PURPOSE: The objective of this study was to determine the feasibility of exploiting the overexpression of somatostatin subtype-2 receptors (sstr(2)) on human medulloblastoma cells to develop targeted radiodiagnostics and radiotherapeutics for this disease. EXPERIMENTAL DESIGN: The following radioiodinated peptides were prepared using chloramine-T and evaluated: [(131)I-Tyr(3)]octreotide ([131]I TOC), [(131)I-Tyr(3)]octreotate ([(131)I]TOCA), involving substitution of Thr(ol)(8) in TOC with Thr(8), and glucose-[(131)I-Tyr(3)]octreotide ([(131)I]Gluc-TOC) and glucose-[(131)I-Tyr(3)]octreotate ([(131)I]Gluc-TOCA), prepared by conjugation of glucose to the peptide NH(2) terminus. Specific internalization of the peptides by sstr(2)-expressing AR42J rat pancreatic carcinoma cells in vitro was evaluated in paired-label assays. The tissue distribution of i.v. administered [(131)I]TOC, [(131)I]TOCA, [(131)I]Gluc-TOC, and [(131)I]Gluc-TOCA was evaluated in athymic mice bearing s.c. D341 Med human medulloblastoma xenografts. RESULTS: Compared with [(125)I]TOC, internalized radiiodine levels were higher for the other three peptides. For example, internalized counts were 1.9 +/- 0.2, 2.0 +/- 0.3, and 5.7 +/- 1.9 times higher for [(131)I]Gluc-TOC, [(131)I]TOCA, and [(131)I]Gluc-TOCA after a 3-h incubation, respectively,
demonstrating that carbohydration and COOH-terminus modification significantly improved the retention of radioiodine activity in sstr(2)-expressing tumor cells. COOH-terminus modification significantly increased (131)I localization in D341 Med medulloblastoma xenografts [(131)I]TOCA, 8.1 +/- 2.2% of injected dose/g (% ID/g); [(131)I]TOC, 3.9 +/- 0.5% ID/g at 1 h], whereas carbohydration of the NH(2) terminus resulted in even higher gains in tumor accumulation [(131)I]Gluc-TOC, 11.1 +/- 1.8% ID/g; [(131)I]Gluc-TOCA, 21.4 +/- 7.3% ID/g). In addition, the three modified peptides exhibited liver activity levels that were less than half those of [(131)I]TOC. Uptake of the two glucose-peptide conjugates in this human medulloblastoma xenograft was blocked by coinjection of 100 micro g of octreotide, demonstrating that it was receptor-specific. Tumor:normal tissue uptake ratios for [(131)I]Gluc-TOCA generally were higher that those for [(131)I]Gluc-TOC. At 1 h, tumor:normal tissue ratios for [(131)I]Gluc-TOCA were 29:1, 15:1, 8:1, 8:1, 240:1, and 82:1 for blood, liver, kidney, spleen, brain, and muscle, respectively. CONCLUSIONS: Our findings suggest that additional investigation of radiolabeled Gluc-TOCA analogues for the imaging and targeted radiotherapy of medulloblastoma is warranted.