An Exploratory Study of 3-[^{18}F]Fluoro-*p*-hydroxyphenethylguanidine ([^{18}F]3F-PHPG) in Patients with Neuroendocrine Tumors

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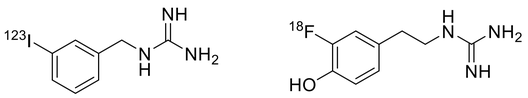
INTRODUCTION

3-[^{18}F]fluoro-*p*-hydroxyphenethylguanidine ([^{18}F]3F-PHPG) is a new radiotracer developed at our institution for positron emission tomography (PET) studies of cardiac sympathetic innervation. It is taken up into sympathetic nerve varicosities as a substrate of the norepinephrine transporter (NET) and stored in norepinephrine storage vesicles by the second isoform of the vesicular monoamine transporter (VMAT2). Similarly, this mechanism of action drives cardiac sympathetic nerve uptake of [^{123}I]metaiodobenzylguanidine ([^{123}I]MIBG; AdreView™), which is also an FDA approved agent for diagnostic localization of some neuroendocrine cancers, such as pheochromocytoma, paraganglioma and neuroblastoma. Since [^{18}F]3F-PHPG is a structural analog of [^{123}I]MIBG, and is a good substrate of NET and VMAT2 transporters, this suggests that it could be use for diagnostic localization of neuroendocrine tumors with the high spatial resolution and sensitivity of PET imaging.



[^{123}I]MIBG [^{18}F]3F-PHPG

OBJECTIVES

The goal of this Investigator Award from NETRF is to evaluate the diagnostic performance of [^{18}F]3F-PHPG for tumor localization in patients with pheochromocytoma and paraganglioma (n = 24). For comparison purposes, some of the subjects (n = 12) will also have a whole body planar scintigraphy study with [^{123}I]MIBG. We also anticipate that many of the subjects scanned with [^{18}F]3F-PHPG will have a prior PET scan with the somatostatin type 2 receptor (SSTR2) radioligand [^{68}Ga]DOTATATE (NETSPOT™). A second goal is to use immunohistochemistry to measure tumor expression levels of the NET and VMAT2 transporters, as well as VMAT1 transporters, in all tumors that are surgically resected from patients after they have been imaged with [^{18}F]3F-PHPG. This data will provide key insights into the importance of each transporter in driving tumor uptake of [^{18}F]3F-PHPG.

PRECLINICAL TESTS

We previously performed some preclinical tumor imaging tests with [^{11}C]-*p*-hydroxyphenethylguanidine ([^{11}C]PHPG), which lacks the 3-fluoro group of [^{18}F]3F-PHPG. Tumor xenografts of rat pheochromocytoma (PC12) cells in mice were clearly visualized with [^{11}C]PHPG (Figure 1) [1]. Since rat PC-12 cells only express the VMAT1 isoform of the vesicular monoamine transporter and not VMAT2, this suggests that [^{11}C]PHPG and [^{18}F]3F-PHPG are also good substrates of VMAT1. In human adrenergic tumors, expression levels of NET, VMAT1 and VMAT2 can vary widely [3], so the fact that [^{18}F]3F-PHPG is a good substrate for all three transporters may allow it to consistently localize in these tumors.

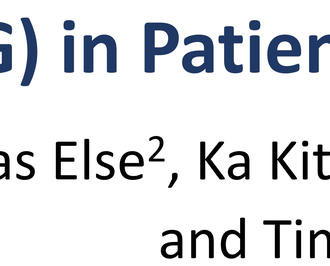


Figure 1. [^{11}C]PHPG uptake into a rat PC12 xenograft in a mouse.

METHODS

For all subjects, 8 to 12 mCi of [^{18}F]3F-PHPG will be injected intravenously and whole-body PET/CT scans will be acquired at two time points: 90 min and 180 min after tracer injection. During the tracer uptake period before imaging, six venous blood samples will be acquired to evaluate the metabolic breakdown of the tracer in plasma. Uptake of [^{18}F]3F-PHPG into tumors and metastases will be measured as tissue activity concentrations (kBq/cc) and as standardized uptake values (SUV_{avg} and SUV_{max}).

Following the lifting of restrictions on human research at the University of Michigan due to COVID-19, we recently completed our first study with [^{18}F]3F-PHPG in a 29 year old male subject with metastatic paraganglioma, who carries an *SDHB* germline mutation (8.7 mCi injected dose). The patient had a prior [^{68}Ga]DOTATATE scan from July 2020 for comparison.

RESULTS OF FIRST STUDY

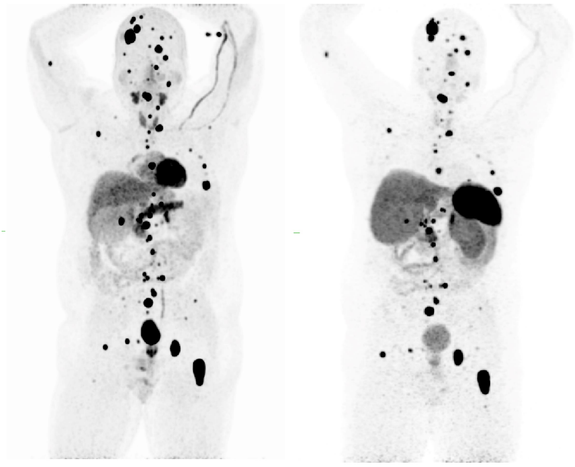


Figure 2. [^{18}F]3F-PHPG scan acquired 90 min after injection in a patient with metastatic paraganglioma (left) compared with a prior [^{68}Ga]DOTATATE scan in the same patient (right).

The first study of [^{18}F]3F-PHPG in metastatic paraganglioma was successful, showing high uptake of the radiotracer in multiple foci throughout the body (**Figure 2, left**). [^{18}F]3F-PHPG scans at 90 min and 180 min were comparable in quality, with an increase in lesion activity concentrations of 6% between the two time points. There was high concordance between the lesions seen in the [^{18}F]3F-PHPG scan and a prior [^{68}Ga]DOTATATE scan in this patient (**Figure 2, right**, and **Figure 3**). Table 1 compares SUV_{max} values for the two tracers in two lesions with highest uptake (large lesion in the right frontal skull; lesion in the upper left femur).

Table 1. SUV_{max} values in two lesions with high tracer uptake.

Lesion	[^{18}F]3F-PHPG	[^{68}Ga]DOTATATE
Skull	145	106
Femur	91	117

RESULTS OF FIRST STUDY

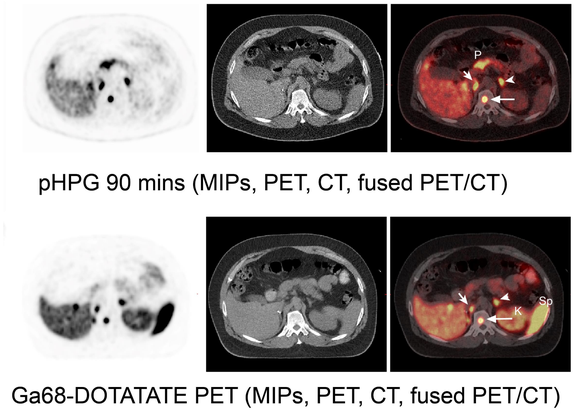


Figure 3. Axial slices at the same level for [^{18}F]3F-PHPG (top) and [^{68}Ga]DOTATATE (bottom), showing 3 concordant lesions (arrows in fused PET/CT). P = pancreas, K = kidney, Sp = spleen.

CONCLUSIONS

- The results of our first study with [^{18}F]3F-PHPG in a patient with metastatic paraganglioma are very encouraging.
- Since some neuroendocrine tumors do not express the SSTR2 receptors that bind [^{68}Ga]DOTATATE, [^{18}F]3F-PHPG could find clinical use as an alternative tracer for tumor localization.
- It may be possible to develop a companion radiotherapeutic agent based on the chemical structure of [^{18}F]3F-PHPG.

REFERENCES

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