Radionuclide therapy and apoptosis using an hybrid peptide

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Aim: Receptor-targeted scintigraphy and radionuclide therapy using radiolabelled somatostatin analogues are successfully used to image and treat somatostatin receptor-positive tumours. RGD (Arg-Gly-Asp) peptides can also induce apoptosis through caspase-3 activation. To combine these characteristics in one compound we synthesized the hybrid peptide RGD-DTPA-Tyr^3-octreotate. In this *in vitro* study we evaluated the tumouricidal effects of the ^{111}In-labelled hybrid peptide RGD-DTPA-Tyr^3-octreotate in comparison with the two separate peptides DTPA-RGD and DTPA-Tyr^3-octreotate. Subsequently caspase-3 activation in tumour cells after incubation with the various labelled and unlabelled peptides *in vitro* was investigated.
Materials and Methods: The tumouricidal effects of ^{111}In-labelled RGD-DTPA-Tyr^3-octreotate, DTPA-RGD and DTPA-Tyr^3-octreotate were investigated in different cell lines using a colony-forming assay. In the somatostatin receptor subtype 2 positive (sst_2+) rat pancreatic tumour cell line CA20948, also the caspase-3 activity was measured using a CASPASE-3 Cellular Activity Assay Kit after incubation with these labelled compounds. The caspase-3 activity was also measured after incubation with the unlabelled compounds in various cell lines.
Results: In the colony-forming assay RGD[^{111}In-DTPA]octreotate had superior therapeutic effects compared to [^{111}In-DTPA]Tyr^3-octreotate and [^{111}In-DTPA]RGD. Of the ^{111}In-labelled compounds RGD[^{111}In-DTPA]Tyr^3-octreotate also showed the highest increase in caspase-3 levels. The caspase-3 activation measured was time and dose-dependent. For all cell lines used the unlabelled compound RGD-DTPA-octreotate also showed the highest increase in caspase-3 levels.
Conclusions: These *in vitro* studies show that the radiolabelled RGD-DTPA-Tyr^3-octreotate has a more pronounced tumouricidal effect than [^{111}In-DTPA]RGD and [^{111}In-DTPA]Tyr^3-octreotate. The effects found were time and dose-dependent. The tumouricidal effect of the hybrid peptide is probably the result of increased apoptosis, induced by caspase-3 activation, as shown by increased caspase-3 activity after incubation with RGD-DTPA-Tyr^3-octreotate. Increased caspase-3 levels were found with the labelled as well as with the unlabelled hybrid peptide. RGD-DTPA-Tyr^3-octreotate is a very promising peptide for increasing apoptosis induction with radionuclide therapy in somatostatin receptor-positive tumours.

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session 4