A new PET probe, ^{18}F -tetrafluoroborate, for the sodium/iodide symporter: possible impacts on nuclear medicine

Hyewon Youn · Jae Min Jeong · June-Key Chung

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As early as 1915, it was found that iodide is required in the thyroid gland for the production of thyroid hormones. Since then, radioiodines have been used as tracers in thyroid function tests and as agents for the treatment of hyperthyroidism and benign thyroid diseases. Furthermore, knowledge of the importance of the role played by iodine transport in thyroid cancer cells provides the rationale for the use of radioiodines to diagnose and treat thyroid cancer (1, 2). In fact, the clinical utilization of radioiodines led to the birth of nuclear medicine.

Today, it is known that the iodide pump is a sodium/iodide symporter (NIS), an intrinsic membrane protein of the thyroid gland follicular cells (3, 4), and that the NIS-catalysed accumulation of iodide in cells from the interstitium is achieved against its transmembrane electrochemical gradient, which is maintained by sodium-potassium adenosine triphosphatase. The identification of the human NIS (hNIS) gene created many new diagnostic and therapeutic opportunities, and in particular, researchers are currently investigating the use of hNIS as a reporter gene for gene therapy and molecular and genomic imaging (5).

Various negative ions, like ClO_4^- , ReO_4^- , TcO_4^- , I^- , SCN^- , ClO_3^- and Br^- , are transported by NIS (6), and thus, radiolabelled forms of these agents can be used for thyroid and NIS imaging. The apparent common denominator of these substrates is that they are monovalent anions with a size close to that of iodide. Tetrafluoroborate (TFB) is a fluorine-containing ion that interacts with NIS (7), and Anbar et al. (8) reported that radiolabelled TFB has the potential for thyroid imaging, because it specifically accumulates in the thyroid and inhibits iodide uptake by the thyroid. It is hydrolytically stable under physiological conditions, is not significantly metabolized and has low toxicity.

For more than 65 years, radioiodines like ^{131}I , ^{123}I and ^{125}I have been used as probes for NIS (2). However, the half-lives of gamma-emitting radioiodines are longer than those required for imaging, and thus, absorbed radiation doses are unnecessarily high. The resolution and sensitivity of positron emission tomography (PET) are significantly better than those of gamma camera images and single photon emission computed tomography (SPECT), and better quantifications of the absolute amounts of a tracer in small regions are also possible by PET.

The first choice for a PET NIS imaging agent should be ^{124}I , which can be produced by a cyclotron. ^{124}I is a positron emitter with a half-life of 4.18 days, which is appropriate for dosimetric calculation of ^{131}I . However, its positron emission rate is only 23% and it emits several high-energy gamma photons with energy values of 603 (61%), 723 (10%) and 1,691 keV (10%), and these high emissions result in high radiation doses and relatively poor image quality as compared with ^{18}F . Furthermore, ^{124}I production requires a special solid ^{124}Te target and an accelerated proton beam (9), and this type of system is unavailable in the majority of cyclotron centres.

H. Youn · J. M. Jeong · J.-K. Chung (✉)
Department of Nuclear Medicine, Seoul National University
College of Medicine,
101 Daehang-Ro, Jongno-Gu,
Seoul, Korea 110-744
e-mail: jkchung@snu.ac.kr

H. Youn · J. M. Jeong · J.-K. Chung
Laboratory of Molecular Imaging and Therapy, Cancer Research
Institute, Seoul National University College of Medicine,
Seoul, Korea

H. Youn · J. M. Jeong · J.-K. Chung
Institute of Radiation Medicine, Medical Research Center,
Seoul National University,
Seoul, Korea

^{18}F is the most widely used radionuclide for PET and is available from almost all cyclotrons. ^{18}F can be produced by irradiating ^{18}O -water with an accelerated proton beam and has a half-life of 110 min, which is appropriate for short-term imaging. Accordingly, the idea of developing an ^{18}F -labelled NIS imaging agent is still very much alive.

In a study published in this issue of EJNMMI, Jauregui-Osoro et al. (10) found that TFB had been used as a substrate for NIS and labelled it with ^{18}F using an isotope exchange method under acidic conditions at 120°C for 10 min. The procedure was simple but specific activities were low, though labelling, purification and quality control procedures were straightforward. The precursor TFB is commercially available at a low price, and the labelled ^{18}F -TFB is easily purified using sequential treatment through a silver ion-loaded cation exchange column and two alumina columns. Quality control can be performed by alumina thin-layer chromatography using a methanol mobile phase.

Although the reported specific activity of ^{18}F -TFB was about 1 GBq/ μmol , which is much lower than ^{18}F -labelled radiopharmaceuticals used for receptor imaging, high thyroid uptakes and excellent images were obtained in the experimental mice. This high uptake is explained by the fact that negative ion uptake by NIS has much greater capacity than uptakes by receptor binding. Generally, receptor binding agents require specific activities of higher than 30 GBq/ μmol for PET. A preliminary biological assessment of ^{18}F -TFB showed that it is similar to $^{99\text{m}}\text{Tc}$ -pertechnetate and that it justifies evaluation in humans.

The main advantages of ^{124}I PET imaging are its high resolution and the dosimetric information provided. Because ^{131}I is the mainstay of therapy for thyroid cancer, and because treatment success or failure depends on the degree of iodine uptake by tumour cells, ^{124}I PET imaging will increasingly act as a indicator of this treatment. Absolute ^{124}I accumulation in residual cancer tissues can be obtained from PET/CT images, and radiation doses can be calculated, although recovery correction is mandatory for ^{124}I PET quantifications (12). Freudenberg et al. (13) reported that compared to an empirical fixed dose protocol, ^{124}I dosimetry findings changed management in 25% of patients. PET dosimetry could provide useful routine procedures for radioiodine therapy in advanced differentiated thyroid cancer and might allow safer or more effective radioiodine dose and earlier multimodal interventions than standard empirical protocols. In addition, PET can be used for dosimetric calculation in patients with Graves' disease and autonomously functioning nodule (11).

It might be possible to use ^{18}F -TFB as a detector for functioning cancer tissues. However, it is questionable to use ^{18}F -TFB for dosimetry, because it has some problems, such as the pharmacokinetic and pharmacodynamic differences between it and radioiodines. Although ^{18}F -TFB can

be taken up by NIS, its transportation rate differs from that of iodide. Furthermore, it cannot be incorporated into thyroglobulin for the synthesis of thyroid hormones like iodide. Thus, a compensatory calculation method should be applied for simulating radioiodine uptake, and comparative studies with other NIS imaging agents, such as $^{99\text{m}}\text{Tc}$, ^{123}I and ^{131}I , are required.

Immunostaining using hNIS antibodies was found to produce positive results in only a few malignant papillary or follicular thyroid cells (14), but the presence of this small amount of NIS determines the effectiveness of radioiodine therapy in residual thyroid cancer. We evaluated the outcomes of radioiodine therapy in 22 patients with recurrent lesions and found that 80% of patients positive by NIS immunostaining responded to therapy, whereas only 33.3% of patients negative for NIS did so (15). Thyroid cancer tissues expressing NIS take up more radioiodines and respond better to the therapy, which strongly suggests that ^{18}F -TFB NIS imaging is important for patient management. It may be important for staging thyroid cancer before thyroidectomy and for detecting recurrence/metastases during follow-up.

Reporter imaging of NIS using a gamma camera is easier for radioiodines and $^{99\text{m}}\text{Tc}$, because a suitable gamma camera is available in most nuclear medicine departments (5). The use of NIS for reporter imaging allows the noninvasive and repeated visualization of NIS-expressing cells in living animals, and these images even provide the locations, durations and magnitudes of NIS gene expression in cells and information on the migration and differentiation of NIS-expressing cells. The most commonly used NIS reporter imaging system is a cis-promoter/NIS system. This type of system can be based on endogenous or exogenous NIS gene expression controlled by specific promoters, and thus, increased radioiodine uptake for such a system represents the increased activity of a particular promoter. Furthermore, this strategy can be applied to NIS radionuclide therapy by killing NIS-expressing cells (16).

Most conventional PET imaging reporter genes, such as HSV-tk and D2R, require the synthesis of complicated substrates, but NIS has the advantage of a wide range of available substrates. Radioiodines and $^{99\text{m}}\text{Tc}$ have been used as NIS imaging substrates, and more powerful therapeutic nuclides with shorter half-lives, such as ^{188}Re and ^{211}At , can also be used for NIS radiotherapy. However, the routinely available PET agents still have been highly requested for small animal PET imaging. Despite the advantage of wide substrate availability of NIS, no specific cost-effective PET agent with a lower imaging dose has been developed.

^{18}F -TFB has demonstrated the capability to overcome the limitations of the small animal PET imaging of NIS (10). The use of labelled TFB has considerable promise because it shows high stability, low metabolic potential and

low toxicity (rat LD₅₀=550 mg/kg s.c.). The low positron energy (633 keV) and the high positron yield (96.7%) of ¹⁸F reduce possible radiation damage to animals and provide sufficient positrons to maintain image quality. Although Jauregui-Osoro et al. (10) did not demonstrate transport of the TFB ion into cells by NIS or direct binding to NIS, their PET images and biodistribution studies indicated that the specific activity of ¹⁸F-TFB for NIS was sufficient in small animal imaging.

In conclusion, the development of ¹⁸F-TFB has a possibility of inducing a big impact on the diagnosis and treatment of thyroid disorders, especially thyroid carcinoma. ¹⁸F-TFB can be used for the sensitive imaging method to detect metastatic cancer before thyroidectomy and residual cancer after operation. In addition, it can be used in making decisions about radioiodine therapy and prediction of therapy result in individual tumour lesions. For the dosimetric application of ¹⁸F-TFB in ¹³¹I therapy, compensatory calculations should be established following pharmacokinetic and pharmacodynamic studies. ¹⁸F-TFB has several merits for small animal PET imaging of the NIS reporter gene. However, it is still necessary to develop an improved method to obtain higher specific activity of ¹⁸F-TFB.

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