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Identification of Alzheimer's Disease by Molecular Imaging: Progress and Prospects

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Abstract: Alzheimer's disease (AD) which is characterized by the development of β-amyloid plaques and neurofibrillary tangles in the brain parenchyma can result in synaptic and neuronal loss. Clinical signs including deteriorating memory deficiencies may bring catastrophic effects on the elderly. Research on brain imaging and its application in the study of AD has advanced extraordinarily over the past 30 years. However, widely used imaging methods are only capable of identifying structural or metabolic alterations at the anatomical level of the brain, and can only be utilized for drawing inferential distinctions. As a disease with complex pathophysiological mechanism, AD has many different molecular pathological features and molecular biomarkers. Therefore, molecular imaging for AD pathology indicators provides a practical method for the early diagnosis and impartial assessment of AD. The present review discusses the pathogenesis of AD, as well as the detection methods and principles of molecular imaging, such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT) techniques. Meanwhile, various tracers and probes applying in molecular imaging that detect Aβ deposits, tau protein accumulation, and neurotransmitter, are also reviewed. Molecular pathological tracers provide the possibility to accurately quantify brain changes by molecular imaging.

1. Introduction

As a leading contributor to dementia, Alzheimer's disease (AD) is a progressive neuro-degenerative condition. The commonest presentation of AD is with insidious, progressive problems centred on episodic memory of elderly individuals, which may meet the requirements of mild cognitive impairment (MCI) at this stage. Challenges with navigation as well as multitasking and confidence issues frequently surface. A patient can be diagnosed with AD dementia when cognitive impairments develop more severe and pervasive and begin to interfere with daily activities. As the condition progresses, increasing reliance is the typical, and subsequently behavioral changes, decreased mobility, hallucinations, and seizures may appear. Average time to death after presentation is 8.5 years(1). According to the Alzheimer's Association, 60–80 percent of dementia cases globally are caused by AD. In the United States, 6.7 million people aged 65 or older will be diagnosed with Alzheimer's disease in 2023, according to estimates(2). According to recent estimates, 44 million individuals worldwide currently suffer with dementia. As the population ages, this is anticipated to more than treble by 2050, when the yearly cost of dementia in the USA alone may surpass US$600 billion(3).

There is currently a lack of knowledge on the precise pathophysiological pathways underlying AD. From a neuropathological standpoint, AD is characterized by: (1) extracellular neuritic plaques, which are extracellular deposits of β-amyloid(Aβ); (2)neurofibrillary tangles (NTFs), which are neuronal aggregates of hyperphosphorylated tau; (3) neuronal loss particularly in the medial temporal lobe structures and the temporo-parietal association cortex(4). Along with the aberrant protein deposition, various biochemical processes such as inflammation, oxidative damage, and lysosomal dysfunction occur,

supporting the hypothesis that the etiological factors contributing to the disease process are heterogeneous and interact until the full disease pathway is established(5).

The diagnosis of dementia is typically determined by the patient's medical history, the pattern of cognitive deficits, and other factors evaluated through clinical investigations, such as blood testing and structural imaging of the brain, to rule out nondegenerative causes of the symptoms. Early-stage clinical diagnosis of AD is still challenging and requires a thorough medical history, as well as a battery of neuropsychological tests for the diagnosis of dementia and to distinguish AD from other causes like vascular dementia, frontotemporal dementia, and Lewy body dementia(6). The remaining functioning neurons in the AD brain cannot currently be directly measured in vivo; instead, postmortem pathological examination is used to determine the disease's definitive diagnosis(7). The amyloid cascade hypothesis states that amyloid production occurs 10 years or more before the start of clinical symptoms (8). Thus, investigating new techniques for the in vivo early and precise identification of AD is crucial for treatments to be effective.

Research on brain imaging and its application in the study of AD has advanced extraordinarily over the past 30 years(9). Currently, a number of imaging techniques have been utilized to clinically diagnose AD. Computed tomography (CT), nuclear magnetic resonance imaging (MRI), and different derivative technologies may be utilized to classify these technologies in general terms. However, widely used imaging methods are only capable of identifying structural or metabolic alterations at the anatomical level of the brain, and can only be utilized for drawing inferential distinctions. As a disease with complex pathophysiological mechanism, AD has many different molecular pathological features and molecular biomarkers. Therefore, molecular imaging for AD pathology indicators provides a practical method for the early diagnosis and impartial assessment of AD(10).

Functional neuroimaging using positron emission tomography (PET) and single-photon emission computed tomography (SPECT) has been used to study various metabolic and biochemical alterations in the brain in vivo in AD, contributing to early diagnosis and differential diagnosis and providing essential data for the understanding of underlying pathology. Different molecular radiotracers have been employed to estimate impairments in neurotransmitters, regional blood flow, and glucose metabolism, among other aspects of brain function (11). These molecular imaging approaches will be essential for the accurate patient selection and the assessment of therapeutic response in light of new medicines. The imaging of aberrant protein deposits was made possible by recent developments in technology and radiopharmacology(12), while targeting new biochemical and molecular processes with the use of novel probes is a growing aspect of nuclear medicine imaging in the field of AD(13). Herein, we review the pathogenesis of AD, as well as the detection methods and principles of molecular imaging, such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT) techniques. Meanwhile, various tracers and probes applying in molecular imaging that detect Aβ deposits, tau protein accumulation, and neurotransmitter, are also reviewed.

2. Pathogenesis of AD

The pathological phenomenon of AD is complex. Brain tissue examination results showed that senile plaques(SP) formed b β-amyloid (Aβ) plaques outside brain nerve cells were common in patients with AD. Neurofibrillary tangles (NFTs), neuron loss, neurodystrophy, synaptic loss and other pathological phenomena formed by SP and abnormal phosphorylation of tau protein [3]. However, the relevant pathogenesis is still unclear. The following section covered the pathogenesis of AD, which is seen in Figure 1.

Figure 1. Summary of mechanisms for pathogenesis of AD. A. Central Cholinergic System Injury. B. Aβ Deposits. C. Tau Protein Accumulation. D. Neuroinflammation. E. Oxidative Stress.

2.1 Central Cholinergic System Injury

The injury theory of cholinergic system is the earliest theory of AD. Acetylcholine (ACh) is an important central excitatory neurotransmitter, which is related to a variety

of advanced behaviors such as learning and memory. Central cholinergic nervous system affects the level of central acetylcholine by regulating the synthesis and release of acetylcholine(14). Early studies showed that severe neurodegeneration occurred in the basal nucleus of Meynert (mainly composed of cholinergic neurons) in the basal forebrain of patients with AD. At the same time, the presynaptic cholinergic transmitters in the cerebral cortex were severely depleted and the activity of choline acetyltransferase (ChAT) was significantly decreased(15). The above two points indicate that severe cholinergic system damage occurred in the brain of patients with AD.

Studies have shown that cholinergic nerve imbalance can accelerate the deposition of A β, and acetylcholinesterase (AChE) can directly bind to presenilin-1 (PS-1), a key enzyme in the production of A β, and significantly enhance its expression, thus increasing the level of A β and accelerating cognitive impairment(16). In addition, abnormal central cholinergic changes can also induce abnormal phosphorylation of tau protein, neuronal inflammation, apoptosis and imbalance of neurotransmitter and neurohormone system(16).

2.2 Aβ Deposits

Aβ is a peptide produced by the cleavage of amyloid precursor protein (Amyloid precursor protein, APP) mediated by β-secretase and γ-secretase. It has 37043 amino acid residues(17). Toxic oligopeptides generated by disrupting the assembly of APP fragments comprise 39–43 fragments, including protofibrils or fibrils. These then result in deposits that become apparent under a microscope. BACE 1 cleaves APP at β-sites Asp1 and Glu11. γ-secretase further cleaves the 99 amino acid residues that are linked to the C-terminal membrane, resulting in the production of the isoforms Aβ1-42 and Aβ1-40. Presenilin 1 (PS1) or presenilin 2 (PS2) are the primary forms of γ-secretase. The typical soluble isoform is Aβ1-40, but if the cleavage pattern is altered, it could result in Aβ1-42, which aggregates readily and forms plaque because it contains two extra amino acids: alanine and isoleucine (18). Mutations in the APP, presenelin 1 and presenelin 2 genes, or the apolipoprotein E (APOE4) gene cause this shift the cleavage pattern. In addition to genetic mutations, a multitude of neuropeptides may play a role in the development of plaque. For instance, low levels of somatostatin, neuropeptide Y, and corticotrophin-releasing hormone (CRH) may be linked to plaque formation, while higher levels of Angiotensin II may contribute to irregular APP cleavage or poor removal of the Aβ1-42 fragment(19). Different parts of the brain experience the formation and deposition of Aβ plaques. The brain recognizes these plaques as foreign material, which triggers an immunological and inflammatory response by triggering microglia and releasing cytokines. This ultimately results in cell death and dementia.(20).

A total of 26 A β protein forms were identified from the cerebrospinal fluid of patients with AD, among which A β 1-40 and A β 1-42 with 40 and 42 amino acid residues were the main components of accumulated A β. A β 1mur42 is more hydrophobic and easier to gather (21), which is believed to be the main culprit for the initiation of senile plaques in the brain. An increase in the level or proportion of A β 1mur42 can induce the formation of A β amyloid fibers, which develop into senile plaques in the brain and lead to neurotoxicity (22). A β aggregate can activate cysteine protease, which can cleave tau protein and change the conformation of normal tau protein, so that tau protein can not bind to microtubules and aggregate, which induces the pathology of tau protein and leads to AD.

2.3 Tau Protein Accumulation

Micro tubular neuronal proteins are called tau proteins. The micro-tubule binding domain of tau proteins is important in the stabilization and polymerization of the microtubule assembly, hence preserving the cytoskeleton's integrity. Numerous kinases, including Fyn Kinase, glycogen synthase kinase-3β (GSK3β), and cyclin-dependent kinase-5 (CDK5), phosphorylate the serine and/or threonine residues to control this interaction. CDK5 may be involved in the development of neurofibrillary tangles. Calpain is activated

by Aβ, and p35, an activator of CDK5, is deregulated. Phosphorylated tau is hyperphosphorylated as a result of p35 splitting into p25 in response to an excess of cytosolic calcium. This hyperactivates CDK5(23). The hyperphosphorylation of tau proteins causes a reduction in their affinity for microtubules. The hyperphosphorylated tau loses its ability to preserve the cell's structure when it produces NFTs and is deposited in the cytoplasm. Additionally, typical cellular functions like as synaptic transmission, axonal transport, signal transduction, and progressive cell degeneration are impacted by this deposition.

The Tau protein is another element involved in the process of plaque formation. It is a factor that facilitates the tubulin protein's particular assembly process. In contrast, tubulin polymerizes and forms microtubules that form the intracellular pathway that the cell's motor proteins travel along or use as a dividing spindle during cell division. The hyperphosphorylation of the Tau protein results in the formation and deposition of neurofibrillary fibers in the pathophysiology of Alzheimer's disease.(24). The loss of physiological function by a normal Tau protein, which results in the instability of microtubules, or the increase of function from toxic to neurons, which causes apoptosis, are the two main mechanisms by which the Tau protein causes neurotoxicity(25). Numerous researchers have also demonstrated a link between the accumulation of β-amyloid and the Tau protein's aggregation, which is the last stage in the pathophysiology of illness(26).

2.4 Neuroinflammation

Microglia are the most important immune cells in the central nervous system, which can recognize and remove damaged nerves, plaques and infectious substances in the central nervous system, which is of great significance to maintain the homeostasis of the central nervous system. Microglia surface receptors can recognize damaged cells and heterogenous substances in the brain, cause microglia activation, produce a series of downstream effects, and play an immune role. However, long-term excessive activation of microglia will release too many inflammatory factors and oxidizing substances, leading to inflammatory reaction, nerve cell damage and neurotoxicity(27). Bambergei et al found that A β can bind and activate receptors on the surface of microglia, and activated microglia release cytokines, chemokines, reactive oxygen species and other neurotoxic substances (such as NO, tumor necrosis factor, superoxide, etc.), leading to inflammation, which proves that neuroinflammation in the brain of patients with AD is closely related to Aβ-induced microglial activation(28).

A key factor in the pathophysiology of AD is neuro-inflammation. Acute inflammation serves as a barrier to prevent brain damage caused by conditions like Aβ plaque buildup. Microglia's ability to release pro-inflammatory cytokines is maintained despite their inability to remove plaque due to chronic activation, which leads to an imbalance between pro- and anti-inflammatory cytokines. Aβ deposits trigger the activation of many Toll-like receptors (TLR2, TLR4, and TLR6) and their co-receptors, which include the microglia-expressed CD36, CD14, and CD47. The immune system produces proinflammatory cytokines of the IL-1β family such as IL-1β and IL-18, upon the identification of microorganisms. Upon activation, caspase-1 or caspase-8 express these cytokines. The activation of caspase-1 is aided by inflammatory proteins such as PYHIN (pyrin and HIN domain-containing) and NLR (Nod-like receptor) family. The main inflammasome that is capable of detecting Ab clumps is NLRP3. These proinflammatory cytokines can interfere with microglial clearance of Aβ and damage dendritic spines.Nitric oxide (NO) generation is enhanced by neuronal and glial cell expression of inducible isoforms of NO synthase in response to proinflammatory cytokines. As a result, the peptide's capacity to aggregate is enhanced, and its ability to inhibit synaptic plasticity is strengthened(29). As previously mentioned, these cytokines cause CDKs to become activated, which increases tau hyperphosphorylation and Aβ plaque formation(20).

2.5 Oxidative Stress(OS)

Functional imaging of the brains of patients with precursors to AD revealed hyperactivation of neurons in the hippocampus and neocortex regions of the brain(30). Mitochondria are the energy factories of cells, and abnormal neuron excitation indicates increased mitochondrial activity. Mitochondria are the main sites for the generation of intracellular reactiveoxygenspecies (ROS). Under normal circumstances, ROS is produced in a small amount and can function as the second messenger in cells. When neurons are abnormally excited, mitochondrial activity is enhanced and ROS production increases, and the antioxidant defense system cannot clear them in time. Excessive ROS will damage mitochondria and then damage nerve cells, resulting in abnormal neuronal death and promoting the pathological process of AD(31). Mitochondrial defects exist in the brain tissue of AD patients. Pathological phenomena of abnormal mitochondrial function have been found in the detection of brain tissue samples of AD patients, the experiment of AD transgenic mice, and the studies on the expression of mutant APP or Aβ treated cells(32).

Mitochondrial dysfunction may result from cytochrome c oxidase levels that are too low. Furthermore, OS-induced hyperexcitation of glycogen synthase kinase (GSK-3) can change the permeability of mitochondria. This might cause ROS to be produced in excess(33). ROS can be produced by metal ions, particularly copper and zinc, binding to the Aβ plaque. The resulting ROS oxidize the Aβ peptide, making it difficult to remove, and oxidize the cell membrane's lipid and protein membrane, making it permeable and therefore prone to degeneration(34).

3. Molecular Imaging Modalities in AD

At present, there are great differences in neuroimaging results and interpretation, which are not enough to meet the needs of early detection, disease classification, treatment evaluation and accurate prognosis of AD. The initial factors such as the pathological changes at the cellular level are much earlier than the appearance of clinical symptoms and the changes of anatomical structure. In view of the fact that the epidemiological characteristics of AD have not been elucidated and the lack of disease reversal drugs, the need for early detection by molecular imaging of its molecular level changes is quite urgent. Several molecular imaging modalities in AD were summed in Figure 2.

Figure 2. Molecular imaging modalities in AD.

3.1 Positron Emission Tomography (PET)

Using various radioactive tracers depending on the intended target, positron emission tomography (PET) imaging analyzes changes in metabolism (35). PET imaging is the simultaneous detection of gamma rays emitted by positron annihilation events from the radiotracer. Since a radioisotope is utilized to replace one of the tracer's atoms, the radioactive tracers in this case are comparable to common biological compounds like glucose, peptides, and proteins(36). After being injected into the patient, a radioactive tracer enters the targeted organs or tissues through the circulatory system and takes part in metabolic activities there(35). Due to their instability, the radioisotopes in the tracer decay. During this decay, positrons are released and collide with the electrons of nearby atoms, causing an annihilation reaction(37). Two 511 keV gamma rays, separated by around 180 degrees, are produced by the annihilation and are absorbed by scintillation crystals, where they are transformed into low-energy visible photon(37). The light impulses are subsequently translated into electrical signals by a photosensor. Scintillators, detectors, and readout electronics combine to make a detector that measures three parameters: the energy of the gamma ray, its position upon impact, and the moment the ray strikes the detector(38). After that, these electronic signals are processed using reconstruction and correction techniques to create an image. The capacity of PET imaging to map various signals, such as brain metabolic activity, amyloid load, or tau-tracer retention, differs depending on the radiotracer used. PET scans of AD patient and non-patient groups are compared as a diagnostic technique to observe variations in uptake patterns.

3.2 Structural Magnetic Resonance Iimaging (sMRI)

The most widely utilized brain imaging technique in the research of AD has been structural MRI. Clinically affected patients have increased ventricular and sulcal volumes, reduced gray matter or cortical thickness in other cerebral regions, such as the precuneus and posterior cingulate, parietal, and temporal cortex, and accelerated rates of decline in these and whole brain measurements over time. They also have significantly reduced hippocampal and entorhinal cortex volumes, gray matter, and cortical thickness (8). Hippocampal and entorhinal cortex size reductions seem to be associated with early memory decline and predict the development of more severe clinical stages, such as Alzheimer's dementia and moderate cognitive impairment (MCI)(39). In the clinical setting, structural MRI is often recommended to help rule out potentially reversible.

3.3 Single photon emission computed tomography (SPECT)

PET and SPECT are quite comparable. When used to measure cerebral perfusion in dementia patients, SPECT produces results that are similar to those of clinical diagnostic PET scanning of glucose metabolism. SPECT research has demonstrated the ability to forecast MCI deterioration(40) and pertain to the results of autopsies (41). For a long time, the scarcity of PET led to a significant reliance on SPECT scanning. Nevertheless, with the increasing number of PET scanners and their usage in clinical settings for oncological purposes, PET's availability and potential for use in dementia research and care have grown.

3.4 Noninvasive Fluorescence Imaging

By verifying the fluorescence of Aβ, tau, and other AD-associated proteins, optical fluorescence imaging is the most effective technique for diagnosing AD pathology and neural networking. Endogenous and/or exogenous fluorophores that emit light in response to laser excitation are used in fluorescence imaging. In particular, because of low light scattering, low light absorption in surrounding tissues, and negligible autofluorescence, NIR fluorescence imaging (650–1000 nm for NIR-I and 1000–1700 nm for NIR-II) can provide great sensitivity and specificity for the real-time imaging of biological systems(42). To facilitate noninvasive imaging of AD, fluorescence imaging probes must meet three requirements: (1) they must be (pseudo)permeable to cross the pathologically vulnerable blood–brain barrier (BBB); (2) they must bind to AD-specific cells and proteins, such as tau proteins in the brain; and (3) they must have absorbance and fluorescence emission spectra in the NIR window (650–1700 nm)(42).

4.Radioactive Tracer/ Fluorescence Imaging Probes in Molecular Imaging

AD molecular imaging is to design molecular probes or imaging agents based on indicative molecular targets. The commonly used criteria for testing and evaluating the performance of the designed tracers are high affinity, high binding specificity, high specific activity, high blood-brain barrier penetration and low side effects. Before achieving these goals, the metabolism and mechanisms of the peripheral and central nervous systems need to be fully studied. Their emission energy and half-life should be consistent with the target application. In addition, tracers need to maintain the same biological properties after positron or single-photon isotope labeling. Tracers and fluorescence imaging probes in application on AD is summarized in Table 1.

4.1 Targeted β-amyloid tracer/Probes

In vitro experiments, Congo red and sulfur T were the first compounds found to bind to β-fiber cross structures, but their ionic charges prevented them from crossing the blood-brain barrier (55). Based on the structures of these two compounds, many PET tracers with 11C or 18F as radioisotopes have been developed to directly visualize A β and its distribution in vivo to evaluate neuroinflammatory plaques.

The first compound used in vivo to recognize β-amyloid protein is BSB, which has good blood-brain barrier penetration and plaque-specific binding power. Marie L. et al. compared the results of using BSB with standard histochemical dyes like thioflavin S and

immunohistochemical stains specific for the same lesions in postmortem tissues from patients with a variety of neurodegenerative diseases. The diagnostic lesions were characterized by fibrillar intra- or extracellular lesions. These findings indicate that BSB binds not only to external amyloid beta protein but also to a variety of intracellular lesions made up of aberrant tau and synuclein proteins. This suggests that derivatives of radioiodinated BSB or comparable ligands could be helpful imaging agents to track various amyloids in vivo(43).

After testing synthetic Aβ fibers and cadaveric specimens of AD patients, 6-OH-BAT-1, or PIB, finally stood out among more than 100 chemicals. During the prodromal phase of AD, PIB binding increases, showing bimodal behavior: approximately 50% of positive individuals subsequently progress to AD. In prospective studies, increased PIB ligand retention was able to identify 82% of AD patients at follow-up, with only one prediction failure, demonstrating its high sensitivity and specificity. In addition, both amygdala and hippocampus atrophy were found to be positively correlated with PIB binding, suggesting differences in susceptibility to Aβ toxicity in different brain regions. Although this tracer seems promising for showing an increase in Aβ deposits before clinical onset of AD, there is A ceiling effect and large multicenter studies are still needed to develop objective evaluation criteria(44).

Based on sensitivity and specificity, the U.S. Food and Drug Administration has approved three radiopharmaceuticals that bind to the fiber-aggregating form of beta-amyloid. Flutimol, as a benzothiazole derivative, can estimate plaque density with a sensitivity of 88% and specificity greater than 80%, and no adverse reactions in Phase III clinical trials (45).

Osama et al. compared in vivo PET imaging with post-mortem histopathology in an open-label, nonrandomized, multicenter, phase 3 research to validate the (18)F-labeled β-amyloid tracer florbetaben. Flubetaben demonstrated a 97.9% sensitivity and an 88.9% specificity in identifying Aβ plaque, as validated by histology. As a result, Florbetaben PET may be a useful addition to clinical diagnosis, especially for the exclusion of AD, as the results revealed good sensitivity and specificity for the detection of neuritic β-amyloid plaques verified by histology(46).

Viola et al. attached oligomer-specific antibodies to magnetic nanostructures to construct a stable compound, which can enter the central nervous system through intranasal administration and combine with A β oligomers to produce detectable MRI signals. Targeting neurotoxic Aβ oligomers, these nanostructures have the potential to be valuable in assessing the effectiveness of novel medications and, eventually, in diagnosing and treating Alzheimer's disease in its early stages(47).

4.2 Targeted Phosphorylated Tau Protein Tracer/Probes

Fluorine-containing radioactive tracers have been developed to bind tau fibers with high precision. Watanabe [11] constructed a compound called BIP-Nme2. As a tau imaging probe, BIP-NMe2 demonstrated a strong and specific affinity for tau aggregation in brain slices from AD patients. Furthermore, BIP-NMe2 showed a strong initial uptake into the normal mouse brain and a rapid washout from it, indicating that its pharmacokinetics are advantageous for tau aggregation in vivo imaging(48).

The tracers labeled with ^{11}C are ^{11}C-THK5351 and ^{11}C-PPB. Konstantinos evaluated the binding of two chemically different tau-specific PET tracers (^{11}C-THK5351 and ^{11}C-PBB3) in a head-to-head, in vivo, multimodal design. It is found that the former signal is more closely related to the pre-determined distribution of tau protein, while the latter is more closely related to the co-deposition of β-amyloid protein and tau(49).

A PET radiotracer called ^{18}F-T807 was created to image tau protein aggregates, which have been linked to neurologic conditions like Alzheimer's and traumatic brain injury (TBI). Dustin et al. used metabolite-corrected arterial input functions and dynamic PET imaging to describe the pharmacokinetics of 18F-T807 in human participants. The results

indicated that ^{18}F-T807 can detect tau protein quantitatively and the plasma clearance rate is high(50).

Though its value in early diagnosis or detection is inferior to that of A β-targeted tracers, the pathology of tau protein is more closely linked to the clinical symptoms of AD and appears relatively late in the disease's progression, making its imaging more commonly used in clinical trials to assess how well drugs delay the disease's progression.

4.3 Targeted Neurotransmitter Tracer/Probes

The most important energy consumption site of neurons is synapse, that is, the place where active electrical activity and material exchange take place (56). Neuronal dysfunction and loss of function are usually reflected in the reduction of neurotransmitters or their receptors produced and released(57). Neurotransmitters and their receptors are generally considered to be markers of specific types of neurons(57).

Weinberger et al. found that when ^{123}I-4-IQNB was used in SPECT, the brain region with strong binding to muscarinic acetylcholine receptor was not correlated with the glucose metabolism intensity measured by FDG-PET, and the defect range was larger in AD patients. In patients with AD, the signal of the tracer showed differences in the expression of receptors in different brain regions(51).

Drugs targeting vesicular ACh transporters are also under development: ^{123}I-IBVM, as a representative, has been found that its signal intensity is inversely proportional to age and symptom severity. In addition, the decrease of affinity was limited to parietal lobe and occipital lobe in patients with Parkinson's disease (PD), but decreased in whole cortex in patients with PD and AD. Therefore, this compound is also considered to be used to detect cholinergic neuronal degeneration, but its specificity and sensitivity for the diagnosis of AD need to be determined(52).

Dopaminergic neurons are widely studied in diseases such as PD, schizophrenia and drug abuse. Tracers targeting dopamine transporters, such as 123i-fluoropropyl carboxylmethoxydeoxane (^{123}I-FP-CIT), help to distinguish between PD dementia, Lewy body dementia and AD. Niels advocated for the use of 123I-FP-CIT SPECT as a supplemental diagnostic technique to enhance the identification of prodromal DLB and probable dementia with Lewy Bodies (DLB) in a group of individuals with concurrent mental health symptoms. When DLB patients arrive with nigrostriatal dysfunction, the psychiatric onset is more common than the MCI onset. This suggests the value of extensive clinical phenotyping in memory clinics, which includes psychopathology assessment(53).

Higuchi et al. developed ^{11}C-doxepin a radioligand for H(1) receptors, and positron emission tomography, the cerebral histamine H(1) receptor binding in vivo and assessed it in ten individuals with Alzheimer's disease and eleven normal people (five elderly and six young). The results showed that low signal intensity in the frontal and parietal lobes in patients with AD. More importantly, the expression concentration of the corresponding receptors represented by the signal in specific brain regions is closely related to the severity of the disease(54).

5. Summary and Conclusions

Molecular pathological tracers provide the possibility to accurately quantify brain changes by molecular imaging. The absence of diagnostic criteria to detect AD early is the main obstacle to theranostics in this field. As evidenced by our explanation of the pathophysiology of AD, various brain imaging modalities, and radioactive tracer/fluorescence probes, molecular imaging enhances our understanding of AD by establishing more crucial links between various patient groups throughout the disease. Typically, at least one type of imaging data demonstrates that an AD diagnosis and the exclusion of dementia due to intracranial causes require structural alterations in the brain. Subjective vision is dependent on technology and software and has limitations when used to assess hippo-

campus volume or medial temporal lobe atrophy. In the future, the issues with conventional imaging techniques may be resolved by fusing automatic computer-aided techniques with different tracers or multimodal imaging.

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