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Use of transnationally controlled tumor protein-derived protein transduction domain for improved intranasal delivery of insulin

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Statement of the Problem: Insulin is given to patients with diabetes by subcutaneous injection. However, noninvasive intranasal administration is easier for patients requiring daily treatment. Protein transduction domains (PTDs) are recognized as promising vehicles for the delivery of macromolecular drugs. We have previously shown that a region in the N-terminus (residues 1–10) of translationally controlled tumor protein (TCTP) contains aPTD (TCTP-PTD), MIIYRDLISH, which can serve as a vehicle for the delivery of macromolecules into the cells and tissues. In the current study, we evaluated the potential and safety of TCTP-PTD and its mutant analogs as nasal absorption enhancers for delivery of insulin. The goal of the current study was to examine whether the co administration of a drug with TCTP-PTD or its mutant analogs, can efficiently deliver insulin into the nasal mucosal membranes of animals.

Methodology & Theoretical Orientation: We examined the degree to which insulin was absorbed in nasal mucosa and also if any mucosal damage occurs following such nasal delivery of insulin using TCTP-PTDs as a vehicle. The systemic delivery of insulin was assessed by measuring the changes in blood glucose levels after nasal co administration insulin and TCTP-PTDs.

Findings: Of the 4 TCTP-PTD analogs examined, TCTP-PTD 13 significantly enhanced the nasal absorption of insulin in normal mice as well as alloxan induced diabetic rats. The binding between the TCTP-PTD analog and insulin may enable the penetration of insulin through the nasal mucosa. Histological examination of mice and rat nasal mucosa 7 days after repeated nasal administration showed no evidence of toxicity at the site of nasal administration.

Conclusion & Significance: In this study using insulin as a test system we demonstrate that the TCTP-PTD analog offers a promising approach for nasal peptides and protein-drugs delivery.

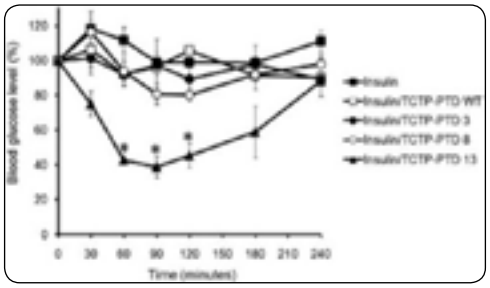

Figure 1: Changes in blood glucose levels in normal mice following nasal administration of insulin (1 IU/kg) mixed with different PTDs. Insulin solution without PTDs was used as a control

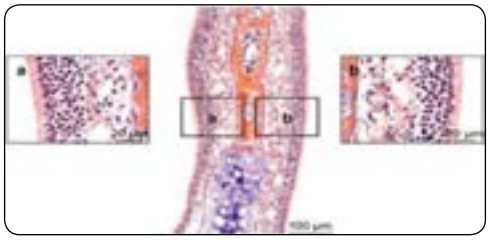

Figure 2: Photomicrographs of nasal septum excised from mice with STZ-induced diabetes nasally administrated a mixture of insulin/TCTP-PTD 13, once a day for 7 days (a) dosed side (b) un-dosed side

Recent Publications

1. Bae S Y, Byun S, Bae S H, Min D S, Woo H A and Lee K (2017) TPT1 (tumor protein, translationally - controlled1) negatively regulates autophagy through the BECN1 interactome and an MTORC1-mediated pathway. Autophagy 13(5):820-833.
2. Jin X H, Lim J, Shin D H, Maeng J and Lee K (2017) Dimerized translationally controlled tumor protein-binding peptide ameliorates atopic dermatitis in NC/Nga Mice. International Journal of Molecular Sciences 18(2):256-268.
3. Bae H D, Lee J, Jin X H and Lee K (2016) Potential of translationally controlled tumor protein-derived protein transduction domains as antigen carriers for nasal vaccine delivery. Molecular Pharmaceutics 13(9):3196-3205.
4. Bae S Y, Kim H J, Lee K J and Lee K (2015) Translationally controlled tumor protein induces epithelial to mesenchymal transition and promotes cell migration, invasion and metastasis. Scientific Reports 27:8061-8070.
5. Kim H Y, Kim S, Pyun H J, Maeng J and Lee K (2015) Cellular uptake mechanism of TCTP-PTD in human lung carcinoma cells. Molecular Pharmaceutics 12(1):194-203.

Biography

Kyunglim Lee received PhD degrees from Tufts University, MA, USA. She had Postdoctoral research training in Molecular and Cellular Biology, Harvard University. Since 1995, she has been with the College of Pharmacy, Ewha Womans University, where she is currently a Full Professor. Her main areas of research interest are pathophysiology of hypertension, allergy, and tumorigenesis caused by translationally controlled tumor protein. Currently, she serves as an Editorial Board Member of *Scientific Reports* and *SM Journal of Nephrology* and *Therapeutics*. She is a Member of the American Society for Biochemistry and Molecular Biology, Korean Society of Biochemistry and Molecular Biology, Korean Society for Molecular and Cellular Biology, Pharmaceutical Society of Korea.

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