. 2019). Distribution volumes show little variation in most cortical regions and are higher in brainstem and striatum. No differences were found between uptake in healthy controls and patients with PD. [^{18}F]JNJ64413739 has a structure related to [^{11}C]JNJ54173717 but has a longer radioactive half-life and has been investigated in healthy subjects (Koole et al. 2019). Future work should prove the value of this tracer in PET studies on P2X7 receptors.

1.22 (Re)Myelination

Demyelination is a major hallmark of multiple sclerosis (MS). Neuroinflammation results in the formation of demyelinated lesions. In the pathogenesis of MS, failure of compensatory mechanisms such as remyelination results in disability. Remyelination seems to be a dynamic phenomenon in MS, which is not well understood and is evident in white matter lesions. Some drugs have a positive impact on remyelination. The development of remyelination strategies may be boosted by PET with appropriate tracers to quantitatively assess remyelination. Beta amyloid tracers have been tried for this purpose but are not sufficiently selective. [^{11}C]MeDAS, a stilbene derivative, showed favorable binding characteristics for PET imaging of myelin. Its binding was limited to white matter regions, and [^{11}C]MeDAS showed high sensitivity and specificity for myelin in animal models (de Paula Faria et al. 2014). The clinical value of [^{11}C]MeDAS needs to be determined.

1.23 Cannabinoid Receptors

Cannabinoid (CB) receptors are G-protein-coupled receptor proteins. There are two subtypes CB1 and CB2. CB2 has mostly been studied with PET as this subtype is involved in neuroinflammatory processes and activated microglia. It has been demonstrated that CB2 is strongly overexpressed during neuroinflammation. The most promising tracer for CB receptors that has been developed thus far is [^{11}C]NE40. This tracer has been applied in humans, and its biodistribution in AD patients and healthy control subjects was compared (Ahmad et al. 2016). Full kinetic modeling was performed. Surprisingly, the binding of [^{11}C]NE40 was significantly lower in AD patients than in controls. The authors suggest that [^{11}C]NE40 may have a higher affinity/selectivity for CB1 than for CB2 receptors.

1.24 Conclusions

For a variety of neurotransmitter systems and transporters, useful PET and SPECT tracers are currently available that can be applied to study neurologic and psychiatric diseases in man. These tracers have proven to be able to image the molecular target of interest. Some of them are labeled with ^{18}F and commercially available. Increased availability of PET tracers will stimulate multicenter studies that may demonstrate their value for clinical diagnosis and treatment evaluation. Since most physiological processes interact, studies combining two or more CNS tracers will become more common. Several examples of such studies have already been published in the literature. Clinical applications of PET will be highlighted in more detail in other chapters of this book.

Recent review papers have summarized the current status of tracers for neurodegenerative diseases (Tiepolt et al. 2019; Narayanaswami et al. 2018; Bauckneht

Table 1.2 Overview of targets that are under investigation with respect to the development of nuclear medicine tracers

Target	Related disease	Tracers (preclinical application)	Binding mechanism
Alpha-synuclein	AD, PD	No suitable tracers	Staining agent
D_3 receptor	Psychosis, neurodegeneration	Mixed D_2/D_3 tracers	Antagonists
ROS	Neuroinflammation	[^{11}C]hydromethidine	Trapping by oxidation
Sphingosine 1-phophate receptor	MS	[^{11}C]TZ3321	CNS homeostasis
Toll-like receptor	Neuroinflammation	No tracers available	Antagonists
Receptor for advanced glycation end products (RAGE)	AD	[^{18}F]RAGER	Beta-amyloid transport
NLRP3	AD	No tracers available	Antagonist
COX-1 COX-2	Neuroinflammation Neuroinflammation	[^{18}F]PS2 [^{11}C]MC1	Enzyme inhibitor Enzyme inhibitor

et al. 2019). Besides the processes mentioned in Sects. 1.2–1.23, several other targets in the brain may need to be investigated to gain understanding of the pathophysiology of neurologic and psychiatric diseases. Table 1.2 summarizes some of these targets. Several new tracers are in the preclinical stage of development. For the sake of clarity, only a few tracers are listed in the table.

In conclusion, several tracers have been validated and can be applied in patient studies in order to measure physiological processes quantitatively. Several new targets have also been discovered, and tracers for these targets are under development. This demonstrates the huge interest in clinically validated tracers for PET imaging.

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