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In vitro NK1R affinity evaluation of novel radioconjugates based on peptide antagonist SPANTIDE I and Ga-68/Lu-177 theranostic-like isotopes for glioma cancer

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1. Background and goal of the study:

The NK-1 receptor and its endogenous agonist - Substance P (SP) is a system that have been connected with many physiological processes like angiogenesis, wound healing and activation of inflammation state mediators synthesis. Moreover, the overexpression of NK-1 receptor is observed on certain types of cancer cells especially glioma, astrocytoma, melanoma, neuroblastoma and some types of lymphomas. This makes NK-1 receptor a potential target for cancer diagnosis and antitumor agents therapy. Presently there are some known glioblastoma treatment trials with labeled derivatives of SP but none of them is effective enough.

High affinity to NK-1 receptor exert also antagonists of this receptor. SPANTIDE I [D-Arg1,D-Trp7,9, Leu11]SP is a SP-analogue peptide antagonist designed with higher in vivo stability than natural SP (half-life of 2-3 minutes in human blood). There are also reports that inhibition action on NK-1 receptor can be correlated with antitumor activity of the inhibitor. That is why our goal is to synthetize novel radioconjugates based on peptide antagonist SPANTIDE I and evaluate their affinity and toxicity against glioma cancer cell lines.

1. Methodology:

In the course of this research we have synthesize two types of conjugates consisting of DOTA chelator and full peptide SPANTIDE I (1-11) or shorten peptide SPANTIDE I (5-11). Afterwards we have obtained desired radioconjugates by labeling with Ga-68 or Lu-177, and performed an assessment of physicochemical parameters like lipophilicity and stability in human serum. Later, prepared radioconjugates have been evaluated on in vitro assay with chosen NK-1 overexpressed cell lines to determine their affinity to the receptor after structural modification. In the next step cytotoxicity assay has been performed.

1. Results and discussion:

We have successfully obtained with high specific activity all four radioconjugates: shorten SPANTIDE I (5-11)-DOTA and full SPANTIDE I (1-11)-(DOTA)2 labeled with Ga-68 or Lu-177. Presence of two DOTA chelators in full SPANTIDE I radioconjugates affects significantly on lower radioconjugates logP parameter in comparison with shorten SPANTIDE I (5-11) radioconjugates with one chelator. All four radioconjugates show full stability in human serum for more than 4 times of applied isotope half-life. In vitro assays confirm maintenance of receptor affinity of obtained radioconjugates on glioma cell line.

1. Conclusion:

In conclusion, obtained radioconjugates fulfill many crucial aspects for the potential radiopharmaceuticals strictly required from the clinical application point of view. Gallium-labeled radioconjugates may show an usefulness in diagnosis of NK-1 receptor overexpression and lutetium-labeled SPANTIDE I peptides may complement the therapeutic application by similar in vivo action in theranostic idea of designed radioconjugates. Application concept of peptide NK-1 receptor antagonists may be a helpful reference in further development of tumor treatment solutions.

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