Chapter

Positron Emission Tomography in the Neuroimaging of Autism Spectrum Disorder

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Abstract

Autism spectrum disorder (ASD) is a pervasive developmental disease characterized by persistent impairment, repetitive and stereotypical behaviors in social interaction, as well as restricted interests and activities. The etiology of ASD is not clear yet, which results in difficulties in clinical diagnosis and treatment, and also brings heavy burden to patients and society. Positron emission tomography (PET) is a frequently used molecular imaging technology in quantitative, dynamic and in vivo research for therapeutic efficacy evaluation, pathophysiological mechanism investigation, thereby promoting development of ASD therapeutic drugs. More and more imaging studies have been reported on ASD recently, and the physiological changes featured by PET have been disclosed. This chapter reviews the specific radioligands for PET imaging of critical biomarkers involved in ASD. Herein, we discuss cerebral blood perfusion, cerebral glucose metabolism, and neurotransmitter system (transporters, precursors and receptors), as well as some other novel targets, including arginine vasopressin receptor targets and neuroinflammation related targets. The status of application and future prospect of the PET technology in research of ASD were discussed. This chapter provides a detailed and comprehensive literature review on ASD PET probe development, thereby can help readers intuitively and conveniently understand the status quo of research on ASD PET, and develop new research directions in this field.

Keywords: autism spectrum disorder, ASD, neuroimaging, positron emission tomography, PET, radioligands

1. Introduction

Autism spectrum disorder (ASD) is a pervasive developmental disorder characterized by persistently impaired interpersonal communication and social interactions, significantly limited activities and interests, as well as repetitive, stereotyped and limited behaviors. The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) published in 2013 revolutionized the ASD diagnostic criteria [1], and identified four previously defined pervasive developmental disorders that are now referred to as ASD: pervasive developmental disorder not otherwise specified (PDD-NOS), autistic disorder, childhood disintegrative

syndrome (also known as Heller Syndrome), and asperger syndrome (AS). The diagnostic criteria were reduced to two items: social dysfunction, and stereotypical and repetitive behavior. The previous diagnostic criteria including and non-verbal and verbal communication disorders are ascribed to social disorders. These changes have impacted the diagnosis and therapy of a variety of pervasive developmental disorder subtypes, and influenced the comparability and consistency of imaging studies. Each document cited will be marked with "ASD/AS/AutismPDD" according to diagnostic criteria to avoid unnecessary confusion.

The understanding of etiology of idiopathic ASD is still not sufficient, and the current evidence indicates that ASD might be driven by affected synaptic function, cortical networks as well as brain maturations induced by environmental and genetic factor interactions. Obstetric complications and early childhood environmental influences may play critical roles in ASD development [2, 3]. Moreover, children who experience obstetric complications are also more likely to exhibit genetic causation of the disease [4]. The latest large gene study has identified 102 risk genes associated with ASD in human [5]. Most risk genes are closely correlated with neurodevelopment and neurophysiology and are expressed in early stage of brain development, especially in inhibitory and excitatory neurons, consistent with ASD-associated excitation/inhibition imbalances.

Currently, ASD diagnosis is mainly based on clinical evaluation and medical history of patients as well as medical history of patients' families. Autism Diagnostic Interview Revised (ADI-R), a structured interview for patients' family members [6], and the Autism Diagnostic Observation Schedule (ADOS), a play-based interview for children and their families or high-functioning children, adolescents, or adults [7] are two collection tools for medical history data, which are considered gold standard for clinical ASD diagnosis. ASD patients' clinical evaluation mainly includes neurological and physical examinations [8], as well as neuroimaging. Though no specific biomarkers can be used for ASD diagnose thus far, neuroimaging techniques have exhibited potentials for explaining signs and symptoms in ASD [9], and have been applied in elucidation of pathophysiologic mechanisms underlying ASD-related abnormalities in neurotransmitter system, blood perfusion, and brain glucose metabolism in the past decades. Therefore, neuroimaging techniques will act as important tools in ASD diagnosis, therapeutics and efficacy evaluation.

2. Positron emission tomography

Positron emission tomography (PET) detects processes associated with the metabolism and distribution of positron emitting radionuclide-labeled probes *in vivo*. The commonly used radionuclides include ^{11}C ($T_{1/2}$ ~ 20.4 min), ^{18}F ($T_{1/2}$ ~ 109.8 min), ^{13}N ($T_{1/2}$ ~ 10.0 min) and ^{15}O ($T_{1/2}$ ~ 2.0 min). It should be noted that radionuclides with short half-lives, such as ^{11}C ($T_{1/2}$ ~ 20.4 min) and ^{15}O ($T_{1/2}$ ~ 2.0 min), can only be used with onsite cyclotrons at tertiary medical centers. With the probe distribution in the body, nuclear decay occurs, emitting positrons, which collide with electrons surrounding to generate two gamma photons (511 keV each) in a 180° reverse manner. The gamma photon signals detected are then processed by computer software to generate three-dimensional images [10]. Compared to magnetic resonance imaging (MRI) and single photon emission computed tomography (SPECT), PET has significant advantages in spatial resolution, sensitivity, and time efficiency, and therefore is much more advantageous quantification of

substantial parameters including protein synthesis rate, enzyme activity and receptor density, glucose metabolic rate, and gene expression..

Based on radioactive probe, PET imaging technology has dramatic advantages in detection a variety of receptors, transporters, metabolites, enzymes, as well as drugs. With microdose, PET tracers can be applied in preclinical and early clinical studies to investigate in vivo drug physiological performance, pharmacodynamics and pharmacokinetics, target occupancy, providing critical information for clinical trials [11]. PET probe can be used for both clinical diagnose and evaluation. More than 1000 PET probes have been developed and applied in numerous fields including labeling of metabolic analogs or substrates including fatty acids, amino acids, and glucose, the [12], labeling specific proteins, such as transporters or receptors [13, 14], as well as labeling in signal transduction, immunological features, hypoxia, angiogenesis, apoptosis and genes [15, 16]. PET probes as effective neuroimaging tools have high binding specificity and affinity, good brain penetration ability, and a good distribution volume and metabolic stability. **Table 1** lists the main ASD research targets and the corresponding PET probes.

3. PET molecular imaging in ASD

The development of PET has provided noninvasive and dynamic technical support for the study of ASD *in vivo* [17]. Though the pathology and etiology of ASD remain unclear, during the past decades, PET has been widely applied in many fields of ASD research, and substantial valuable information and evidence has been obtained [18–26].

The neuroimaging studies on ASD have been reviewed in several articles with different focuses [25–28]. Some focused on the state of ASD imaging research [26, 27]. Others focused on the application of specific neuroimaging techniques [28]. With the development of ASD PET probes, the newly research results need to be updated. In this review, we discuss neurotransmitter system (receptors, precursors, and transporters), cerebral blood perfusion, cerebral glucose metabolism, as well as some new research targets including arginine vasopressin receptor targets and neuroinflammation related targets. The current application and future prospect of PET technology in ASD research were discussed through summarizing both clear ASD pathophysiological mechanism and unclear research conclusions. This review provides a detailed comprehensive literature review on ASD PET probe development, thereby can help readers intuitively and conveniently understand the status quo of research on ASD PET more, and develop new research directions in this field.

3.1 Cerebral glucose metabolism

Glucose is the main energy source of brain cells, therefore, glucose metabolism can reflect brain function changes. [^{18}F]fluorodeoxyglucose ([^{18}F]FDG) is glucose analog, and can be taken up by brain cells, however, [^{18}F]FDG cannot be used in glycolysis due to the absence of oxygen at site 2, therefore, [^{18}F]FDG can be used to reflect glucose uptake and distribution in brain cells [29]. [^{18}F]FDG is therefore very valuable in ASD PET research due to its excellent imaging characteristics, including a long half-life, short scanning time, mature preparation process, and relatively simple scanning process [25].

Brain glucose metabolism has been most frequently studied in ASD PET. Most studies have focused on changes in brain glucose metabolism in ASD patients. However, no consistent conclusion has been drawn FDG metabolism changes in ASD

Target	PET probe	Chemical formula	Clinical application
Glucose	[^{18}F]FDG	$C_6H_{11}{}^{18}FO_5$	Y
CBF	[^{15}O]H2O	$H_2{}^{15}O$	Y
	[^{15}O]CO2	$CO^{15}O$	Y
	[^{11}C]butanol	$C_2{}^{11}CH_8O$	Y
5-HT precursor	[^{11}C]AMT	$C_{11}{}^{11}CH_{14}N_2O_2$	Y
5-HTT	[^{11}C](+)McN5652	$C_{18}{}^{11}CH_{21}NS$	Y
	[^{11}C]DASB	$C_{15}{}^{11}CH_{17}N_3S$	Y
	[^{11}C]MADAM	$C_{15}{}^{11}CH_{20}N_2S$	Y
	[^{18}F]FMeNER-d2	$C_{18}H_{18}D_2{}^{18}FNO_3$	Y
	[^{11}C]ADAM	$C_{14}{}^{11}CH_{17}IN_2S$	N
	[^{11}C]DAPA	$C_{14}{}^{11}CH_{17}BrN_2S$	N
	[^{11}C]AFM	$C_{15}{}^{11}CH_{19}FN_2S$	N
5-HT$_{2A}$R	[^{18}F]setoperone	$C_{21}H_{24}{}^{18}FN_3O_2S$	Y
	[^{11}C]MDL100907	$C_{22}H_{18}{}^{18}FNO_3$	Y
	[^{18}F]altanserin	$C_{22}H_{22}{}^{18}FN_3O_2S$	N
5-HT$_{1A}$R	[^{18}F]MPPF	$C_{25}H_{27}{}^{18}FN_4O_2$	Y
	[^{18}F]F13714	$C_{21}H_{25}ClF^{18}FN_4O$	N
OXT OXTR	[^{11}C]PF-3274167	$C_{18}{}^{11}CH_{19}ClFN_5O_3$	N
	[^{11}C]EMPA	$C_{22}{}^{11}CH_{26}N_4O_4S$	N
DA precursor	[^{18}F]FDOPA	$C_9H_{10}{}^{18}FNO_4$	Y
DAT	[^{11}C]WIN35,428	$C_{15}{}^{11}CH_{20}FNO^2$	Y
	[^{11}C]methylphenidate [^{11}C]cocaine	$C_{14}H_{19}NO_2$ $C_{17}H_{21}NO_4$	N N
	[^{18}F]FE-PE2I	$C_{20}H_{25}{}^{18}FINO_2$	N
D_2R	[^{11}C]NMS	$C_{23}{}^{11}CH_{28}FN_3O_2$	Y
	[^{11}C]raclopride	$C_{14}{}^{11}CH_{20}Cl_2N_2O_3$	Y
D_2R、D_3R	[^{18}F]fallypride	$C_{20}H_{29}{}^{18}FN_2O_3$	N
	[^{11}C]-(+)-PHNO	$C_{14}{}^{11}CH_{21}NO_2$	N
D_1R	[^{11}C]NNC112	$C_{18}{}^{11}CH_{18}ClNO_2$	N
	[^{11}C]SCH23390	$C_{16}{}^{11}CH_{18}ClNO$	Y
GABA GABA$_B$R	[^{18}F]1b	$C_{16}H_{16}Cl^{18}FN_2O_3$	N
GABA$_A$R	[^{18}F]FMZ	$C_{15}H_{14}{}^{18}FN_3O_3$	Y
	[^{11}C]Ro15–4513	$C_{14}{}^{11}CH_{14}N_6O_3$	Y
AChE receptor	[^{18}F]FA	$C_9H_{11}{}^{18}FN_2O$	N
precursor	[^{11}C]MP4A	$C_7{}^{11}CH_{15}NO_2$	Y
Leucine	[^{11}C]leucine	$C_5{}^{11}CH_{13}NO_2$	Y

Target	PET probe	Chemical formula	Clinical application
Glutamate			
mGLuR5	[^{18}F]FPEB	$C_{14}H_7{}^{18}FN_2$	Y
	[^{11}C]ABP-688	$C_{14}{}^{11}CH_{16}N_2O$	N
mGLuR1	[^{11}C]ITMM	$C_{18}{}^{11}CH_{18}N_5O_2S$	N
mGLuR7	[^{11}C]MMPIP	$C_{18}{}^{11}CH_{15}N_3O_3$	N
TSPO	[^{11}C]PK11195	$C_{20}{}^{11}CH_{21}ClN_2O$	Y
	[^{11}C]DPA713	$C_{20}{}^{11}CH_{28}N_4O_2$	N
	[^{18}F]FEPPA	$C_{22}H_{21}{}^{18}FN_2O_3$	N
	[^{11}C]PBR28	$C_{20}{}^{11}CH_{20}N_2O_3$	Y
	[^{11}C]ER176	$C_{19}{}^{11}CH_{20}ClN_3O$	N
	[^{18}F]GE180	$C_{20}H_{27}{}^{18}FN_2O_2$	N
	[^{18}F]FEPPA	$C_{22}H_{21}{}^{18}FN_2O_3$	N
P2X7R	[^{11}C]A-740003	$C_{25}{}^{11}CH_{30}N_6O_3$	N
	[^{11}C]JNJ-717	$C_{18}{}^{11}CH_{17}Cl_2N_5O_2$	N
	[^{18}F]JNJ64413739	$C_{18}H_{14}F_3{}^{18}FN_6O$	N
	[^{11}C]SMW139	$C_{18}{}^{11}CH_{21}ClF_3NO_2$	N
MAO-B	[^{11}C]SL25.1188	$C_{15}{}^{11}CH_{17}F_3N_2O_5$	N
COX-1	[^{11}C]PS13	$C_{17}{}^{11}CH_{16}F_3N_3O_3$	N
COX-2	[^{11}C]MC1	$C_{16}{}^{11}CH_{17}N_3O_3S_2$	N
CSF1R	[^{11}C]CPPC	$C_{21}{}^{11}CH_{27}N_5O_2$	N
AVP	[^{18}F]SRX246	$C_{42}H_{48}{}^{18}FN_5O_5$	N
V1aR	[^{11}C]SRX246	$C_{42}{}^{11}CH_{51}N_5O_5$	N
	[^{11}C](1S,5R)-1	$C_{25}{}^{11}CH_{30}N_2O_2$	N
	[^{11}C]PF-184563	$C_{20}{}^{11}CH_{23}ClN_6$	N

Abbreviations: Application, Whether applied in ASD research; CBF, Cerebral Blood Flow; 5-HT, 5-Hydroxytryptamine/Serotonin, 5-HT; 5-HTT, 5-Hydroxytryptamine Transporter/Serotonin Transporter; 5-HT$_{2A}$R, Serotonin 2A Receptor; 5-HT$_{1A}$R, Serotonin 1A Receptor; OXT, Oxytocin; OXTR, Oxytocin Receptor; DA, Dopamine; DAT, Dopamine Transporter; D$_1$R, Dopamine D1 Receptor; D$_2$R, Dopamine D$_2$ Receptor; D$_3$R, Dopamine D$_3$ Receptor; GABA, γ-Aminobutyric Acid; GABA$_A$R, γ-Aminobutyric Acid Type A Receptor; GABA$_B$R, γ-Aminobutyric Acid Type B Receptor; AChE, Acetylcholinesterase; mGLuR1, metabotropic Glutamate Receptor 1; mGLuR5, metabotropic Glutamate Receptor 5; mGLuR7, metabotropic Glutamate Receptor 7; TSPO, 18 kDa Translocator Protein; P2X7R, Purinergic P2X7 Receptor; MAO-B, monoamine oxidase B; COX-1, Cyclooxygenase 1; COX-2, Cyclooxygenase 2; CSF1R, Colony Stimulating Factor 1 Receptor; AVP, Arginine Vasopressin; V1Ar, Vasopressin 1a Receptor; Y, Yes; N, No.

Table 1.
Summary of ASD research targets and their corresponding PET probes.

patients. As early as 1985, Rumsey et al., performed a brain [^{18}F]FDG PET study and found that the cerebral glucose metabolism in ASD patients was more diffuse compared with that in controls [30]. However, most of the following [^{18}F]FDG PET studies found a reduced brain glucose metabolism in ASD patients than controls except for specific brain regions [31–38]. Chugani et al. observed reduced glucose metabolism in cerebellum, frontal cortex, anterior cingulate gyrus, right temporal cortex, and bilateral medial temporal regions in four autistic children with wine spotting [39]. The glucose metabolism asymmetry in frontal temporal lobe was different from the symptom in typical autism children. More studies showed that ASD patients

exhibited either increased or decreased glucose metabolism in different regions of brain [40–45]. In addition, earlier studies also reported no significant difference in cerebral glucose metabolism between the autism and control subjects [46–48]. No consensus has been drawn on glucose metabolism change in different specific brain regions in ASD patients, however, some common findings included decreased glucose metabolism in temporal lobe as well as abnormal glucose metabolism in the highly connected areas including the adjacent limbic cortex, parietal lobe, and frontal lobe, which is consistent with the anatomical connectivity between the associative and supratemporal cortexes [49–51] and is supported by findings on the brain functional network for glucose metabolism [52–54].

[^{18}F] FDG PET is applied in both study of glucose metabolism changes in specific brain regions of ASD patients and ASD treatment evaluation via neuroimaging. An [^{18}F]FDG PET study performed on fluoxetine treated ASD patients found that the glucose metabolic rate in the right frontal lobe, especially in the orbitofrontal cortex and anterior cingulate gyrus, was remarkably increased after treatment. Moreover, they found the patients with higher glucose metabolic rates in the anterior cingulate and medial frontal lobe before treatment exhibited a more significant response to fluoxetine, indicating that response to fluoxetine is closely correlated with baseline cingulate metabolism [55]. However, the cerebral glucose metabolism in ASD patients after treatment does not consistently exhibit an increasing glucose metabolism. Another [^{18}F]FDG PET study conducted on a 14 years old ASD patient showed that after two years of treatment with nucleus accumbens (NAc) deep brain stimulation (DBS), the patient's clinical symptoms were significantly improved with brain [^{18}F] FDG PET results showing that the glucose metabolism in the occipital, frontal, and prefrontal cortexes was dramatically reduced after treatment [56]. Another [^{18}F] FDG PET study was conducted on a 6 years old ASD patient to assess the efficacy of ketogenic diet (KD) treatment, a commonly used therapy for refractory epilepsy. Glucose metabolism bilateral local reduction was observed in the cerebellum, proximal meso-temporal lobe, and basal ganglia region in patient, and after a 12-month KD treatment, glucose metabolism was markedly decreased throughout the entire cerebral cortex [57], with the main brain cell energy changing from glucose to ketone bodies as the underlying mechanism [58, 59]. The findings taken together suggest that ASD therapy can alter the cerebral glucose metabolism state and improve patients' clinical symptoms. The [^{18}F]FDG PET application in glucose metabolism assessment can help screen subjects for further efficient clinical therapy, as well as evaluate treatment efficacy. It is worth noting that the effects of ASD therapeutic drugs targeting dopamine, 5-hydroxytryptamine, gamma-aminobutyric acid, as well as other neurotransmitter systems on brain glucose metabolism need further study.

3.2 Cerebral blood flow

The [^{15}O]CO_2 steady-state inhalation technique has been widely used in the early stages of PET imaging to study cerebral perfusion, but its reliability is insufficient. Imaging with probes that have a small relative molecular weight and are uncharged and fat-soluble (mainly [^{15}O]H_2O) are now more preferable. These probes can go through the blood–brain barrier, so the probe amount in brain cells is positively related to regional cerebral blood flow (rCBF), which is directly correlated with local brain function. Therefore, cerebral perfusion imaging can reflect the local brain function to a certain extent. To calculate rCBF, the dynamic intracranial distribution of probe in human body is recorded, and blood samples are collected continuously

to assess the input function of carotid artery. With image processing, the radiation concentration-time curves are obtained for calculation of the rCBF values for different brain regions [60].

In early experiments, cerebral perfusion imaging was performed on 6 ASD patients and 8 normal controls after nasal inhalation of $[^{15}O]CO_2$ and no difference in rCBF was found [47]. These negative results may be due to the influence of $[^{15}O]CO_2$ absorption on cerebral perfusion imaging quality or limitations of early low-resolution PET cameras. High-resolution PET combined with statistical parameter mapping was able to find some local abnormalities that the low-resolution PET failed to detect [61]. In subsequent experiments, $[^{15}O]H_2O$ was administrated to ASD patients via intravenous injection for cerebral perfusion imaging. The cerebral perfusion imaging was performed with patients carrying out various tasks or social functions such as listening, speaking, thinking, emotional processing, etc., and based on the voxel statistical parameters, the image data analysis was performed to compare perfusion in distinct brain regions between ASD patients and controls [62–64]. The different activation regions for different tasks shown by cerebral perfusion imaging were correlated with behavioral function control areas in brain. Due to the influence of factors, such as IQ and age on ASD patients' ability to perform tasks, the results from different studies were not comparable. However, continuous studies revealed general rules for rCBF and brain function changes in ASD patients. When $[^{15}O]H_2O$ PET was used to study the differences in rCBF in four ASD patients and five controls during a verbal task [63], it was found that the left frontal region 46 and right dentate nucleus were activated more during motor speech function while less during hearing, speech, and expressive language in ASD patients compared with controls. During speech expression, the thalamus exhibited similar intergroup differences with those in region 46. In 1999, $[^{15}O]H_2O$ PET was used to explore differences in rCBF between five highly functioning adult ASD patients and five typical developing controls during a verbal task [65]. The results showed that the patients' hearing was closely related to left hemisphere dominance reversal, and cerebellar and bilateral superior temporal gyrus rCBF decreased in ASD patients, indicative of reduced involvement of cerebellar in language expression and non-verbal auditory perception. These results are consistent with a previous report that dentate-thalamo-cortical pathway was affected by dys-serotonin synthesis in ASD boy patients, indicating the dentate-thalamo-cortical pathway atypical functional specialization, in line with brain regional-specific biochemical disorder in autism development. [66]. Three studies using $[^{15}O]H_2O$ to explore changes of rCBF in ASD patients during a language task observed decreased rCBF in the left temporal lobe area of patients' brain and the resulted abnormal function of the temporal lobe, consistent with the glucose metabolism pattern changes in brains of ASD patients [61, 67, 68].

For task-state cerebral perfusion imaging, functional magnetic resonance such as arterial spin labeling (ASL) sequence has unique advantages [69]. Comparative studies or joint imaging with PET and fMRI will have a wider application in the future.

3.3 5-hydroxytryptamine system

5-hydroxytryptamine (5-HT)/serotonin, is a well-known inhibitory neurotransmitter, which regulates synaptogenesis and neuronal migration in brain development [70]. The abnormalities of the 5-HT system in autism were first reported in 1961 [71]. In a whole blood test study, 5-HT was found to be significantly increased in 23 children with autism and severe mental disability, and slightly increased in 7 children

without autism but had severe mental disability. In contrast, normal level of 5-HT was tested in 12 children with mild mental retardation and four non-autistic and non-mentally handicapped children. Enhanced 5-HT levels in whole blood in ASD patients was further confirmed in follow-up studies; moreover, enhanced whole blood 5-HT levels were also detected in their immediate family members [21]. In addition, 5-HT antagonists can lead to improvement in ASD symptoms [72–74]. 5-HT has been most frequently tested in ASD studies, due to the close relationship between the 5-HT system and ASD. Based on the current ASD-related 5-HT PET imaging studies, the 5-HT system abnormalities in ASD patients mainly include decreased 5-HT transporters in brain, abnormal functions of brain 5-HT receptors, increased whole blood 5-HT levels, and disorder of 5-HT synthesis in brain.

3.3.1 5-HT precursor

Tryptophan hydroxylase is a precursor of 5-HT and α-methyl-L-tryptophan can specifically bind to tryptophan hydroxylase. Therefore, radio-labeled [^{11}C]AMT has been widely used as a specific probe to measure 5-HT synthesis [75, 76]. Unilateral changes in 5-HT synthesis in the dentate-thalamo-cortical pathway in ASD patients were analyzed with [^{11}C]AMT PET [66]. In all the 7 boys with autism tested but not in a girl with autism, 5-HT synthesis asymmetry was observed in cerebellar dentate nucleus, frontal cortex, and thalamus. Decreased 5-HT synthesis was observed in thalamus and left frontal cortex in 5 boys, while in thalamus and right frontal cortex in the other two boys. While increased 5-HT synthesis was detected in the contralateral dentate nucleus of all the 7 boys. Chugani et al. used [^{11}C]AMT PET to test 5-HT synthesis in 30 children with autism, 8 non-autistic siblings of the patients, and 16 non-autistic children with epilepsy. [77]. They found in a non-autistic child before 5 years old, 5-HT synthesis was more than twice that of an adult and then dropped to adult levels after 5 years. However, during the childhood of ASD patients, the whole-brain 5-HT synthesis reduced, but between 2 and 15 years old, it gradually increased, and reached a level 1.5 times that of the normal adult level with no gender difference. Age-dependent differences were observed in 5-HT synthesis between the epileptic and autism groups, as well as between the autism and sibling groups. Chandana et al. used [^{11}C]AMT PET to study the relationship between language and handedness functions and serotonin synthesis local and global abnormalities in children with autism [78]. Abnormal 5-HT synthesis in multiple cortex including non-lateralization, left and right cortex was observed by analysis in 117 children with autism. A more severe language impairment was observed in ASD children with reduced AMT binding in the left cortex, while a higher autism prevalence was found in ambidextrous and left-handed ASD children with reduced AMT binding in the right cortex. The local or global serotonin system abnormal asymmetrical development may both cause faulty neural circuitry.

3.3.2 5-HT transporter

5-hydroxytryptamine transporter (5-HTT), also named serotonin transporter (SERT) can transfer 5-HT to 5-hydroxytryptamergic neurons. Dysregulation of 5-HTT and 5-HT system happens simultaneously in ASD patients, but the association between 5-HTT and ASD remains unclear. The current PET probes for 5-HTT study include [^{11}C]DASB, [^{11}C](+)McN5652, [^{11}C]MADAM, and [^{18}F]Fmener-D2.

[^{11}C](+)McN5652 is the first probe used for 5-HTT imaging [79]. Nakamura et al. used [^{11}C](+)McN5652 PET in study of 5-HTT in ASD patients, and found that the whole brain 5-HTT level in ASD patients was lower than controls [80]. [^{11}C]DASB is more widely used probe than [^{11}C](+)McN5652 due to its high reliability and repeatability resulted from its reversible high-affinity binding with 5-HTT [81]. However, different studies on 5-HTT in ASD patients using [^{11}C]DASB reported different results. Girgis et al. did not find significant difference in 5-HTT between ASD and control groups [82]. Andersson et al., found significantly lower levels of 5-HTT in brain stem, gray matter, as well as nine gray matter subregions in ASD patients compared with controls [83], consistent with previous report that in ASD patients, 5-HTT level is decreased [84]. The different conclusions from different studies might be due to the heterogeneous study subjects, or different imaging for different ASD subtypes. The development of new probes for 5-HTT study (such as [^{11}C]AFM, [^{11}C] ADAM, and [^{11}C]DAPA) will promote elucidation of the association between 5-HTT and ASD, and significantly improve our understanding of the ASD pathophysiological mechanisms [85, 86].

3.3.3 5-HT receptor

Totally 14 subtypes of 5-HT receptor (5-HTR) have been found until now. 5-HT can stimulate different subtypes of 5-HTR, thereby exerting different physiological effects. The relationship between 5-HTR content changes and ASD remains unclear. Among 5-HTR subtypes, only 5-HT$_{1A}$R and 5-HT$_{2A}$R have been used in studies of ASD PET. [^{18}F]F13714 and [^{18}F]MPPF are 5-HT$_{1A}$R targeting probes, and [^{18}F] Altanserin, [^{11}C]MDL100907, and [^{18}F]Setoperone are 5-HT$_{2A}$R targeting probes.

[^{18}F]Setoperone has a high specificity for 5-HT$_{2A}$R [87]. Beversdorf et al., used [^{18}F]Setoperone PET and found much less [^{18}F]Setoperone binding in the thalamus of ASD patients compared with control group, however, no significant difference was observed in other regions [88]. Goldberg et al. used [^{18}F]Setoperone PET and found a significant lower cortical 5-HT$_{2A}$R binding potential (BP$_{ND}$) and also a lower cortical 5-HT$_{2A}$R density in the parents of the ASD children when compared with the control group. A negative correlation was also observed between the platelet 5-HT levels and the cortical 5-HT$_{2A}$R BP$_{ND}$ in the parents of the ASD children [89]. These results were consistent with reduced 5-HT$_{2A}$R expression and function observed in ASD patients, and also further elucidated the pathophysiological mechanism of elevated 5-HT level in ASD patients' peripheral blood. Another study using probe [^{11}C]MDL100907 observed no significant difference in regional [^{11}C]MDL100907 BP$_{ND}$ between adult patients with AS and controls [82].

A PET study using [^{18}F]MPPF, a 5-HT$_{1A}$R-specific probe was carried out on adult ASD patients and controls to study the correlations between gray matter volume (GMV), social personality, and 5-HT$_{1A}$R binding potential [90], and found a regional negative relationship between 5-HT$_{1A}$R BP$_{ND}$ and GMV, while 5-HT$_{1A}$R density was similar between ASD patients and controls. However, the correlations observed in control group between GMV, 5-HT$_{1A}$R, and social personality scores in the striatum were not observed in the ASD group, suggesting in the striatum of ASD patients, there is a 5-HT system disturbance correlated with the changes of 5-HT$_{1A}$R density.

With the development of probe, PET probes targeting other 5-HTR subtypes will be widely applied in ASD research, which can significantly improve elucidation of the ASD pathogenesis [25].

3.4 Oxytocin

Oxytocin (OXT) is a neuropeptide that plays an important role in the regulation of social behavior in mammals by interacting with oxytocin receptor (OTR). Previous studies have found abnormal OXT levels in patients with autism [91]. Numerous studies have demonstrated significantly improved social behavior in ASD patients resulted from intranasal OXT treatment. Guastella et al. reported a significantly improved ASD patient performance in an eye-mind task after administration of OXT via intranasal inhalation [92]. FMRI studies showed that after OXT treatment, several brain regions exhibited enhanced responses to stimuli in ASD patients [93, 94].

Unfortunately, PET probes targeting OTR satisfactorily have yet to be successfully developed. The probes [^{11}C]EMPA [95] and [^{11}C]PF-3274167 [96] have not been widely applied because their physical and chemical properties are not unsatisfactory. 5-HT and OXT are integrated both in structure and function, mediating emotion-based behavior. The amygdala is the key area for 5-HT regulation by OXT. OXT can inhibit the activity of amygdala and reduce anxiety; in contrast, dysregulation of 5-HT and high activity of amygdala are correlated with enhanced anxiety. Substantial studies have been performed to investigate 5-HT system changes after treatment with OXT and further explore the functions and related mechanisms of OXT in ASD. Using [^{18}F]MPPF PET, Mottolese et al. detected changes of 5-HT$_{1A}$R in the brain after OXT treatment, and found that OXT enhanced [^{18}F]MPPF BP_{ND} in the dorsal raphe nucleus (the core region for 5-HT synthesis), orbitofrontal cortex, insula, and amygdala/hippocampus complex [97]. Using [^{18}F]MPPF PET, Lefevre et al. did not find significant difference in the 5-HT$_{1A}$R distribution and content between ASD patients and controls [98]. However, they found OXT dramatically enhanced [^{18}F]MPPF BP_{ND} in some regions of brain in control group, but not in ASD group. Using [^{11}C]DASB PET, Hirosawa et al. observed significantly increased [^{11}C]DASB BP_{ND} in the left inferior and left middle frontal gyrus in ASD patients after treatment with OXT. However, no close relationship was found between [^{11}C]DASB BP_{ND} and symptom changes in clinic [99]. Taken together, these studies revealed the inhibitory effect of OXT on 5-HT signaling, and the relationship between serotonergic system changes and prosociality after treatment with OXT. The relationship between OXT and ASD needs further studies.

3.5 Dopamine system

Dopamine (DA) is a neurotransmitter of catecholamine, and it is involved in various central nervous system functions, including social motivation and social reward. A correlation between DA transporter and receptor-associated gene mutations and ASD clinical symptoms has been reported by numerous studies [100–102]. Some DA system-targeting psychotherapeutic medicines have exhibited good efficacy in improving ASD clinical symptoms, suggesting the critical roles of DA system in mediating behaviors of ASD patients. Many PET studies have been conducted on DA system, however, no consensus has been drawn on changes of DA transporters, receptors and precursor in the brains of ASD patients.

3.5.1 DA precursor

Dopa, the precursor of DA, can be absorbed, metabolized, and stored by dopaminergic endings, and [^{18}F]FDOPA imaging can be used to analyze DA synthesis

in brain. Using [^{18}F]FDOPA PET, Ernst et al. analyzed the brain DA synthesis difference between 14 ASD children and controls [103], and they found a 39% reduction in DA ratio in anterior medial prefrontal cortex/occipital cortex of ASD children compared with controls. Another study found increased [^{18}F]FDOPA inflow value (Ki) in the striatum and frontal cortex of ASD patients compared with control group [104]. However, other similar studies did not detect significant difference in dopamine production by striatum between ASD patients and controls [105, 106]. The inconsistent results of these studies might be due to the heterogeneity of the study subjects.

3.5.2 DA transporter

A study using [^{11}C]McN-5652 to detect 5-HTT and using [^{11}C]WIN-35,428 to measure DAT observed a remarkably higher DAT binding in the orbital prefrontal cortex of ASD patients when compared with controls. Moreover, in the orbitofrontal cortex of ASD patients, the DAT binding was inversely correlated with 5-HTT binding [80].

3.5.3 DA receptor

Fernell et al. conducted a PET study using [^{11}C]NMS on ASD children treated with R-BH4 (a tyrosine hydroxylase cofactor in the serotonin and catecholamine biosynthesis pathways), and found a 10% reduction of dopamine receptor 2 (D_2R) from pre-treatment abnormally high levels to after treatment normal levels in the caudate and putamen of ASD children compared with controls with improvement in ASD symptoms [107]. Fujino et al. used [^{11}C]SCH23390 PET to explore the differences in dopamine receptor 1 (D_1R) between ASD patients and controls, and they found the D_1R binding in the anterior cingulate cortex, striatum, and temporal cortex was positively correlated with emotional perception scores, while negatively correlated with ASD detail attention scores [108]. However, no significant differences were observed in the anterior cingulate cortex, striatum, and temporal cortex. Another study using [^{11}C]raclopride PET found decreased D_2R/D_3R binding in left caudate nucleus and bilateral putamen in ASD group compared with the control group [109].

3.6 Amino acid neurotransmitters

Protein synthesis is critical and necessary for a series of processes in the brain, including long-term memory, synaptic plasticity, and experience-dependent development. Atypical synapse protein synthesis is very important in ASD due to the close correlation between ASD and single-gene mutations, such as in neuroprotein 1, shank 3, and glial 3/4 [110]. The basic protein components are amino acids, therefore, quantitative analysis of amino acids and their receptors can help reveal abnormal protein synthesis in ASD.

3.6.1 Gamma-aminobutyric acid

Gamma-aminobutyric acid (GABA) is a key inhibitory neurotransmitter, which plays a crucial role in regulation of development and synaptic pruning. GABA dysfunction can induce imbalance in excitation/inhibition of the nervous system, which is closely correlated with ASD [111]. Previous human genetics studies found numerous mutations in the $GABA_A$ receptor gene as well as genes related to GABA synthesis in ASD patients [112, 113]. Autoradiography studies revealed reduced $GABA_A$ in the

hippocampus and anterior cingulate cortex of ASD patients [114, 115]. Studies on rodent ASD models of found a prolonged neuronal excitation caused by early GABA inhibition, which may be an underlying ASD induction mechanism [116]. A substantial evidence indicates that GABA changes might relate to ASD, however, current PET studies on GABA are very few.

PET has been widely used to explore the roles of GABA in ASD pathogenesis. A study performed by Mendez et al. using [^{11}C]RO15–4513 PET found markedly decreased $GABA_A$ α5 subtype levels in the bilateral amygdala and NAc in the brains of ASD patients compared with controls [117]. These results provide support for further study of GABA system abnormalities in ASD patients. However, another study using [^{18}F]FMZ or [^{11}C]RO15–4513 did not find differences in either $GABA_A$ receptors or $GABA_A$ α5 subtype in any region of the brain between ASD and control groups [118]. Fung et al. measured GABA concentrations using ^{1}H-MRS and total $GABA_A$ receptor densities using [^{18}F]FMZ PET. [^{18}F]FMZ PET showed no significant difference in $GABA_A$ receptor density in the left dorsolateral prefrontal cortex (DLPFC) and bilateral thalamus between the ASD and control groups However, ^{1}H-MRS detection revealed a significantly higher GABA/Water ratio in the left DLPFC of ASD patients compared to the control group [119].

3.6.2 Glutamate

Due to the imbalance in brain excitation/inhibition in ASD patients, glutamate is also a focus of ASD neuroimaging research [120]. A series of glutamate receptor specific probes including [^{11}C]ITMM, [^{11}C]MMPIP, and [^{18}F]FPEB have been reported, which can specifically bind to metabolic glutamate receptor 1 ($mGluR_1$), metabolic glutamate receptor 7 ($mGluR_7$), and metabolic glutamate receptor 5 ($mGluR_5$), respectively [121–124]. However, only [^{18}F]FPEB has been widely applied in clinical ASD PET research.

The correlation between glutamate system imbalance and ASD has been demonstrated by animal model studies using [^{18}F]FPEB PET. of a Shank3 complete knockout mouse model (Shank3B−/−) showed that of A significantly increased mGluR5 BP_{ND} was observed in the thalamus, striatum, amygdala, and hippocampus in Shank3B−/− mice compared with normal mice as shown in [^{18}F]FPEB PET imaging [125]. Using [^{18}F]FPEB PET, Fatemi et al. found a remarkably higher [^{18}F]FPEB BP_{ND} in the cerebellum and posterior central gyri of ASD patients [126]. A negative relationship between [^{18}F]FPEB BP_{ND} and age was observed in the cerebellum, but not in the posterior central gyrus. A positive relationship was observed between precuneus [^{18}F] FPEB BP_{ND} and sleepiness scale score on the Abnormal Behavior Checklist (ABC), while a negative relationship was observed between cerebellar [^{18}F]FPEB BP_{ND} and ABC hyperactivity subscale, ABC inappropriate speech subscale, and ABC total score. These results showed altered mGluR5 binding in key regions of ASD patient brains, indicative of abnormal glutamate signaling in these areas, which might influence ASD symptoms. Brašićet al., used [^{18}F]FPEB PET to study the mGluR5 distribution in brain of patients with fragile X syndrome (FXS), TD and idiopathic autism spectrum disorder (IASD) [127], and they observed a significantly increased mGluR5 expression in the cortical regions of IASD patients when compared with TD patients, while they observed a significantly decreased mGluR5 expression in all regions of FXS patients when compared with TD patients.

Currently, some mGluR7 and mGluR1 probes are also under investigation. Future imaging studies will elucidate more pathophysiological mechanisms of glutamate in ASD.

3.6.3 Leucine

Leucine impacts neuron protein synthesis and plays a critical role in dendritic spines regulation, therefore functions in neuropsychiatric diseases [128]. Shandal et al. investigated the leucine involvement in protein synthesis using [^{11}C]Leucine PET [129], and found increased protein synthesis in the temporal lobe language region of stunted children with PDD. Consistently, previous studies showed abnormal protein synthesis in the language region and abnormalities in the temporal lobe region of children with PDD and developmental delay. However, another study reported no significant differences in cerebral protein synthesis between patients with Fragile X syndrome and controls using [^{11}C] Leucine PET for measurement [130]. In contrast, another study using robust radiolabeled assay found decreased protein synthesis in peripheral blood mononuclear cells (PMCS) and platelets of patients with Fragile X syndrome when compared with controls [131]. Taken together, these studies suggest that more research is needed to demonstrate the correlation between leucine abnormality and ASD.

3.6.4 Acetylcholine

A series of studies showed that inhibition of acetylcholinesterase (AChE) attenuated inattention, aggression, and overall ASD symptoms in both ASD patients and ASD animal models [132–134], indicative of the critical roles of the cholinergic system in ASD etiology. However, only one PET study was reported. A lack of cholinergic innervation was observed in the fusiform gyri of ASD patients when using the acetylcholine analog [^{11}C]MP4A to detect the activity of acetylcholinesterase [135]. Additional targeted PET studies in the future will help clarify the role of cholinergic dysfunction in the pathogenesis of ASD.

3.7 Neuroinflammation

Immune-mediated mechanisms are considered to be among the pathophysiological factors leading to ASD [136]. Inflammation including microglial activation and related changes of microglial pathology has been found in central nervous system of ASD patients, and many psychotropic agents have exhibited direct effect on microglia [137]. However, the correlation between microglia and ASD remains unclear.

Microglia play critical roles in development of immunity and central nervous system. The translocator protein (TSPO) is an important neuroinflammation imaging biomarker, which is overexpressed in activated microglia. A series of TSPO probes have been developed including [^{11}C]PK11195, the first generation, [^{18}F]FEPPA, [^{11}C]PBR28 and [^{11}C]DPA713, the second generation and [^{11}C]ER176 and [^{18}F]GE180, the third generation [138, 139]. Suzuki et al. investigated microglia activation differences between ASD patients and controls using [^{11}C]PK11195 [140], and they found increased [^{11}C]PK11195 binding in prefrontal cortex, fusiform gyrus, midbrain, cerebellum and cingulate cortex in ASD patients compared with controls. Another study using [^{11}C]PBR28 reported a lower regional TSPO expression in bilateral precuneus/posterior cingulate gyrus, bilateral temporal gyrus, bilateral insular cortex, superior limbic gyrus, and angular gyrus of brain in ASD patients than in controls [141]. These two studies reported inconsistent results, possibly due to the heterogeneity of ASD patients or the influence of TSPO gene polymorphism. The applications of more TSPO probes have been reported [142–145]. Future imaging studies will help us understand the relationship between neuroinflammation and ASD.

A series of novel neuroinflammation targets and corresponding probes have been developed including cyclooxygenase (COX)-1 and its specific probe [^{11}C]PS13, monoamine oxidase B (MAO-B) and its specific probe [^{11}C]SL25.1188, colony-stimulating factor 1 receptor (CSF1R) and its specific probe [^{11}C]CPPC, and purinergic P2X7 receptor (P2X7R) and its specific probes [^{11}C]JNJ-54173717 (JNJ-717), [^{18}F] JNJ-64413739, and [^{11}C]SMW139, as well as cyclooxygenase (COX)-2 and its specific probe [^{11}C]MC1. These probes have been successfully applied in neuroimaging to explore the potential functions of these targets in neuroinflammation, as well as the potential relationships with ASD [24].

3.8 Arginine vasopressin

Arginine vasopressin (AVP) plays a series of physiological roles in mammals including increasing blood pressure, regulating social behavior, releasing adrenal corticosteroid, as well as antidiuretic activity [146, 147]. Since early animal studies have found that AVP plays critical roles in regulating biosocial behaviors, including parentage, mating, aggression and sociability, an increasing number of studies have focused on the correlation between AVP and ASD [148–150]. Regarding the differences in AVP contents between ASD patients and controls, although no consistent conclusion has been drawn, AVP related signaling pathways have been demonstrated to be promising and studies on them could help ASD diagnosis and treatment [151–154]. V1a receptor antagonists have been shown to be able to regulate AVP functions, thereby improving the ASD symptoms. A novel V1a receptor antagonist of Balovaptan can improve the Vineland-II Adaptive Behavior Scale (including social interaction, daily living skills, and secondary endpoints of communication) in ASD adults [155], but not in ASD children and adolescents [156]. The V1a receptor has become a new focus of ASD research, and a series of V1a receptor probes including [^{11}C]SRX246, [^{18}F]SRX246 [157], [^{11}C](1S,5R)-1 [158], and [^{11}C]PF-184563 [159] have been developed recently. These PET probes have exhibited their values in in autoradiography and animal studies, however, they have not been applied in human studies yet. The development of PET probes that can be widely used inhuman ASD studies will help elucidate the relationship between AVP and ASD.

4. Conclusion

ASD is a disease induced by both environmental and heredity factors, and its major cause and induction process still remain unclear. Early and clear diagnosis of ASD is conducive to improving ASD symptoms in patients, thereby affecting treatment efficacy. PET can be applied to quantitatively and dynamically evaluate cerebral glucose metabolism, task and resting states, neurotransmitter system biomarkers, and cerebral blood flow perfusion, explore ASD pathophysiology, and promote ASD therapeutic drug development, as well as in ASD diagnosis and treatment. The identification of ASD biomarkers and PET probes is critical in ASD diagnosis, and drug development and evaluation. Numerous ASD associated biomarkers have been identified in cerebral blood perfusion, glucose metabolism, neuroinflammation, and neurotransmitter systems. However, due to the differences in ASD subtypes, experimental design (e.g., imaging conditions, anesthesia/sleep/awake, and/or task-state/resting-state), and subjects (e.g., gender, IQ and age), contradictory conclusions may be drawn from different studies [160]. There a limitation in the current ASD studies.

The PET imaging studies showed that there might be differences in the pathophysiological mechanisms for different ASD subtypes and therefore different results may be observed and different conclusions may be drawn for different ASD subtypes. Therefore, more attention should be paid on this in future ASD PET studies to explore the possible differences in the pathophysiological mechanisms of different ASD subtypes, and selection of experimental subjects and design of experiments should be determined and performed based on these differences to provide more valuable references for clinical diagnosis and treatment of ASD [161].

In this chapter, several ASD related targets, including cerebral blood perfusion, cerebral glucose metabolism, neuroinflammation, arginine vasopressin receptor, neurotransmitter system, as well as the corresponding probes and their applications in ASD imaging studies and the experimental results are summarized. PET studies using different probes can obtain similar results, while PET studies using the same probe can also produce different results due to the heterogeneity of ASD patients and the influence of TSPO gene polymorphism. [162]. Therefore, although identify new biomarkers and develop novel PET probes are very helpful for ASD study, evaluation the application value of each probe in the existing system is difficult. Therefore, it is crucial to seek and investigate the associations between a probe, a biomarker, and a specific ASD subtype at molecular level [163], which is the most valuable exploration direction in future ASD studies.

PET molecular imaging is very helpful for ASD diagnosis and treatment, however, there are still some limitations and difficulties in execution. First, patients are required to lie on a machine for PET/MR and PET/CT scanning, and protection from radiation is required during the imaging process, so high coordination of patients is very important. Second, ASD patients often have a large age span and significant differences in IQ, so professional technicians need to train some patients to make them get familiar with drug injection, task process or even anesthesia operation and adapt to scanning environment. Therefore, the joint efforts of patients, doctors, technicians, nurses, researchers, as well as other specialists in neuropsychiatry, rehabilitation, and nuclear medicine to promote continuous advancements in ASD research, diagnosis and treatment.

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Conflicts of interest

The authors declare no conflicts of interest.

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