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Radiopharmaceuticals for Positron Emission Tomography in Dementia Diagnosis

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ABSTRACT

Positron emission tomography (PET) is a method of nuclear medical imaging which, using molecules traced by the positron radionuclides (radiopharmaceuticals), allows insight into the metabolic processes in the body. Introducing new radiopharmaceuticals, the range of possibilities that PET can offer not only in oncology, but also in cardiology, neurology, and psychiatry was expanded. The aim of this paper is to present the new PET radiopharmaceuticals in dementia diagnostics. Dementia represents an acquired and persistent disorder of intellectual functions with a deficit in at least three of the following intellectual functions: memory, language, visuospatial abilities, personality and behavior, and other cognitive abilities, such as abstract thinking, computing, reasoning, and planning. Radiopharmaceuticals used in research and diagnosis of patients suffering from dementia are divided according to the target they are supposed to visualize into radiopharmaceuticals for: representation of the energetic metabolism of the brain (glucose/hexokinase transport), visualization of the incorrectly configured proteins (β-amyloid plaques, tau, α-synuclein), representation of the neurotransmitter systems, representation of the synaptic density (synaptic vesicle glycoprotein 2A (SV2A) labeled), and representation of the neuroinflammation. Studies with the PET radiopharmaceuticals for the new pathophysiological processes can result in earlier diagnosis and better classification of the neurodegenerative disorders, as well as in choosing appropriate therapeutic procedure for each individual patient and in improved monitoring of the effects of therapy.

Keywords: radiopharamaceuticals, positrom emission tomography, dementia**.**

INTRODUCTION

The methods of nuclear medicine allow insight into numerous aspects of complex brain functions, thus being an important research tool in different branches of neurosciences. In addition, they are also very useful in clinical neurological practice. The contribution of nuclear medicine in these activities is in its ability to translate neurophysiology and neurochemistry into images. Unlike radiological methods that offer an excellent account of morphological details, nuclear medical images show us the function. Through the application of specific radiopharmaceuticals, an insight is acquired about the type of pathophysiological disorder

(qualitative aspect), its localization and progression, as well as the degree of the disorder (qualitative aspect). Functional morphology displayed on scintigrams, together with the quantitative indicators gained through the scintigram computer processing, is helpful in the diagnosing and differentiating dementia from other neurological disorders, tracking the progression of the disease, and objectively assessing the effects of therapy. Radiopharmaceuticals with their distinctive pattern of distribution point to some of the most common diseases of the brain before a clear clinical manifestation and before anatomical changes visible through other methods start to emerge. [1]

Positron emission tomography (PET) is a method of nuclear medical imaging which, using molecules traced by the positron radionuclides (radiopharmaceuticals), allows insight into the metabolic processes in the body. In the beginning, the use of PET was limited to specialized research centers, and, even though the first commercial PET machines appear in the early 1980s, broader clinical application begins only in the 1990s, when the use of ^{18}F - fluorodeoxyglucose (FDG) as a radiopharmaceutical which can show increased metabolism in tumor tissue was recognized. [2] Introducing new radiopharmaceuticals, the range of possibilities that PET can offer not only in oncology, but also in cardiology, neurology, and psychiatry was expanded. The aim of this paper is to present the role of PET in dementia diagnostics.

DEMENTIA

Cognitive changes should be acquired and sufficiently expressed that they interfere with the professional and social life of the patient. There are different types of dementia, and the most common forms are Alzheimer's disease, dementia with Lewy bodies, frontotemporal dementia, vascular dementia, dementia due to hydrocephalus (make up almost 99% of all the syndromes of dementia with neurological etiology). [3] Dementia is a significant cause of disability in older people. In 2011, there were around 35.6 million patients with dementia around the world, and it is estimated that by the year 2030 the number of patients will be around 65.7 million. [4]

PET RADIOPHARMACEUTICALS IN DEMENTIA DIAGNOSIS

Radiopharmaceuticals used in research and diagnosis of patients suffering from dementia are divided according to the target they are supposed to visualize into radiopharmaceuticals for:

(1) representation of the energetic metabolism of the brain (glucose/hexokinase transport)
(2) visualization of the incorrectly configured proteins (β-amyloid plaques, tau, α-synuclein)
(3) representation of the neurotransmitter systems
(4) representation of the synaptic density (synaptic vesicle glycoprotein 2A (SV2A) labeled)
(5) representation of the neuroinflammation

^{18}F-2-Fluoro-2-deoxy-D-glucose

^{18}F - fluorodeoxyglucose (FDG) is a radiopharmaceutical utilized for a number of years first of all in oncology, and also in the PET research of the brain. FDG is a glucose analogue and it is accumulated in tissues where there is increased glucose utilization, thus allowing metabolic visualization. [5] After entering the cell, FDG is phosphorylated by hexokinase, while the resulting deoxyglucose-6-phosphate does not enter further into metabolic reactions and

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remains in the cells long enough for its concentration to be measured.[6] FDG concentration in the brain is a reflection of the local glucose consumption which is closely linked to the function of neurons because it serves as a source of energy for the maintenance of ionic gradients and synthesis of neurotransmitters. Glucose metabolism is especially linked to the synthesis of glutamate and its recycling through neuroglia. Therefore, synaptic dysfunction and neurodegeneration lead to decreased glucose metabolism in the afflicted parts of the brain.

In healthy human subjects at rest, cerebral metabolic rate for glucose – CMRglc is 40-60 μmol glucose / 100g tissue / min for gray matter, and approximately 15 μmol glucose / 100g tissue / min for white matter (figure 1). There are regional variabilities, especially in the phylogenetically older structures, such as the medial temporal cortex and small brain, whose metabolic rates for glucose are lower than average for gray matter, but still higher than for white matter. There is also moderately decreased glucose metabolism related to aging that primarily affects the frontal association cortex.

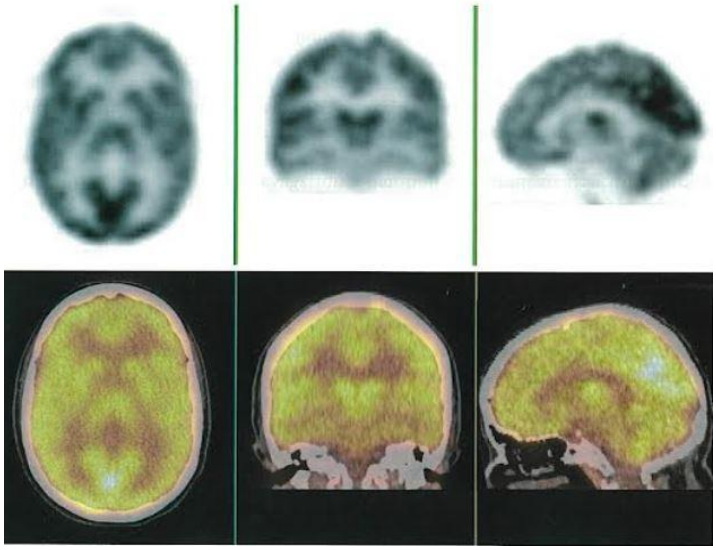

Figure 1: ^{18}FDG PET/CT of the endocranium, physiological distribution FDG. Top line PET scans, bottom line fused PET/CT scans. From the book Nuclear Medicine, Faculty of Medicine, Belgrade 2020.

Since many neurodegenerative disorders, especially in early stages, affect specific areas of the brain, variabilities in FDG distribution represented by the positron emission tomography offer valuable diagnostic data.[7] For more than 20 years, numerous studies have shown that the glucose metabolism and blood flow in patients with AD are decreased in the temporoparietal association cortex, where angular gyrus is primarily affected. Frontal association cortex can also be affected, but this finding is changeable and usually present only in progression of AD. Unlike other types of dementia, glucose metabolism is maintained in the basal ganglia, primary motor and visual cortex and small brain, which allows for the differentiation of these diseases based on PET findings (figure 2). [8] It is interesting to note that, despite of the prominent atrophy of the hippocampus and parahippocampal structures, which are the main finding in the structural representation of the brain of the patient with AD, in most cases there is no significant decrease of the local metabolic rate for glucose. The reason for that is that the hippocampus has a decreased basal metabolism at rest compared to the neocortex, due to

which, in visual analyses, changes are difficult to notice. However, the correlation with the MRI images and the standardized region of interest on PET images, has enabled the determination of hypometabolism in the hippocampus, especially in the entorhinal cortex.

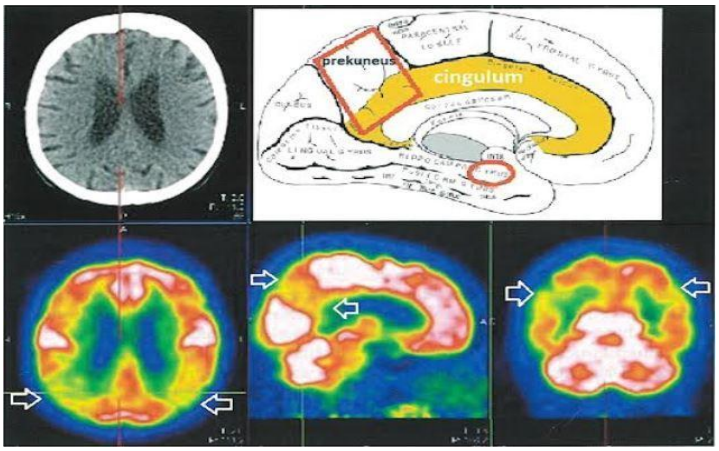

Figure 2: ^{18}FDG PET/CT in patients with Alzheimer's disease; on transverse (bottom left) and coronal plane (bottom right) weakened FDG accumulation is detected in the cortex of lateral parts of the parietal lobes, and on sagittal plane through the mesial cortex of the right parietal lobe (bottom center) weakened FDG accumulation in the precuneus and posterior cingulate cortex. From the book Nuclear Medicine, Faculty of Medicine, Belgrade 2020.

Differences between typically affected and unaffected regions of the brain are less prominent in patients with the late onset of AD (where disease begins after age 65), which is the majority of patients [9], reducing diagnostic accuracy in FDG-PET utilization. This probably reflects the fact that in old age there is a multifactorial brain damage by ischemia, for instance, that impacts regions typically affected by AD. That is why sensitivity of FDG-PET in diagnosing AD is 90-95%, while specificity is only 65-75%. [10]

In the last few years, the concept of "mild cognitive impairment" (MCI) has started to appear, which describes patients with memory impairments similar to those with AD, but without other clinical criteria needed to make the diagnosis. There has been more and more research that shows that FDG-PET has a significantly better prognostic value for conversion of MCI to AD than clinical criteria. Hence, Herholz et al. showed that in 60-70% of patients with mild or severe hypometabolism of the association cortex progress toward clinical dementia within 2 years, while the same happens in 10-20% of patients without such changes. [7]

A growing recognition has been given to the detection of AD with the aid of FDG-PET in the stage where mild cognitive deficits begin to appear in patients, but before the clinical picture of dementia. This is especially significant in patients with high levels of premorbid cognitive functioning, where a significant decrease in cognitive functions can happen before they reach the lower limit of what is considered normal work according to the standard neuropsychological tests. In patients with high familial risk of developing AD due to the homozygous apolipoprotein E ε4 (ApoE ε4), metabolic changes are visible in the asymptomatic stage decades before the probable onset of the disease. [10] However, it should be kept in mind that some patients can have hypometabolism visible by PET in regions typical for AD even without clinical or histopathological signs of a neurodegenerative disease. Negative FDG-PET

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finding, therefore, offers a high level of certainty about the absence of the disease, but a positive finding doesn't necessarily point to the forthcoming disease. [11]

In frontotemporal dementia (FTD), hypometabolism is prominent in the frontal cortex, especially in the medial frontal cortex. Frontolateral and anterior temporal cortex also show prominent hypometabolism. Distribution of metabolic changes can be highly asymmetrical. Regional distribution of these changes in most patients allows for the differentiation between FTD and AD with the specificity and sensitivity above 85%. [8]

Dementia with Lewy bodies (DLB) often shows a pattern of hypometabolism similar to AD, but with the inclusion of the primary visual cortex, which in AD is mainly spared. (10) Diagnostic value of this finding is, however, questionable, due to the extreme variability of the metabolic activity in the visual cortex, depending on the conditions of the examination (closed or open eyes) (figure 3). [8]

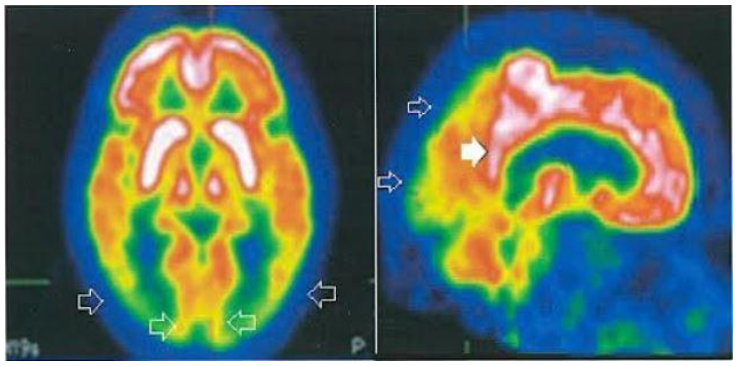

Figure 3: ^{18}FDG PET of the brain of a person with DLB. Transparent arrows mark hypometabolic occipital (optical cortex) and parietal areas, and filled arrow marks preserved metabolism in the posterior cingulate cortex. From the book Nuclear Medicine, Faculty of Medicine, Belgrade 2020.

Vascular dementia (VaD) is a particular diagnostic issue due to a lack of consensus about the clinical criteria for the diagnosis. Additional issue is a lack of representative facts on FDG-PET images. Still, it has been suggested that a typical finding for VaD is a global decrease of the cerebral glucose metabolism. This brings about a possibility to differentiate between AD and VaD based on the hypometabolism in association areas of the cortex, basal ganglia and small brain, which is a typical finding for AD, but not for VaD. [7] FDG-PET utilization in assessing patients with dementia allows for a greater diagnostic accuracy and earlier start of treatment, better planning of future care, as well as reduced uncertainty and anticipation for patients and their families. Additional advantage is a possibility to differentiate between AD and other neurodegenerative diseases in the initial clinical processes. Therefore, FDG-PET represents an efficient and secure method in diagnostic evaluation of patients with progressive cognitive impairment. [12]

Representation of the Amyloid Plaques

^{11}C-Pittsburgh Compound-B:

^{11}C-Pittsburgh Compound-B (PiB) is an analog of thioflavin - ^{11}C. PiB is the first radiopharmaceutical which enables a selective representation of amyloid β (Aβ) *in vivo*.

Numerous studies have shown high PiB sensitivity in binding to amyloid plaques and vascular amyloid *in vivo*, which is typical for amyloid, and does not bind to neurofibrillary tangles. [8] There are significant differences in topography of PiB accumulation between patients with AD and healthy controls. PiB in patients with AD is the most prominently accumulated in the association cortex, and less in white matter. PiB binding is the most prominent in the frontal cortex, next are temporal (especially lateral) and parietal cortex, parts of occipital cortex and striatum. This pattern of accumulation corresponds to the postmortal findings of amyloid plaques in patients.

In healthy controls, PiB accumulation in the cortex is very low or nonexistent, and the relative accumulation is the most prominent in the white matter. There is no difference in absolute values of PiB accumulation in the white matter between ill and healthy subjects. [13]

In the comparative study of patients with AD and FTD, using PiB and FDG, it is determined that the PiB and FDG-PET findings are for the most part in accordance, but not in all the cases (in the cited research 13/17). This result is not expected because FDG reflects topographic distribution of metabolic changes, while PiB points to fundamental pathological changes. It is also determined that the reliability in the interpretation of results by multiple examiners is higher for PiB than for FDG. This shows that in the population of patients with dementia there is a visual interpretation of PiB-PET that is highly reproducible, compared to the FDG-PET which occasionally relies on interpretations of unclear samples of distribution (figure 4). [14] Forsberg et al. did research on PiB utilization in patients with MCI. In that research, it was found that the PiB accumulation in patients with MCI is higher than in healthy controls, but lower than in patients with AD, where in 11/21 patients measured PiB accumulation was comparable to the patients suffering from AD, and in 7/21 patients they found significantly elevated values. In MCI patients with significantly elevated PiB retention, the condition converted to AD within the period of two years until the next check up. [15]

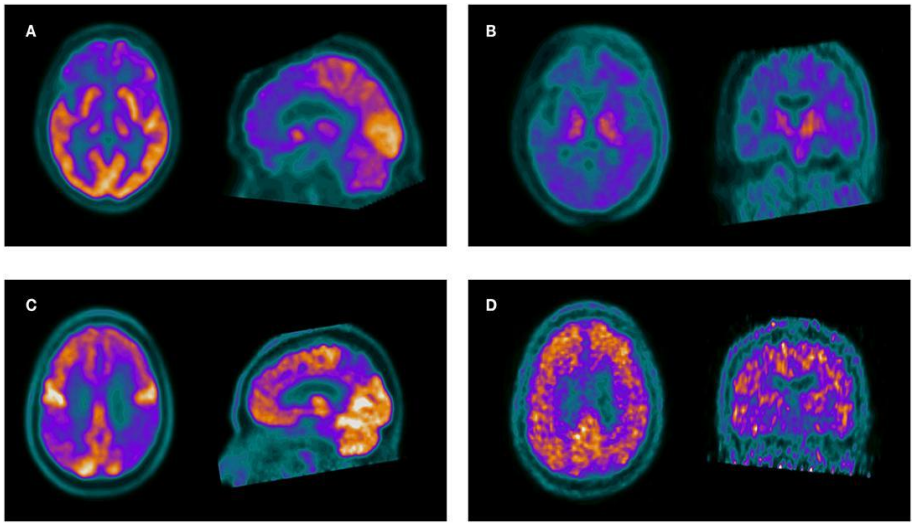

Figure 4: ^{18}FDG PET in the axial and sagittal plane (A) shows frontal hypometabolism which is suggested on FTD. ^{11}C-PIB PET in the axial and coronal plane (B) are negative to the amyloid accumulation, which is confirmed by FTD. ^{18}FDG PET (C) shows hypometabolism in the posterior parietal lobe and precuneus which points to AD. ^{11}C-PIB PET (D) confirms AD. From the Front. Neurol., 04 May 2021 | https://doi.org/10.3389/fneur.2021.630958

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One of the critiques related to the representation of amyloid plaques by PiB-PET is that PiB doesn't show progressive accumulation in the pathological changes in the brain of patients with AD as it is described in pathological studies. Thus, for instance, the pattern of PiB accumulation in patients with MCI is either negative, that is similar to controls, or positive (i.e. similar to patients suffering from AD). In addition, PiB binding in the precuneus is the highest of all the cortical regions, however, obduction findings don't show significantly higher amyloid accumulation in this region compared to other cortical areas. ^{11}C-PiB differentiates patients with AD, patients with mild cognitive deficit and healthy controls better than ^{18}F-FDDNP, but it is limited by its short half-life of 20 min due to which it can only be utilized in centers with cyclotron. [16]

Florbetapir and ^{18}F-FDDNP:

Florbetapir and 2-(1-{6-[(2-[fluor-18]fluoroethyl)(methyl)amino]-2-naphthyl}-ethylidene) malononitrile, ^{18}F-FDDNP (FDDNP) are two recent radiopharmaceuticals also used for the representation of amyloid plaques in patients with AD.

Florbetapir labeled by fluorine-18 has been proved as a radiopharmaceutical that offers results comparable to those gained through PiB utilization. In addition, half-life of ^{18}F (110 minutes) is significantly longer than the half-life of ^{11}C (~20 minutes), which makes florbetapir a much more suitable radiopharmaceutical to use outside of the context of research, when cyclotron is not immediately available (figure 5). [17]

2-(1-{6-[(2-[fluor-18]fluoroethyl)(methyl)amino]-2-naphthyl}-ethylidene) malononitrile (FDDNP) is the only currently available radiopharmaceutical which, in addition to binding to Aβ, allows for the representation of neurofibrillary tangles in patients with AD, and the only one that allows for the representation of the pathological changes in hippocampus, area which is afflicted by the pathological changes among the first. In a comparative study of two radiopharmaceuticals (PiB and FDDNP) on the same group of patients with AD, PiB binding is constantly low, and FDDNP binding is high in the medial temporal cortex, while the simultaneous accumulation of both PiB and FDDNP is significantly elevated in the neocortex of patients with AD compared to healthy controls. One of the flaws which is often mentioned in FDDNP is a small difference in the signal from the cortex between controls and AD patients. In vivo difference in FDDNP binding in some parts of the neocortex between controls and AD is significantly lower (approximately 10-15%) than between those in PiB-PET (which is around 80%), when the small brain is used as a reference value. If, on the other hand, adjacent white matter is used as a reference, this difference is reduced to 25-30% for PiB and 10-15% for FDDNP. It should also be noted that the difference in FDDNP binding in the medial temporal cortex (where the earliest pathological changes appear in patients with AD) between controls and patients with AD is significantly higher (~ 30%) compared to PiB (~ 5%). It was considered that, unlike PiB, FDDNP-PET shows an increase in cortical affliction by the pathological changes following the progression of the disease. Even though this could potentially make the quantification of data gained by the FDDNP-PET more difficult, if the aim is the group differentiation (i.e. controls compared to AD patients), it still shows the progression of the pathology in AD better. [16]

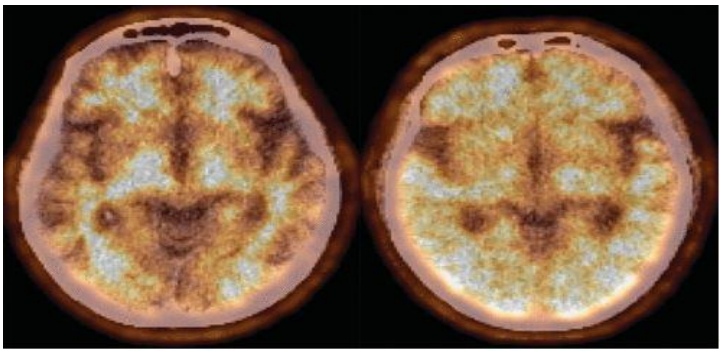

Figure 5: Normal finding for the florbetapir accumulation (left) and abnormal accumulation (right) with binding for both white and gray matter with the loss of contrast between white and gray matter in the representation of amyloid. From Citation: American Journal of Roentgenology. 2018;211: 246-259. 10.2214/AJR.18.19822

^{18}F-flutemetamol:

^{18}F-flutemetamol (FMM) is a ^{18}F- PiB derivative which, due to its longer half-life, is imposed as a more economical and practical alternative to that radiopharmaceutical.

Hatashita et al. showed that FMM-PET differentiates patients with AD and older healthy controls with the sensitivity of 97,2% and specificity of 85,3%, while in younger healthy controls specificity increases to a 100%. They note that FMM retention in the white matter was higher than PiB retention, even though binding varied depending on the subject. They conclude that FMM as a Aβ biomarker can identify preclinical AD and that it offers images comparable to those gained through PiB-PET, without the limitation of the short half-life. [18]

Landau et al. compared FMM and PiB concluding that there is a high correlation in findings gained with these radiopharmaceuticals, and confirmed that FMM retention in the white matter is higher than PiB retention. [19]

Curtis et al. did research on the FMM-PET utilization in terminally ill patients concluding that the interpretation of findings allows for in vivo Aβ detection in the brain with high specificity and sensitivity, as well as high accordance of examiners in interpretation. They conclude that, in the population of terminally ill patients with a wide span of Aβ deposit in the brain, FMM is a secure radiopharmaceutical which offers high specificity and sensitivity. [20]

Representation of the Neurotransmitter Systems

Alzheimer's disease also affects the neurotransmitter systems, primarily the cholinergic, noradrenergic and serotonergic nerve endings in the cerebral cortex. In Parkinson's disease (PD) and related dementia, the dopaminergic system is also affected. Even though impact of these systems to the symptomatology of the disease in people has not been thoroughly examined, there are indications that the affliction of these ascendant projections affects the formation of the pathological protein deposits such as amyloid plaques. [8] Research in this area is still in its inception, but it has the potential to offer a better understanding of the origin of these diseases and monitoring of the response to the treatment, perhaps even development of the target treatment.

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Cholinergic System:

Cholinergic neurotransmission is an important process to understand memory and cognitive functions. If a cholinergic antagonist, such as the medicine scopolamine, is given to an experimental animal or to volunteers, the memory function will be temporarily and conspicuously damaged showing symptoms similar to AD. [21] On the other hand, medicines that block the acetylcholine breakdown can occasionally improve the memory function in patients in the early stage of AD. [22, 23, 24]

Cholinergic deficits are also noticed in several disorders related to cognitive impairment. [25] Reduced acetylcholine synthesis or the loss of cholinergic neurons can also be the primary cause of the disease, or can be instigated by the accumulation of the incorrectly configured proteins and be the secondary phenomenon in the disease process. Based on the MRI brain examination, the loss of cholinergic neurons in the frontobasal brain area is considered an early AD indicator. [26] Although the cholinergic system plays a significant part in cognitive functions, the cholinergic deficit can also impact many other functions of the human brain where deficit appears. [27]

The cholinergic system attracted the most interest by the researchers when it is related to AD. Several different radiopharmaceuticals have been used to represent different parts of this system, including ^{11}C-MP4A (acetylcholinesterase activity), ^{11}C-nicotine and ^{18}F-A85380 (for nicotine receptors) and ^{11}C-NMPB and ^{18}F-FP-TZTP (for muscarinic receptors). Studies have shown decreased cortical cholinergic activity in patients with AD, especially in the temporal cortex. In addition, these are the radiopharmaceuticals used to monitor the response to therapy with medicines such as donepezil, rivastigmine and galantamine, which aim at inhibiting the function of acetylcholinesterase. [28]

Radioligands for vesicular acetylcholine transporters can also be used to show the loss of cholinergic nerve endings, since the vesicular acetylcholine transporter protein (vAChT) is expressed only on neurons. PET studies of the cerebral VAChT are done by applying the (-)-5-(^{18}F)fluoroethoxybenzovesamicol (FEOBV). This radiopharmaceutical shows the regional distribution in the brain which corresponds to the known distribution of the cholinergic endings. [31] In the comparative research of the PET tracers (FEOBV (za vAChT), ^{18}F NAV4694 (for β-amyloid) and ^{18}FFDG for glucose metabolism), ^{18}F FEOBV showed the highest sensitivity in differentiating AD patients from healthy controls. [30] Even though the FEOBV results are promising, the shortcoming of this agent is its slow kinetics in basal ganglia, which can lead to a long duration of imaging, or protocols where imaging is done after a longer period of time. [29]

Dopaminergic System:

Dopamine neurotransmitter is not only involved in the processes of motor control, motivation and addiction, but in the cognitive processes, as well. ^{18}F-fluorodopa can be used to show functional integrity of the dopaminergic system. [30] Another way for the quantitative representation of the loss of the dopaminergic neurons is PET with a radioligand for the dopamine transporter (DAT). [31] Deficit in the dopamine synthesis similar to that in Parkinson's disease (PD) was found in DLT, even in the studies where parkinsonism has not yet been expressed. The presynaptic dopaminergic function imaging can be used to differentiate AD from DLT. Regional hypometabolism (similar to that in AD) combined with the reduced

availability of the striatal DAT goes in favor of the potential DLT diagnosis. Decreased ^{18}F-fluorodopa uptake by the putamen in DLT can be used to differentiate DLT from AD. [32] In patients with FTD, the loss of the dopaminergic nigrostriatal neurons (quantified by PET and ^{11}C-CFT) are monitored, and they point to potential correlation with the numerous extrapyramidal symptoms, especially rigidity and akinesis. [33] However, in patients with AD ^{18}F-fluorodopa uptake by the striatum is not significantly reduced, indicating that the extrapyramidal symptoms in AD and PD (or FTD) can derive from other neurochemical bases. [34] PD is correlated to the significant reduction in ^{18}F-fluorodopa uptake by the striatum, but the size of reduction in patients with PD with or without dementia is not significantly different. [35]

Radiopharmaceutical in the Representation of the Synaptic Density

Synaptic vesicle glycoprotein 2A (SV2A) appears in the brain and is involved in the transmission of the neural impulses. Several neurodegenerative and neuropsychiatric disorders are related to the loss of synaptic density in some areas of the brain. Significant synaptic loss is described in AD, PD and major depression. The scope of these losses is linked to the degree of cognitive impairment in AD and the degree of depression in major depression. [36, 37, 38]. Until recently, we were able to quantify synaptic density only post mortem. Levetiracetam derivatives labeled by the positron emitters have been developed with the aim to enable measuring of the SV2A availability in patients by the application of PET. Reduced SV2A availability is expected in the synaptic loss, albeit changed binding of the tracer can (in theory) also reflect changed affinity of the protein for the radioligand, or changed competition of the endogenous substances with the tracer for a limited number of binding sites. PET of the synaptic density can enable quantification of the reduced neuronal correlation in human pathology, and examination of the impact that therapy has on the progression of these losses. [39]

Radiopharmaceutical in the Representation of the Neuroinflammation

Neurodegenerative diseases are not only related to the accumulation of the incorrectly configured proteins, but also to the neuroinflammation. [40]

Significance of the inflammatory processes in the brain is subject to a serious discussion: some believe it is one of the disease-causing factors, while others think that it is a secondary phenomenon necessary for neuron and neuronal processes protection, as well as for active removal of cell debris. Anti inflammatory agents have been, therefore, suggested as a therapeutic means that can slow down the progression and postpone the onset of AD. [41]

Astrogliosis and microgliosis show a linear increase during the progression of AD, which corresponds more to the accumulation of the neurofibrillary tangles than of the amyloid plaques. More radiopharmaceuticals in the brain have been taken into account as an indirect measure of neuroinflammation that can be applied for PET, but they are mainly in the experimental and preclinical stages. [42]

The most effort in the representation of the neuroinflammation and neurodegenerative diseases has been done by radioligand binding to translocator protein (known as TSPO or peripheral benzodiazepine receptor). Research interest for TSPO is a consequence of the fact

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that it is highly expressed in activated microglia compared to the same one at rest, as well as to the lower degree in activated atrocities. [43]

The first successful PET radiopharmaceutical for TSPO was ^{11}C-PK11195. Considering its shortcomings (short half-life), another group of radiopharmaceuticals has been developed that are mainly labeled by fluorine, but are under a strong influence of the rs6971 polymorphism. [44] The third generation of the TSPO radiopharmaceuticals has been developed with the aim to reduce the influence of this gene polymorphism. One of these new radiopharmaceuticals is GE180 (known as flutriciclamide), but its specific signal is much lower than that of ^{11}C-PBR28, a radiopharmaceutical of the second generation. ^{11}C-ER176 binding is enough for the microglia visualization even in humans with a low genotype activity. [45] Since it has good characteristics for imaging, better than ^{11}C-PBR128, it is a promising agent for further research. Even though many radiopharmaceuticals as biomarkers of neuroinflammation have been developed, most of them did not pass the preclinical and first examinations on humans.

CONCLUSION

Significant advancement has been achieved in the medical imaging of the brain in the past 15 years. FDG/PET utilization for the quantification of the regional glucose metabolism in the brain has proven to be exceptionally justified in dementia examination. Three radiopharmaceuticals for β-amiloide plaques have been approved by the Food and Drug Administration (American drug agency) and the European Medicines Agency (European medical agency). Several radiopharmaceuticals for tau neurofibrillary tangles are already being applied in clinical research. Many new agents are in the preclinical or experimental stages of development, which speaks in favor of the assumption that in the future further improvement in the clinical application of PET can be expected. Studies with the established PET radiopharmaceuticals for the new pathophysiological processes can result in earlier diagnosis and better classification of the neurodegenerative disorders, as well as in choosing appropriate therapeutic procedure for each individual patient and in improved monitoring of the effects of therapy.

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