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EDITORIAL COMMENTARY

One-step synthesis of an ^{18}F-labeled boron-derived methionine analog: a substitute for ^{11}C-methionine?

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Abstract

Amino acid-based tracers have been extensively investigated for positron emission tomography (PET) imaging of brain tumors, and ^{11}C-methionine (^{11}C-MET) is one of the most extensively investigated. However, widespread clinical use of ^{11}C-MET is challenging due to the short half-life of ^{11}C and low radiolabeling yield. In this issue of the *European Journal of Nuclear Medicine and Molecular Imaging*, Yang and colleagues report an ^{18}F-labeled boron-derived methionine analog, ^{18}F-B-MET, as a potential substitute for ^{11}C-MET in PET imaging of glioma. The push-button synthesis, highly efficient radiolabeling, and good imaging performance in glioma models make this tracer a promising candidate for future clinical translation.

Keywords Positron emission tomography (PET) · Cancer · Amino acid transporter · ^{18}F-B-MET · Boramino acid · ^{11}C-Methionine (^{11}C-MET)

Since ^{18}F-FDG has high uptake in normal brain tissue which can interfere with the diagnosis of certain brain tumors, amino acid-based tracers have been extensively investigated for brain tumor positron emission tomography (PET) imaging [1]. Several comparative studies have shown that amino acid-based tracers have better performance than ^{18}F-FDG in brain tumor diagnosis [2–4]. Whereas ^{18}F-FDG uptake is generally a measure of glucose metabolism, amino acid-based PET can provide information on amino acid metabolism and the function of various amino acid transporters. Currently, amino acid-based PET scans are often performed in the clinic when a brain tumor is diagnosed by either magnetic resonance imaging (MRI) or computed tomography (CT), which can aid in personalized treatment planning. In addition, amino acid-based PET has also demonstrated significant advantages in monitoring of brain tumor therapy over the anatomical imaging modalities, including earlier diagnosis/prognosis, detection of metastatic brain tumors, better brain tumor staging, more accurate monitoring of treatment response, and the detection of tumor recurrence [5, 6].

Currently, four amino acid-based tracers are commonly used in the clinic for brain tumor imaging, including ^{11}C-methionine (^{11}C-MET), ^{18}F-fluorodihydroxyphenylalanine (^{18}F-DOPA), ^{18}F-fluoroethyltyrosine (^{18}F-FET) and ^{11}C-α-methyl-L-tryptophan (^{11}C-AMT) [7]. Some other amino acid-based tracers are also under investigation, including ^{76}Br-α-methyl-phenylalanine [8] and others [9, 10]. Among these PET tracers, ^{11}C-MET is one of the most important amino acid tracers, and is very useful for imaging of the L-type amino acid transporter 1 (LAT-1) [11]. It has been widely used in clinical PET imaging for brain tumor delineation and staging, as well as for detection of metastasis and recurrence [11–13]. However, widespread clinical application of ^{11}C-MET is not

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possible due to the short half-life of ^{11}C (20.38 min) and low efficiency in radiolabeling (radiochemical yield usually <5%). The use of ^{18}F to label methionine, without interfering with its biological activity, may solve this problem due to the longer half-life of ^{18}F (109.7 min) and its wide availability at the majority of PET centers. However, direct labeling of methionine with ^{18}F is very challenging, since even minor modification of the side chain will significantly alter the biological properties of the resulting methionine analog.

In this issue of the *European Journal of Nuclear Medicine and Molecular Imaging*, Yang and colleagues report an ^{18}F-labeled boron-derived methionine analog, ^{18}F-B-MET, as a potential substitute of ^{11}C-MET for PET imaging of glioma [14]. The investigators applied an isotope exchange method for highly efficient radiolabeling of ^{18}F to trifluoroborate methionine, yielding ^{18}F-B-MET which is the first ^{18}F-labeled methionine-based tracer (Fig. 1a). The radiolabeling method is simple and very efficient: with the prepared precursor molecules, the one-step kit-like labeling produces highly pure (>99% purity) ^{18}F-B-MET with high specific activity (>37 GBq/μmol) in a short time (from ^{18}F-fluoride to ^{18}F-B-MET in less than 25 min). Even though the labeling is very simple, the stability of the tracer in plasma is very good (<1% of tracer degraded after 2 h of incubation in murine plasma) and therefore there is no obvious defluorination or bone uptake of the tracer. The critical feature is that such a labeling method does not change the side chain of methionine. Therefore, the transportation and uptake properties of methionine are preserved.

This work is a follow-up of the previous work by the same investigators, in which they developed a general method to synthesize trifluoroborate amino acid derivatives, boramino acids (BAAs), to mimic natural amino acids without changing the side chain (Fig. 1b) [15]. The structure of a BAA is identical to that of the corresponding natural amino acid, except for the replacement of the carboxylate with a BF_3 group. Based on in vitro assays, the uptake of ^{18}F-BAA is mediated by various amino acid transporters and they are kinetically indistinguishable from natural amino acids, and hence they truly mirror the uptake behavior

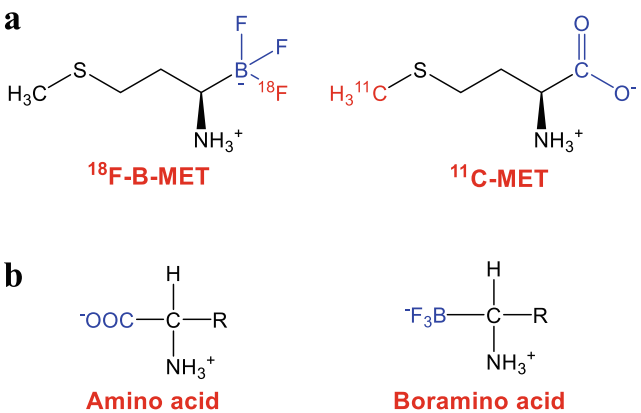

Fig. 1 **a** ^{18}F-B-MET and ^{11}C-methionine (^{11}C-MET). **b** Amino acid and boramino acid (BAA)

of natural amino acids, although they are not incorporated into proteins. With this strategy of amino acid mimicry, in addition to the one-step ^{18}F-labeling method utilizing an organotrifluoroborate which was also developed by the same investigators [16, 17], the BAAs may serve as general PET imaging probes for amino acid transporters. All amino acids can be radiolabeled in a similar fashion for imaging amino acid transporter activity and tumor metabolism, which could complement the use of ^{18}F-FDG in the imaging of tumor types in which ^{18}F-FDG does not work well (e.g. brain tumors).

In this study, the researchers performed systematic in vitro and in vivo experiments to assess the tumor imaging performance of ^{18}F-B-MET in three glioma models (C6, GL26, and U87) [14]. ^{18}F-B-MET was found to be able to effectively and specifically detect glioma tumors in both the subcutaneous and orthotopic tumor models. Contrast-enhanced MRI was performed to confirm the anatomical location of orthotopic brain tumors and ex vivo H&E and immunohistochemical staining also validated the tumor presence and high LAT-1 expression levels in these tumor models. What is probably more important is that ^{18}F-B-MET uptake in normal brain was very low, which provided excellent contrast for brain tumor visualization. Whole-body biodistribution studies in the mouse tumor models showed high accumulation of ^{18}F-B-MET in the liver and pancreas, which is consistent with the natural metabolism of methionine.

The cellular transport and uptake specificity of ^{18}F-B-MET was investigated via a competitive inhibition assay. Natural methionine (L-MET) and the transporter inhibitor BCH [18] both showed efficient inhibition of ^{18}F-B-MET uptake in the C6, GL26 and U87 cell lines. An interesting finding was that L-MET and D-MET (i.e. the unnatural amino acid) inhibited the cellular uptake of ^{18}F-B-MET with similar efficiency, which should be investigated in detail in future studies. Presumably, only L-MET should specifically inhibit the cellular uptake of ^{18}F-B-MET since these two molecules are very similar in chemical structure. Perhaps, dose-dependent inhibition assays should be performed to investigate the transport specificity in detail, even though in vitro assays, in vivo PET imaging, and ex vivo histology all suggested that LAT-1 is responsible for tracer uptake in the brain tumor models. Of note, in a previous study, cellular uptake of ^{14}C-labeled L-leucine was found to be inhibited by both L-MET and D-MET in certain cell lines, suggesting that D-MET could be transported by LAT-1 [19]. Structurally, there is not much space for further optimization of ^{18}F-B-MET since, as mentioned above, side chain modification is not well tolerated; hence, it would be very difficult to further optimize the tracer without jeopardizing its biological properties. Thus, it is likely that ^{18}F-B-MET will be the tracer for subsequent more detailed investigation.

In the quantitative analysis of dynamic PET imaging data in this study, the time–activity curve showed rapid clearance of the

tracer from the orthotopic C6 and U87 glioblastoma tumors, which could be a concern for this tracer since the absolute tracer uptake in the tumor was not very high. For ^{18}F-FDG PET, the tracer is trapped once it is taken inside the tumor cells; hence, tumor uptake of ^{18}F-FDG usually increases over time. In the case of ^{18}F-B-MET, there is no trapping mechanism. In addition, ^{18}F-B-MET may also be transported out of the cells by other amino acid transporters, which may further reduce tracer uptake in tumor cells. Luckily, the very low background uptake in normal brain is a major advantage which can come to the rescue since contrast is more important than the absolute signal for imaging applications. For quantitative monitoring of therapeutic response, such rapid clearance could indeed be an issue.

The successful preparation of ^{18}F-B-MET, as well as its favorable biological properties documented in the study, is a vivid demonstration of the tumor detection ability of such BAA-based PET tracers. The push-button synthesis, highly efficient radiolabeling, and good imaging performance in glioma models make this tracer a promising candidate for future clinical translation. The study also indicates the necessity for preclinical evaluation of other BAA-based PET tracers for potential clinical applications. The longer half-life and wider availability of ^{18}F over ^{11}C can certainly facilitate these future imaging applications. Besides diagnosis of brain cancer, such tracers could also be used to detect other diseases related to upregulated amino acid transporter activity or dysregulated metabolism. With continued input of preclinical investigation, as well as efficient clinical translation, ^{18}F-B-MET and other BAA-based tracers hold great promise for broad biomedical applications in oncology and other diseases.

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Compliance with ethical standards

Conflicts of interest None.

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

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