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EDITORIAL

TSPO PET using ^{18}F-GE-180: a new perspective in neurooncology?

Karl-Josef Langen[1,2] · **Antje Willuweit**[1]

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As early as the 1980s binding sites for the mitochondrial translocator protein (TSPO), which is also referred to as the peripheral benzodiazepine receptor, were identified in glioma cells and brain tumour tissue by Olson et al. [1]. These findings were confirmed years later by immunohistochemical methods [2]. By that time, the feasibility of PET imaging of glioblastoma (GBM) in patients had been demonstrated using the TSPO ligand ^{11}C-PK11195 [3]. Further studies, however, were hampered by partially nonspecific binding and low tumour-to-brain contrast of ^{11}C-PK11195. In recent years, the development of so-called second generation TSPO ligands with lower nonspecific binding characteristics has initiated more preclinical studies exploiting the utility of TSPO imaging for diagnosis of brain tumours [4, 5]. Unfortunately, these new ligands are sensitive to a single-nucleotide polymorphism (rs6971 polymorphism, A147T) which is present in the human, but not the rodent, TSPO gene, resulting in variable binding affinities to the protein [6]. The polymorphism divides the human population into high-, medium- and low-affinity binders depending on the homozygosity or heterozygosity of the allele. To overcome this clear limitation of the existing TSPO ligands, radiochemists around the world are currently working on new ligands.

GE-180 is a novel ^{18}F-labelled so-called third generation TSPO ligand with promising characteristics, although some sensitivity to the polymorphism has also been reported [7–9]. In several preclinical studies in which TSPO tracers were directly compared with each other, ^{18}F-GE-180 has been proven to be superior to other TSPO ligands. In an ischemia model of the rat, ^{18}F-GE-180 showed a higher signal-to-noise ratio and lower nonspecific binding than ^{11}C-PK11195 [10]. Also, in a mouse model of mild neuroinflammation obtained by injecting low doses of endotoxin into the brain, only ^{18}F-GE-180, and not the second generation tracer ^{18}F-DPA-714 demonstrated a significantly higher binding potential and signal-to-noise ratio than ^{11}C-PK11195 [11]. ^{18}F-GE-180 was also able to pick up neuroinflammation in a mouse model of Alzheimer's disease, in which another second generation tracer, ^{18}F-PBR06, showed no significant differences compared with wild-type control mice [12].

The superior imaging quality of ^{18}F-GE-180 appears to be particularly relevant when the inflammatory activity is only slightly pronounced or diffuse neuroinflammation is present, as in neurodegenerative diseases. For imaging of gliomas, a high tumour-to-brain ratio was detected with several TSPO ligands in preclinical studies [5, 13, 14] and in patients using ^{11}C-PK11195 [15] owing to the high expression of TSPO in glioma cells. However, there have been no PET studies directly comparing the imaging properties of different TSPO ligands in glioma-bearing animals and patients. High binding potential to glioma cells and low nonspecific binding to the surrounding brain tissue might allow improved tumour delineation, but discrimination between tumour mass and brain tissue can be critical at the tumour rim where glia-associated microglia/macrophages (GAM), which also express TSPO,

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✉ Karl-Josef Langen
k.j.langen@fz-juelich.de

Antje Willuweit
a.willuweit@fz-juelich.de

[1] Institute of Neuroscience and Medicine, Forschungszentrum Jülich, 52425 Jülich, Germany

[2] Department of Nuclear Medicine, RWTH Aachen University Clinic, 52425 Jülich, Germany

are known to be present [16]. Here, a TSPO ligand with high and specific binding characteristics, such as ^{18}F-GE-180, might be particularly beneficial.

In this edition of the *EJNMMI*, Albert et al. [17] present the first data on brain tumour imaging with the novel TSPO ligand ^{18}F-GE-180. High uptake of ^{18}F-GE-180 was shown in untreated and pretreated GBM partially extending beyond the contrast enhancement on MRI. After genotyping, no difference in ^{18}F-GE-180 uptake was found between medium-affinity and high-affinity binders, nor in tumours and normal brain, indicating a relatively low sensitivity of ^{18}F-GE-180 to the rs6971 polymorphism. The image quality obtained with TSPO PET using ^{18}F-GE-180 appears to be definitively superior to that obtained with previous TSPO ligands [10, 15]. The conclusions that can be drawn from these data with respect to the identification of tumour extent, however, are limited since no data on regional histology were provided. Furthermore, it cannot be excluded that increased uptake of ^{18}F-GE-180 in pretreated gliomas is partially caused by GAM removing debris in necrotic areas. A previous study using ^{11}C-PK11195 indicated that TSPO is predominantly expressed in neoplastic cells with GAM only partially contributing to the PET signal and no expression in reactive astrocytes [15]. In that study, TSPO was detectable only in a subpopulation of microglia and macrophages, overall accounting for about 16% of GAM. Thus, the data are promising and further studies comparing ^{18}F-GE-180 uptake with histological data and with PET imaging using established tracers for brain tumour imaging such as radiolabelled amino acids or advanced MRI methods are highly recommended [18].

A recent study by Jensen et al. [19] compared the uptake of ^{18}F-fluoroethyltyrosine (^{18}F–FET) with TSPO expression as shown by the SPECT tracer ^{123}I-CLINDE in three patients with GBM. There was a considerable discrepancy in the spatial distribution of the two tracers. ^{123}I-CLINDE exhibited low uptake in wide areas of ^{18}F-FET-positive tumour tissue, but intense uptake in normal-appearing brain areas outside abnormal ^{18}F-FET uptake and contrast enhancement on MRI. In the further course of the disease, tumour progression was observed in those brain areas indicating that TSPO expression might be an early imaging biomarker of GBM progression. In any case, the combination of amino acid PET and TSPO imaging using ^{18}F-GE-180 may open up a new window to the further development of neurooncological diagnostics. This is very desirable, as the cost of brain tumour treatment is high and efficient use of these therapies is very important for both the patient and the clinical community.

Compliance with ethical standards

Conflicts of interest None.

Ethical approval This Editorial does not discuss any studies with human participants or animals performed by any of the authors.

References

1. Olson JM, Junck L, Young AB, Penney JB, Mancini WR. Isoquinoline and peripheral-type benzodiazepine binding in gliomas: implications for diagnostic imaging. Cancer Res. 1988;48:5837–41.
2. Vlodavsky E, Soustiel JF. Immunohistochemical expression of peripheral benzodiazepine receptors in human astrocytomas and its correlation with grade of malignancy, proliferation, apoptosis and survival. J Neurooncol. 2007;81:1–7.
3. Pappata S, Cornu P, Samson Y, Prenant C, Benavides J, Scatton B, et al. PET study of carbon-11-PK 11195 binding to peripheral type benzodiazepine sites in glioblastoma: a case report. J Nucl Med. 1991;32:1608–10.
4. Buck JR, McKinley ET, Hight MR, Fu A, Tang D, Smith RA, et al. Quantitative, preclinical PET of translocator protein expression in glioma using ^{18}F-N-fluoroacetyl-N-(2,5-dimethoxybenzyl)-2-phenoxyaniline. J Nucl Med. 2011;52:107–14.
5. Tang D, Hight MR, McKinley ET, Fu A, Buck JR, Smith RA, et al. Quantitative preclinical imaging of TSPO expression in glioma using N,N-diethyl-2-(2-(4-(2-^{18}F-fluoroethoxy)phenyl)-5,7-dimethylpyrazolo[1,5-a]pyrimidin-3-yl)acetamide. J Nucl Med. 2012;53:287–94.
6. Owen DR, Yeo AJ, Gunn RN, Song K, Wadsworth G, Lewis A, et al. An 18-kDa translocator protein (TSPO) polymorphism explains differences in binding affinity of the PET radioligand PBR28. J Cereb Blood Flow Metab. 2012;32:1–5.
7. Wadsworth H, Jones PA, Chau WF, Durrant C, Fouladi N, Passmore J, et al. [^{18}F]GE-180: a novel fluorine-18 labelled PET tracer for imaging translocator protein 18 kDa (TSPO). Bioorg Med Chem Lett. 2012;22:1308–13.
8. Fan Z, Calsolaro V, Atkinson RA, Femminella GD, Waldman A, Buckley C, et al. Flutriciclamide (^{18}F-GE180) PET: first-in-human PET study of novel third-generation in vivo marker of human translocator protein. J Nucl Med. 2016;57:1753–9.
9. Feeney C, Scott G, Raffel J, Roberts S, Coello C, Jolly A, et al. Kinetic analysis of the translocator protein positron emission tomography ligand [^{18}F]GE-180 in the human brain. Eur J Nucl Med Mol Imaging. 2016;43:2201–10.
10. Boutin H, Murray K, Pradillo J, Maroy R, Smigova A, Gerhard A, et al. ^{18}F-GE-180: a novel TSPO radiotracer compared to ^{11}C-R-PK11195 in a preclinical model of stroke. Eur J Nucl Med Mol Imaging. 2015;42:503–11.
11. Sridharan S, Lepelletier FX, Trigg W, Banister S, Reekie T, Kassiou M, et al. Comparative evaluation of three TSPO PET radiotracers in a LPS-induced model of mild neuroinflammation in rats. Mol Imaging Biol. 2017;19:77–89.
12. James ML, Belichenko NP, Shuhendler AJ, Hoehne A, Andrews LE, Condon C, et al. [^{18}F]GE-180 PET detects reduced microglia activation after LM11A-31 therapy in a mouse model of Alzheimer's disease. Theranostics. 2017;7:1422–36.
13. Winkeler A, Boisgard R, Awde AR, Dubois A, Theze B, Zheng J, et al. The translocator protein ligand [^{18}F]DPA-714 images glioma and activated microglia in vivo. Eur J Nucl Med Mol Imaging. 2012;39:811–23.
14. Buck JR, McKinley ET, Fu A, Abel TW, Thompson RC, Chambless L, et al. Preclinical TSPO ligand PET to visualize human glioma xenotransplants: a preliminary study. PLoS One. 2015;10:e0141659.
15. Su Z, Roncaroli F, Durrenberger PF, Coope DJ, Karabatsou K, Hinz R, et al. The 18-kDa mitochondrial translocator protein in human gliomas: an ^{11}C-(R)PK11195 PET imaging and neuropathology study. J Nucl Med. 2015;56:512–7.
16. Zinnhardt B, Pigeon H, Theze B, Viel T, Wachsmuth L, Fricke IB, et al. Combined PET imaging of the inflammatory tumor

microenvironment identifies margins of unique radiotracer uptake. Cancer Res. 2017;77:1831–41.
17. Albert NL. Unterrainer M, Fleischmann DF, Lindner S, Vettermann F, Brunegraf A, et al. TSPO PET for glioma imaging using the novel ligand 18F-GE-180: first results in patients with glioblastoma. Eur J Nucl Med Mol Imaging. 2017. https://doi.org/10.1007/s00259-017-3799-9
18. Langen KJ, Galldiks N, Hattingen E, Shah NJ. Advances in neuro-oncology imaging. Nat Rev Neurol. 2017;13:279–89.
19. Jensen P, Feng L, Law I, Svarer C, Knudsen GM, Mikkelsen JD, et al. TSPO imaging in glioblastoma multiforme: a direct comparison between ^{123}I-CLINDE SPECT, ^{18}F-FET PET, and gadolinium-enhanced MR imaging. J Nucl Med. 2015;56:1386–90.