Tracking the Humoral and Cellular Components of Neuroinflammation

Subjects: Anatomy & Morphology

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Positron emission tomography (PET) is an imaging technique that uses the radioactive decay of specifically designed radiotracers. In PET imaging, the annihilation of two photons that are produced back-to-back after positron emission from the radiotracer is measured by a technique called coincidence detection. After amplifying the signal, reconstruction algorithms are used to generate the image. One of the most commonly used diagnostic radiotracers in patients with neurodegenerative disorders (PwND) is [^{18}F]-fluorodeoxyglucose, which serves as a surrogate marker of glucose metabolism.

Keywords: PET imaging ; stress ; adenosine

1. Introduction

Positron emission tomography (PET) imaging has been extensively used in several movement disorders, including PD [1] and atypical parkinsonism [2][3]. Within the scope of neuroinflammation, PET imaging has been used for detecting microglia and astrocyte activation [4], the expression levels of adenosine receptors [5], as well as other neuroinflammatory molecules [6], but also oxidative stress and mitochondrial dysfunction [7]. Even though the current understanding of neuroinflammation underlines its complexity, PET imaging can help to disentangle specific components of the neuroimmunological response [6]. One of the most commonly applied PET radiotracers in studying neuroinflammation is targeting the mitochondrial translocator protein (TSPO). However, other potential molecular targets for PET radiotracer development have been identified, including monoamine oxidase type B (MAO-B), cannabinoid receptor type 1/2 (CB1-/CB2-R), and phosphodiesterase type 4 [8]. In addition, the cellular components of neuroinflammation have been investigated using radiotracers targeted against cyclooxygenase (COX, as a marker of resting microglia), thrombospondin, COX type 2, and P2X purinoreceptor 7 (P2XR7, as a marker of activated microglia). In addition, TSPO and MAO-B have also been considered proxies for astrocyte activation [6]. The development of new molecule-specific radiotracers is a highly dynamic field of research. For example, new radiotracers have been developed targeting glycogen synthase kinase 3 (GSK-3), phospholipase A2/arachidonic acid pathway, sphingosine-1-phosphate receptor-1, the chemokine receptor CX3CR1, additional purinoreceptors, receptors for advanced glycation end products, proto-oncogene tyrosine-protein kinase MER (MERTK), and triggering receptor expressed on myeloid cells-1 (TREM-1) [9][10]. Many of these molecular targets recapitulate unique features of neuroinflammation.

2. The Mitochondrial Translocator protein in the Context of Mapping Neuroinflammation

TSPO is an 18 kDa protein mainly localized in the outer mitochondrial membrane [11]. The overall concentration of TSPO in mammalian brains is low, but under neuroinflammatory conditions, i.e., following glial activation, the expression of TSPO is greatly enhanced [12]. TSPO is thought to be involved in many cellular pathways, including neurosteroid synthesis, apoptosis signaling, mitochondrial bioenergetics, and ROS processing [13]. However, the precise role of TSPO is still under investigation [8]. Even though TSPO has been recognized as a marker of astrocyte activation, it is also expressed in microglia, vascular endothelial cells, neurons, and immune cells [8]. Several radiotracers have been developed for detecting TSPO expression. These TSPO-targeted radiotracers can be classified into first- and second-generation radiotracers according to their improved pharmacodynamics and overall sensitivity to detect neuroinflammatory changes in brain parenchyma [9].

[^{11}C]-PK11195 is a first-generation TSPO-radiotracer which has been most widely used in studies investigating neuroinflammation in PwND [14]. Despite the limitations of [^{11}C]-PK11195, including poor BBB permeability, non-specific binding, and a relatively low signal-to-noise ratio, it has given valuable insights into PD [9]. In a recent meta-analysis, nine

studies using [^{11}C]-PK11195 in PwPD have been identified [12]. Here, PwPD had significantly higher TSPO levels than HCs in several brain regions, including the midbrain, basal ganglia, cerebellum, thalamus, hippocampus, and cortical areas. Interestingly, the most significant effect was observed in the temporal lobe of PwPD [12]. However, the authors stressed the heterogeneity observed in several neuroanatomical regions [12].

In the same meta-analysis, the authors also included five studies employing second-generation TSPO radiotracers ([^{18}F]-FEPPA, [^{11}C]-DPA713, [^{11}C]-PBR28, [^{11}C]-DPA714) [12].

Here, a pooled analysis revealed significantly higher TSPO levels in the midbrain of PwPD compared to HCs. In contrast to the previously reported results on first-generation TSPO radiotracers, other neuroanatomical regions no longer exhibited relevant group differences [12].

The consistent TSPO overexpression in the midbrain of PwPD is well in-line with our understanding of a predominant DAergic neuronal loss in the SN. Here, TSPO-targeted PET imaging already demonstrated the potential involvement of neuroinflammation in PD pathophysiology [12]; however, TSPO-targeted PET imaging faces several challenges. Even though often considered a proxy of astrocyte activation, TSPO-targeted radiotracers lack cellular specificity. In addition, microglial activation can be beneficial or detrimental in the fine-tuned regulation of neuroinflammation, mainly due to the involved microglia subtype [9]. Besides the improvements of first-generation TSPO radiotracers' drawbacks, the widespread application of these tracers has also been limited by several factors, e.g., the presence of genetically-encoded TSPO polymorphism that can affect radiotracer-binding [15]. Interestingly, TSPO tracers have shown the potential as a treatment response marker [16].

3. The Involvement of Astrocytes in Neuroinflammation: The Potential Role of Monoaminoxidase B and Imidazoline-2 Binding Sites in Radiotracer Development

In general, activated astrocytes and microglia have been observed in many PwND [17]. The involvement of astrocytes in PD is undisputed [18]. Post-mortem studies have shown cytoplasmatic alpha-synuclein (aSyn) inclusions also aggregate in astrocytes [19]. Astrocytes either react or contribute to neurodegenerative processes by changing morphology and secreting proinflammatory cytokines, similar to microglia [17][20].

Astrocytes express high levels of MAO-B. Thus, this molecule has been proposed as a neuroimaging biomarker of astrogliosis. Post-mortem studies have further demonstrated that MAO-B levels are elevated in the frontal cortex of post-mortem PwPD but not in the SN [21]. MAO-B-targeted radiotracers have already been used in PwPD and other ND [22], with [^{18}F]-THK5351 being the first. Originally, [^{18}F]-THK5351 was designed to detect tau aggregates. However, [^{18}F]-THK5351 showed higher binding affinities to MAO-B [17]. In a comparative study, [^{18}F]-THK5351 was applied to differentiate PwPD from patients with progressive supranuclear palsy (PwPSP) and the cerebellar type of multiple systems atrophy (PwMSAc). Here, diencephalic and midbrain [^{18}F]-THK5351 uptake differentiated PwPD from PwPSP. In contrast, pontine and cerebellar uptake of [^{18}F]-THK5351 appeared specific for PwMSAc [23]. Even though there is strong evidence for the interconnected nature of MAO-B activity and mitochondrial dysfunction, there is a significant lack of [^{18}F]-THK5351 studies in PwPD [24]. Considering that the role of MAO-B inhibition is part of the therapeutic arsenal in PwPD, this observation is even more surprising [24]. This also extends to more advanced MAO-B-targeted radiotracers ([^{11}C]-l-deprenyl-D2, [^{11}C]SL25.1188, and [^{18}F]-SMBT-1), where no studies in PwPD were found (Supplementary Tables S1 and S2).

The imidazoline-2 binding sites (I2BS) are located on the cell membrane of astrocytes and are expressed in the cortex, hippocampus, basal ganglia, and brainstem, making them suitable targets for studying PwPD [19]. One study in 22 PwPD and 14 HCs used [^{11}C]-BU99008 as a highly selective I2BS radiotracer [19]. Here, early-stage PwPD exhibited increased [^{11}C]-BU99008 uptake in the frontal, temporal, parietal, and occipital cortex. However, a higher [^{11}C]-BU99008 uptake was seen in the brainstem of PwPD compared to HCs [19]. On the other hand, late-stage PwPD showed a comparable [^{11}C]-BU99008 uptake pattern, but also in the insula, the basal ganglia, the thalamus, and the brainstem [19]. The authors observed that [^{11}C]-BU99008 radiotracer uptake correlated with motor and non-motor symptom severity [19]. These results encourage the use of new radiotracers tracking astrocytosis. However, more research is needed to elucidate further and replicate the above-stated findings longitudinally in larger cohorts [4].

4. The Endocannabinoid System in Neuroinflammation: Opportunities for Neuroimaging Theranostics

Recent studies have highlighted the endocannabinoid system as a relevant regulator in the CNS, including processes such as neuroinflammation and neurogenesis [25]. Different cannabinoid receptors are known. However, the cannabinoid receptor type 2 (CB2-R) has been previously implicated in neuroinflammation [10]. Rodent microglia express CB2-R under normal conditions. The initiation of neuroinflammatory treatments produces a marked CB2-R upregulation in rodents [10]. Studies in PwPD also reveal increased CB2-R levels in SN microglia, corroborating these preclinical findings [26]. Despite the potential role of CB2-R in PwPD, no studies have been found exploring CB2-R-targeted radiotracers in PwPD. This exciting approach may also extend to the cannabinoid receptor type 1 (CB1-R) being highly expressed in the basal ganglia, making it interesting to study the pathophysiology of PD [27]. The radiotracer [^{18}F]-FMPEP-d_2 has been applied to map CB1-R distribution in vivo [27]. This approach has also been evaluated by the use of [^{18}F]-MK-9470 in a 6-hydroxydopamine (6-OHDA) animal model [28] and also in PwPD using the same radiotracer [29]. In summary, these studies have shown decreased subcortical CB1-R availability, but the biological underpinnings of these findings require further research. Current interpretations include the role of CB1-R in coping with oxidative stress and neuroinflammatory excitotoxicity. Thus, further research is necessary to evaluate the role of CB1-R as a specific target to reduce neuroinflammation [28].

5. Propagating Neuroinflammation: The Role of Adenosine Receptors in Precision Imaging

Adenosine receptors are purinergic G-protein coupled receptors broadly expressed in the peripheral and central nervous system (CNS) [30]. In the case of neuroinflammatory processes, neurons and glial cells can release adenosine, which can confer local effects through purinergic receptors leading to the secretion of pro-inflammatory cytokines, activation, and migration of microglia, and alterations in astrocyte function [31]. A2A receptors are highly expressed on neuronal surfaces in the striatum [32]. Several studies have used PET radiotracers targeting these receptors in animal models [33] and humans [34][35][36][37][38]. Even though studies have pointed toward the involvement of adenosine signaling in neuroinflammation, conclusive evidence in humans is scarce as the main use of A2A receptor-targeted radiotracers has been within the scope of their colocalization to D2 receptors [30].

6. Novel Radiotracers on the Brink of Mapping Neuroinflammation

Despite the (pre-)clinical availability of highly specific radiotracers, studies in PwPD on humoral and cellular aspects of neuroinflammation are still generally rare. For example, the role of GSK-3 beta has been implicated in the pathophysiology of PwPD and is considered a potential treatment target [39]. Albeit, GSK-3-specific radiotracers have not yet been evaluated in PwPD. Another example includes COX-2-targeted radiotracers, assessed in PwND but not PwPD [40]. Even if arachidonic acid has been considered a central part of the neuroinflammatory cascade in PwPD, including the synthesis of prostaglandins and leukotrienes, and 1-[^{11}C]-arachidonic acid can be considered a promising radiotracer [41], no studies in PwPD have been performed so far. Sphingosine-1-phosphate receptor 1 is a G protein-coupled receptor that is highly overexpressed during the neuroinflammatory response, and [^{11}C]-TZ3321 is a specific tracer for this molecule. However, only one short report in nonhuman primates as a PD animal model was found [42]. In addition, no studies using TMERK- or TREM1-specific radiotracers in PD research were found. This opens up exciting opportunities for evaluating these new or unused radiotracers, which could complement our current understanding of the complex role of neuroinflammation in PwPD.

References

1. Pagano, G.; Niccolini, F.; Politis, M. Imaging in Parkinson;s disease. Clin. Med. 2016, 16, 371–375.
2. Jin, J.; Su, D.; Zhang, J.; Li, X.; Feng, T. Tau PET imaging in progressive supranuclear palsy: A systematic review and meta-analysis. J. Neurol. 2023, 270, 2451–2467.
3. Xu, Z.; Arbizu, J.; Pavese, N. PET Molecular Imaging in Atypical Parkinsonism. Int. Rev. Neurobiol. 2018, 142, 3–36.
4. Liu, Y.; Jiang, H.; Qin, X.; Tian, M.; Zhang, H. PET imaging of reactive astrocytes in neurological disorders. Eur. J. Nucl. Med. Mol. Imaging 2022, 49, 1275–1287.
5. Li, J.; Hong, X.; Li, G.; Conti, P.S.; Zhang, X.; Chen, K. PET Imaging of Adenosine Receptors in Diseases. Curr. Top. Med. Chem. 2019, 19, 1445–1463.

6. Kreisl, W.C.; Kim, M.J.; Coughlin, J.M.; Henter, I.D.; Owen, D.R.; Innis, R.B. PET imaging of neuroinflammation in neurological disorders. Lancet Neurol. 2020, 19, 940–950.
7. Ikawa, M.; Okazawa, H.; Nakamoto, Y.; Yoneda, M. PET Imaging for Oxidative Stress in Neurodegenerative Disorders Associated with Mitochondrial Dysfunction. Antioxidants 2020, 9, 861.
8. Masdeu, J.C.; Pascual, B.; Fujita, M. Imaging Neuroinflammation in Neurodegenerative Disorders. J. Nucl. Med. 2022, 63, 45S–52S.
9. Jain, P.; Chaney, A.M.; Carlson, M.L.; Jackson, I.M.; Rao, A.; James, M.L. Neuroinflammation PET Imaging: Current Opinion and Future Directions. J. Nucl. Med. 2020, 61, 1107–1112.
10. Narayanaswami, V.; Dahl, K.; Bernard-Gauthier, V.; Josephson, L.; Cumming, P.; Vasdev, N. Emerging PET Radiotracers and Targets for Imaging of Neuroinflammation in Neurodegenerative Diseases: Outlook Beyond TSPO. Mol. Imaging 2018, 17, 1536012118792317.
11. Zhang, L.; Hu, K.; Shao, T.; Hou, L.; Zhang, S.; Ye, W.; Josephson, L.; Meyer, J.H.; Zhang, M.R.; Vasdev, N.; et al. Recent developments on PET radiotracers for TSPO and their applications in neuroimaging. Acta Pharm. Sin. B 2021, 11, 373–393.
12. Zhang, P.F.; Gao, F. Neuroinflammation in Parkinson's disease: A meta-analysis of PET imaging studies. J. Neurol. 2022, 269, 2304–2314.
13. Santoro, A.; Mattace Raso, G.; Taliani, S.; Da Pozzo, E.; Simorini, F.; Costa, B.; Martini, C.; Laneri, S.; Sacchi, A.; Cosimelli, B.; et al. TSPO-ligands prevent oxidative damage and inflammatory response in C6 glioma cells by neurosteroid synthesis. Eur. J. Pharm. Sci. 2016, 88, 124–131.
14. Werry, E.L.; Bright, F.M.; Piguet, O.; Ittner, L.M.; Halliday, G.M.; Hodges, J.R.; Kiernan, M.C.; Loy, C.T.; Kril, J.J.; Kassiou, M. Recent Developments in TSPO PET Imaging as A Biomarker of Neuroinflammation in Neurodegenerative Disorders. Int. J. Mol. Sci. 2019, 20, 3161.
15. Alam, M.M.; Lee, J.; Lee, S.Y. Recent Progress in the Development of TSPO PET Ligands for Neuroinflammation Imaging in Neurological Diseases. Nucl. Med. Mol. Imaging 2017, 51, 283–296.
16. Jucaite, A.; Svenningsson, P.; Rinne, J.O.; Cselenyi, Z.; Varnas, K.; Johnstrom, P.; Amini, N.; Kirjavainen, A.; Helin, S.; Minkwitz, M.; et al. Effect of the myeloperoxidase inhibitor AZD3241 on microglia: A PET study in Parkinson's disease. Brain 2015, 138, 2687–2700.
17. Harada, R.; Furumoto, S.; Kudo, Y.; Yanai, K.; Villemagne, V.L.; Okamura, N. Imaging of Reactive Astrogliosis by Positron Emission Tomography. Front. Neurosci. 2022, 16, 807435.
18. Miyazaki, I.; Asanuma, M. Neuron-Astrocyte Interactions in Parkinson's Disease. Cells 2020, 9, 2623.
19. Wilson, H.; Dervenoulas, G.; Pagano, G.; Tyacke, R.J.; Polychronis, S.; Myers, J.; Gunn, R.N.; Rabiner, E.A.; Nutt, D.; Politis, M. Imidazoline 2 binding sites reflecting astroglia pathology in Parkinson's disease: An in vivo11C-BU99008 PET study. Brain 2019, 142, 3116–3128.
20. Roussakis, A.A.; Piccini, P. Molecular Imaging of Neuroinflammation in Idiopathic Parkinson's Disease. Int. Rev. Neurobiol. 2018, 141, 347–363.
21. Tong, J.; Rathitharan, G.; Meyer, J.H.; Furukawa, Y.; Ang, L.C.; Boileau, I.; Guttman, M.; Hornykiewicz, O.; Kish, S.J. Brain monoamine oxidase B and A in human parkinsonian dopamine deficiency disorders. Brain 2017, 140, 2460–2474.
22. Ezura, M.; Kikuchi, A.; Okamura, N.; Ishiki, A.; Hasegawa, T.; Harada, R.; Watanuki, S.; Funaki, Y.; Hiraoka, K.; Baba, T.; et al. (18)F-THK5351 Positron Emission Tomography Imaging in Neurodegenerative Tauopathies. Front. Aging Neurosci. 2021, 13, 761010.
23. Schonecker, S.; Brendel, M.; Palleis, C.; Beyer, L.; Hoglinger, G.U.; Schuh, E.; Rauchmann, B.S.; Sauerbeck, J.; Rohrer, G.; Sonnenfeld, S.; et al. PET Imaging of Astrogliosis and Tau Facilitates Diagnosis of Parkinsonian Syndromes. Front. Aging Neurosci. 2019, 11, 249.
24. Tan, Y.Y.; Jenner, P.; Chen, S.D. Monoamine Oxidase-B Inhibitors for the Treatment of Parkinson's Disease: Past, Present, and Future. J. Park. Dis. 2022, 12, 477–493.
25. Cassano, T.; Calcagnini, S.; Pace, L.; De Marco, F.; Romano, A.; Gaetani, S. Cannabinoid Receptor 2 Signaling in Neurodegenerative Disorders: From Pathogenesis to a Promising Therapeutic Target. Front. Neurosci. 2017, 11, 30.
26. Gomez-Galvez, Y.; Palomo-Garo, C.; Fernandez-Ruiz, J.; Garcia, C. Potential of the cannabinoid CB(2) receptor as a pharmacological target against inflammation in Parkinson's disease. Prog. Neuropsychopharmacol. Biol. Psychiatry 2016, 64, 200–208.

27. Ajalin, R.M.; Al-Abdulrasul, H.; Tuisku, J.M.; Hirvonen, J.E.S.; Vahlberg, T.; Lahdenpohja, S.; Rinne, J.O.; Bruck, A.E. Cannabinoid Receptor Type 1 in Parkinson's Disease: A Positron Emission Tomography Study with FMPEP-d(2). Mov. Disord. 2022, 37, 1673–1682.
28. Casteels, C.; Lauwers, E.; Baitar, A.; Bormans, G.; Baekelandt, V.; Van Laere, K. In vivo type 1 cannabinoid receptor mapping in the 6-hydroxydopamine lesion rat model of Parkinson's disease. Brain Res. 2010, 1316, 153–162.
29. Ceccarini, J.; Casteels, C.; Ahmad, R.; Crabbe, M.; Van de Vliet, L.; Vanhaute, H.; Vandenbulcke, M.; Vandenberghe, W.; Van Laere, K. Regional changes in the type 1 cannabinoid receptor are associated with cognitive dysfunction in Parkinson's disease. Eur. J. Nucl. Med. Mol. Imaging 2019, 46, 2348–2357.
30. Vuorimaa, A.; Rissanen, E.; Airas, L. In Vivo PET Imaging of Adenosine 2A Receptors in Neuroinflammatory and Neurodegenerative Disease. Contrast Media Mol. Imaging 2017, 2017, 6975841.
31. Beamer, E.; Goloncser, F.; Horvath, G.; Beko, K.; Otrokocsi, L.; Kovanyi, B.; Sperlagh, B. Purinergic mechanisms in neuroinflammation: An update from molecules to behavior. Neuropharmacology 2016, 104, 94–104.
32. Mishina, M.; Ishiwata, K.; Kimura, Y.; Naganawa, M.; Oda, K.; Kobayashi, S.; Katayama, Y.; Ishii, K. Evaluation of distribution of adenosine A2A receptors in normal human brain measured with TMSX PET. Synapse 2007, 61, 778–784.
33. Schroder, S.; Lai, T.H.; Toussaint, M.; Kranz, M.; Chovsepian, A.; Shang, Q.; Dukic-Stefanovic, S.; Deuther-Conrad, W.; Teodoro, R.; Wenzel, B.; et al. PET Imaging of the Adenosine A(2A) Receptor in the Rotenone-Based Mouse Model of Parkinson's Disease with FESCH Synthesized by a Simplified Two-Step One-Pot Radiolabeling Strategy. Molecules 2020, 25, 1633.
34. Ishibashi, K.; Miura, Y.; Wagatsuma, K.; Toyohara, J.; Ishiwata, K.; Ishii, K. Occupancy of adenosine A(2A) receptors by istradefylline in patients with Parkinson's disease using (11)C-preladenant PET. Neuropharmacology 2018, 143, 106–112.
35. Mishina, M.; Ishiwata, K.; Naganawa, M.; Kimura, Y.; Kitamura, S.; Suzuki, M.; Hashimoto, M.; Ishibashi, K.; Oda, K.; Sakata, M.; et al. Adenosine A(2A) receptors measured with TMSX PET in the striata of Parkinson's disease patients. PLoS ONE 2011, 6, e17338.
36. Mishina, M.; Ishii, K.; Kimura, Y.; Suzuki, M.; Kitamura, S.; Ishibashi, K.; Sakata, M.; Oda, K.; Kobayashi, S.; Kimura, K.; et al. Adenosine A(1) receptors measured with (11) C-MPDX PET in early Parkinson's disease. Synapse 2017, 71, e21979.
37. Ramlackhansingh, A.F.; Bose, S.K.; Ahmed, I.; Turkheimer, F.E.; Pavese, N.; Brooks, D.J. Adenosine 2A receptor availability in dyskinetic and nondyskinetic patients with Parkinson disease. Neurology 2011, 76, 1811–1816.
38. Waggan, I.; Rissanen, E.; Tuisku, J.; Joutsa, J.; Helin, S.; Parkkola, R.; Rinne, J.O.; Airas, L. Adenosine A(2A) receptor availability in patients with early- and moderate-stage Parkinson's disease. J. Neurol. 2023, 270, 300–310.
39. Gianferrara, T.; Cescon, E.; Grieco, I.; Spalluto, G.; Federico, S. Glycogen Synthase Kinase 3beta Involvement in Neuroinflammation and Neurodegenerative Diseases. Curr. Med. Chem. 2022, 29, 4631–4697.
40. Prabhakaran, J.; Molotkov, A.; Mintz, A.; Mann, J.J. Progress in PET Imaging of Neuroinflammation Targeting COX-2 Enzyme. Molecules 2021, 26, 3208.
41. Esposito, G.; Giovacchini, G.; Liow, J.S.; Bhattacharjee, A.K.; Greenstein, D.; Schapiro, M.; Hallett, M.; Herscovitch, P.; Eckelman, W.C.; Carson, R.E.; et al. Imaging neuroinflammation in Alzheimer's disease with radiolabeled arachidonic acid and PET. J. Nucl. Med. 2008, 49, 1414–1421.
42. Liu, H.; Zhou, Y.; Luo, Z.; Gu, J.; Yu, Y.; Flores, H.; Dugan, L.; Perlmutter, J.; Tu, Z. PET imaging studies of brain S1PR1 expression in Parkinson disease. J. Nucl. Med. 2019, 60, 183.