Cellular uptake and tumor dosimetry of Ultratrace Iobenguane (MIBG) in a mouse model of pheochromocytoma/paraganglioma (pheo): Towards ^{211}At-MABG alpha therapy

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Background

The norepinephrine transporter (NET) is differentially over expressed on the cell surface of most human pheo and provides a highly specific mechanism for directing uptake of NET ligands into tumors. Metaiodobenzylguanidine (MIBG) is one such compound being investigated as a radiotherapeutic for malignant pheo. In an effort to develop ^{211}At-MABG as an alpha therapy for pheo, we have validated Ultratrace^{125}I-MIBG uptake in a mouse model of malignant pheo as a comparator for ^{211}At-MABG.

Methods

Ultratrace MIBG was synthesized by incubating Ultratrace mBG resin (Molecular Insight Pharmaceuticals) with ^{125}I-NaI and an oxidant, followed by purification by IEC. Radiochemical purity was determined using radioTLC and RP-HPLC.

To evaluate the uptake of MIBG we used MPC 4/30PRR cells derived from mouse metastatic pheo (a kind gift from Drs. Powers and Tischler). In vitro MIBG uptake was assessed over time in the presence of desipramine (DMI) blocking and with the HDAC-inhibitor Trichostatin A (TSA).

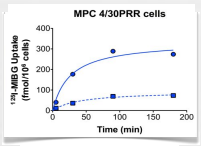
Organ and tumor biodistribution of MIBG was performed in nude mice bearing subcutaneous or metastatic MPC tumors at 24 h post intravenous injection. Digital autoradiography (DAR) was used to confirm microdistribution of MIBG within the tumor.

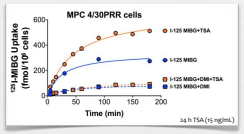
Results

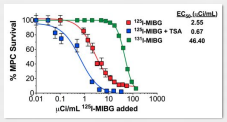
Radiosynthesis:

Zhu X and Hunter DH J. Label. Cmpds and Radiopharm. 1999

In vitro uptake and cytotoxicity studies:





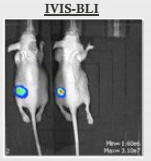


MTT Assay

In vivo biodistribution studies:

Subcutaneous (s.c.) MPC model

IVIS-BLI

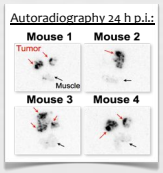


MPC-fLuc (sc)
24 day pi

^{125}I-MIBG Biodistribution

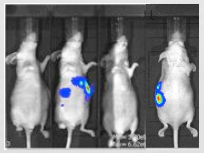
	^{125}I-MIBG Organ Uptake (% ID/g)	
Organ	4 h (n = 5)	24 h (n =4)
Blood	0.45 ± 0.11	0.03 ± 0.01
Heart	5.77 ± 1.20	0.74 ± 0.41
Muscle	0.55 ± 0.07	0.17 ± 0.04
Lung	2.90 ± 0.84	0.39 ± 0.09
Kidney	1.68 ± 0.45	0.32 ± 0.12
Spleen	3.81 ± 1.23	0.77 ± 0.34
Liver	5.35 ± 0.40	0.58 ± 0.09
Brain	0.08 ± 0.01	0.01 ± 0.00
Bone	0.62 ± 0.18	0.14 ± 0.06
Tumor	1.35 ± 0.30	1.06 ± 0.25
Tumor:Muscle	2.51 ± 0.67	6.24 ± 2.08
Tumor:Blood	3.03 ± 0.35	35.33 ± 14.43

Autoradiography 24 h p.i.:

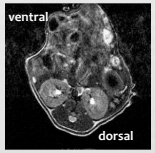


Metastatic MPC model

IVIS-BLI

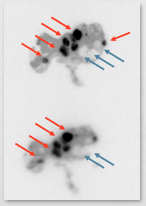


MRI



MPC-fLuc (met)
31 day pi

Autoradiography 24 h p.i.:



Results Summary

Ultratrace MIBG labeled in high yield and radiochemical purity from Resin.

In vitro, MPC cells accumulated MIBG to high levels (274 fmol/10^6 cells at 180 min) compared to cells blocked with DMI (73 fmol/10^6 cells at 60min). HDACi TSA pretreatment significantly increased MIBG uptake (511 fmol/10^6 cells at 180min).

MPC s.c. tumor xenografts (confirmed by BLI) had significant uptake of MIBG (1.06±0.25%ID/g) at 24 h (n = 4), with tumor:blood and tumor:muscle ratios 6.24±2.08 and 35.33±14.43, respectively. Tumor DAR revealed that MIBG uptake was concentrated mainly at the tumor periphery.

Metastatic MPC model reveals liver tumors (confirmed by BLI and MRI) that have heterogenous uptake pattern of MIBG as shown by DAR.

Conclusions

The MPC model of metastatic mouse pheo is appropriate to evaluate the targeting of ligands such as MIBG. Furthermore, quantitative MIBG uptake and dosimetry is a promising approach to plan ^{211}At-MABG alpha therapy of pheo.

Acknowledgements

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PheoPara Alliance

Perelman School of Medicine
University of Pennsylvania