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The development of meta-iodobenzylguanidine analogues for the therapy of neuroendocrine and other tumors

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Meta-iodobenzylguanidine (MIBG) is an analogue of the neurotransmitter, norepinephrine (Fig. 1). Radioiodinated MIBG has been used extensively for the localization and therapy of neuroendocrine tumors such as neuroblastoma and pheochromocytoma. To improve the therapeutic usefulness of this approach, we developed a no-carrier added (n.c.a.) synthesis for MIBG, and several analogues with potential advantages.

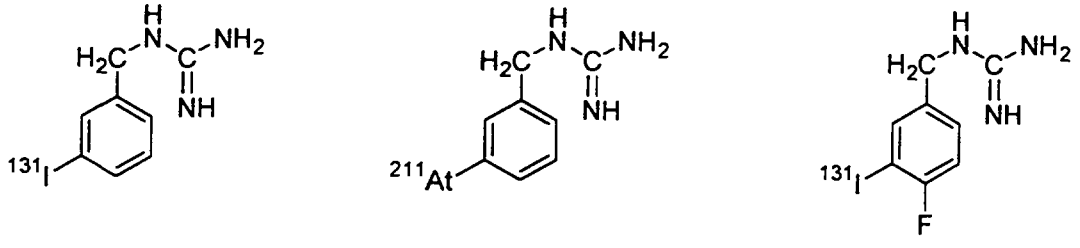

Fig. 1.

To date, radioiodinated MIBG used in clinical applications has been prepared by isotopic exchange (ex MIBG) and hence contains significant amount of unlabeled material (carrier). Since MIBG is taken up by target cells by a saturable active uptake-1 mechanism, it was hypothesized that it might be possible to improve its tumor localization through the use of a n.c.a. preparation. N.c.a. MIBG was prepared in more than 90% radiochemical yield from a silicon precursor under mild conditions [1]. In vitro studies using SK-N-SH human neuroblastoma cells showed that the uptake of n.c.a. [^{131}I]MIBG remained constant over a 2-3-log activity range, while that of ex [^{131}I]MIBG decreased more than 8-fold, demonstrating the saturability of uptake of [^{131}I]MIBG by SK-N-SH cells (Fig. 2). In normal mice, significantly higher uptake of n.c.a. [^{131}I]MIBG over ex [^{131}I]MIBG also was seen in innervated tissues such as heart and adrenals. Higher tumor-to-normal tissue ratios were obtained for n.c.a. [^{131}I]MIBG, compared to that for ex [^{131}I]MIBG, in athymic mice bearing SK-N-BE(2c) human neuroblastoma xenografts.

For the treatment of micrometastases, which are often associated with neuroblastoma, the long range β-particles of ^{131}I may be suboptimal. The α-particles of ^{211}At on the other hand, have a range of only a few cell diameters and thus, could be ideally suited to maximizing fractional dose deposition in micrometastases. In addition, the α-particles are high linear energy transfer radiation with a relative biological effectiveness greater than β-particles. To investigate this possiblity, meta-[^{211}At]astatobenzylguanidine ([^{211}At]MABG) was prepared in excellent radiochemical yields. As shown in Table 1, the in vitro binding of [^{211}At]MABG to SK-N-SH cells was similar to that of n.c.a. [^{131}I]MIBG. Like MIBG, the uptake of [^{211}At]MABG was blocked by various uptake-1 blocking agents and conditions suggesting that

[^{211}At]MABG is an excellent analogue of MIBG. The clonogenic potential of SK-N-SH cells following treatment with [^{211}At]MABG, [^{211}At]astatide and n.c.a. [^{131}I]MIBG as a function of activity concentration gave a D_0 value of 5.8 nCi/ml for [^{211}At]MABG, compared with 10,375 nCi/ml for [^{131}I]MIBG, implying a more than 1,000-fold higher cytotoxicity for the α-particle emitting analogue. That the exquisite cytotoxicity of [^{211}At]MABG is indeed due to its specific uptake and retention in SK-N-SH cells was demonstrated by the fact that the D_0 for [^{211}At]astatide, 482 nCi/ml, was more than 80-fold higher than that for [^{211}At]MABG.

Table 1. Uptake of n.c.a. [^{131}I]MIBG, ex [^{131}I]MIBG and [^{211}At]MABG by SK-N-SH cells in vitro as a function of activity concentration.

Log CPM	Specific uptake (percent of input)		
	n.c.a. [^{131}I]MIBG	[^{211}At]MABG	ex[^{131}I]MIBG
4.0	48.9 ± 0.8	40.3 ± 1.4	41.1 ± 1.1
5.0	48.0 ± 1.1	41.5 ± 0.9	39.1 ± 0.4
5.4	47.3 ± 0.6	37.0 ± 0.4	30.7 ± 1.5
5.7	45.1 ± 1.2	37.8 ± 0.4	21.5 ± 1.6
6.0	43.5 ± 0.6	40.3 ± 0.7	11.4 ± 0.6
6.3	44.3 ± 2.8	33.9 ± 0.9	6.4 ± 0.6

For positron emission tomographic applications, a ^{18}F-labeled analogue of MIBG, 4-[^{18}F]fluoro-3-iodobenzylguanidine ([^{18}F]FIBG), was developed. It will be ideal if the same molecule is amenable for labeling either with a positron emitter or with a therapeutic nuclide without changing the chemical properties. Since the pharmacokinetics/biodistribution of these two molecules are expected to be same, one could predict dosimetry from PET data obtained with the positron emitter-labeled agent for a therapy using the same molecule labeled with therapeutic nuclide. Towards this goal, we have developed a no-carrier-added synthesis of 4-fluoro-3[^{131}I]iodobenzylguanidine, [^{131}I]FIBG (Fig. 1) from a silicon precursor [2].

When performed in a paired-label format, the specific binding of [^{131}I]FIBG to SK-N-SH cells remained fairly constant (45-60%) over 2-3-log activity range and was 11-14% higher ($p < 0.05$) than that of [^{125}I]MIBG. The uptake of [^{131}I]FIBG and [^{125}I]MIBG by this cell line was reduced by various uptake-1 blocking agents suggesting that uptake of [^{131}I]FIBG by this cell line is specific and is mediated through an active uptake-1 mechanism. From a paired-label cell retention study using SK-N-SH cells, it was shown that about 70% of initially bound [^{131}I]FIBG was retained at the end of 3 days. In comparison, this value for [^{125}I]MIBG was about 25%. This suggests that, compared with [^{131}I]MIBG, [^{131}I]FIBG may deliver higher integrated dose to the tumor. Further studies are proceeding in cell culture and animal models to determine if these analogues show sufficient promise to warrant clinical evaluation.

References

1. Vaidyanathan G and Zalutsky MR. No-carrier-added synthesis of meta-[^{131}I]iodobenzylguanidine. *Appl Radiat Isot* 1993;44:621-628.
2. Vaidyanathan G, Zhao X-G, Strickland DK and Zalutsky MR. No-Carrier-Added 4-Fluoro-3-[^{131}I]iodobenzylguanidine: Evaluation of an MIBG Analogue. *J Nucl Med* 1997;38:330-334.