INVITED COMMENTARY

Somatostatin Receptor Imaging: Current Status and Future Perspectives

The neuropeptide somatostatin—a cyclic tetradecapeptide first isolated from ovine hypothalamus (*1*)—is the most widely distributed of the hypothalamic releasing hormones in the central nervous system and in the periphery, including the pancreas, gut, and pituitary. In the brain, somatostatin is believed to function as a neurotransmitter and neuromodulator (*2*). The effect of somatostatin in the periphery is not yet understood to its full extent. The effects of somatostatin are mediated by 7 transmembrane domain G-protein coupled receptors. In vivo and in vitro studies have shown that somatostatin receptors (SSTRs) are expressed on the surface of several cell types in high density to a varying extent, i.e., gastroenteropancreatic (GEP) tumors such as carcinoid tumor, insulinoma, gastrinoma, small cell lung cancer, medullary thyroid carcinoma, and meningioma (*3,4*). Molecular biologic research revealed that various types of SSTRs exist. To date, 5 different SSTR subtypes are known (*5–8*), $SSTR_1$-$SSTR_5$, which differ in their interaction with an extended form of the neuropeptide (somatostatin-28) or synthetic derivatives (*9*), and in their tissue distribution (*10*). Of these, subtype 2, $SSTR_2$, is most often expressed on the surface (*11–14*).

The native ligand of the somatostatin receptor, endogenous somatostatin, has a very short biologic half-life (<2 min); thus, somatostatin itself cannot be used as an imaging agent in nuclear medicine. To overcome this drawback, an analog of somatostatin consisting of 8 amino acids was developed. This octapeptide, called pentetreotide, exhibits a biologic half-life on the order of several hours and can be linked through diethylenetriaminepentaacetic acid to ^{111}In, forming the well-known radiotracer [^{111}In]octreotide. [^{111}In]-octreotide predominantly binds to $SSTR_2$ and can be used for imaging purposes in all of the previously mentioned tumor types.

Clinical nuclear medicine has taken advantage of this characteristic, and SSTR scintigraphy using [^{111}In]-octreotide has become an invaluable tool used extensively in routine patient care (*4,15–17*). Apart from GEP tumors, [^{111}In]octreotide has been shown to be helpful in several clinical settings, such as a patient suspected of having meningioma(s). In these patients, in whom conventional imaging (i.e., CT or MRI) was not decisive, functional imaging using [^{111}In]octreotide reliably differentiated meningioma from neurinoma when tumors were >2.5 cm in diameter (*18*). This is of utmost importance because both tumor entities show a predilection for similar sites, for example, cerebello-pontine angle, cavernous sinus, or spine, but require different surgical strategies because of their different biologic behavior. Moreover, [^{111}In]octreotide was the only imaging modality that accurately detected remaining tumor tissue or relapse of meningioma after neurosurgical treatment (*19*).

Although both whole-body and SPECT images can be obtained, the energy spectrum of photons emitted by ^{111}In (173 keV and 264 keV) necessitate the use of medium energy collimators, thereby degrading image quality and geometric resolution. This, in part, may be the reason for the difficulty detecting small meningiomas (<2.5 cm in diameter) (*18*). Therefore, the work presented by Henze et al. (*20*) in this issue of *The Journal of Nuclear Medicine* is a logical step to overcoming this drawback. In their article they describe a method to link an analog of pentetreotide (1,4,7,10-tetraazacyclododecane-*N*,*N′*,*N″*,*N‴*-tetraacetic-acid-D-Phe^1-Tyr^3-octreotide [DOTATOC]) to a PET nuclide, ^{68}Ga. This new radiotracer, [^{68}Ga]DOTATOC, exhibits several advantages over conventional [^{111}In]-octreotide. The coincidence detection of two photons generated by annihilation of the emitted positron by a modern PET scanner facilitates a geometric resolution in the order of 4–6 mm, and biodistribution can be quantified in (patho)physiologic terms. Furthermore, Henze et al. (*20*) presented high-contrast images of meningiomas measuring only 7–8 mm in diameter, which could be clearly separated both from surrounding brain and bone tissue. This capability is important because meningiomas may cause serious problems to the neurosurgeon because of their tendency to local osseous invasiveness. Moreover, using [^{68}Ga]-DOTATOC, higher activities can be applied in GEP tumors, which would further enhance image quality, and, because of the short half-life of ^{68}Ga, the radiation burden is still in the same range compared with ^{111}In (12 mSv 350 MBq vs. 11 mSv 200 MBq, respectively).

Traditionally, SSTR scintigraphy using [^{111}In]octreotide has been performed in a 2-d protocol including image acquisition up to 24 h after injection. Although PET nuclides in general have short half-lives (in the range of minutes), this is not expected to create problems when using [^{68}Ga]DOTATOC because it could be demonstrated in

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meningiomas that decisive imaging is feasible within 4 h after injection in the majority of patients (*21*).

Finally, [^{68}Ga]DOTATOC shows an even higher specific binding to $SSTR_2$ (IC_{50} = 14 nmol/L), and, together with [^{90}Y]DOTATOC, its renal retention is only half of that described for [^{111}In]octreotide. In this context, Krenning et al. (*22*) presented evidence in a phase-I trial in end-stage neuroendocrine tumors that repeated administration of high doses of [^{111}In]octreotide can be used as a therapeutic agent. This therapeutic effect is based on ^{111}In's emission of Auger and conversion electrons. However, β^--emitting radionuclides such as ^{90}Y may be even more effective than ^{111}In for peptide receptor radionuclide therapy, and it has already been shown that DOTATOC can be labeled with ^{90}Y (*23*). Taken together, these points suggest that [^{68}Ga]DOTATOC may be used for pretherapeutic evaluation of galenic formulations of DOTATOC labeled with β^--emitting radionuclides, which might be used for radionuclide therapy, a field of nuclear medicine in which interest has been growing rapidly in the past few years (*24*,*25*).

In conclusion, [^{68}Ga]DOTATOC has the potential to revitalize SSTR scintigraphy because of both its superior image quality and its possible use for pretherapeutic evaluation of β^--emitting variants of DOTATOC.

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