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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 211At-MABG as an alpha therapy for pheo, we have validated Ultratrace125I-MIBG uptake in a mouse model of malignant pheo as a comparator for 211At-MABG.

Methods: Ultratrace MIBG was synthesized by incubating Ultratrace mBG resin with 125I-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). MIBG uptake in vitro was assessed in the presence desipramine (DMI) blocking and with the HDAC-inhibitor Trichostatin A (TSA). Organ and tumor biodistribution of MIBG was performed in nude mice bearing subcutaneous MPC tumors at 24h post intravenous injection. Digital autoradiography (DAR) was used to confirm microdistribution of MIBG within the tumor.

Results: In vitro, MPC cells accumulated MIBG to high levels (274 fmol/106 cells at 180min) compared to cells blocked with DMI (73 fmol/106 cells at 60min). TSA pretreatment significantly increased MIBG uptake (511 fmol/106 cells at 180min). MPC tumor xenografts had significant uptake of MIBG (1.06±0.25%ID/g) at 24h (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.

Conclusion: 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 211At-MABG alpha therapy of pheo.