Transport of Dendritic Nanoparticles across the Porcine Buccal Mucosa: Implications for Buccal Administration of Dendrimer-Based CNS Nanomedicines

Quan Yuan[1], Yao Fu[2], Weiyuan John Kao[2,3], Damir Janigro[4], Hu Yang[1]
[1]Department of Biomedical Engineering, Virginia Commonwealth University, Richmond, VA 23284, USA
[2] School of Pharmacy, University of Wisconsin-Madison, Madison, WI 53705, USA
[3]Department of Biomedical Engineering, University of Wisconsin-Madison, Madison, WI 53705, USA
[4]Department of Cerebrovascular Research, Cleveland Clinic Foundation, Cleveland, OH 44195, USA

Statement of Purpose: Rapid advances in the molecular neurosciences have revolutionized brain drug delivery design and dramatically expanded the repertoire of drugs that can be delivered to the brain. Most of polymers being used clinically for brain drug delivery exhibit low drug loading capacity because of the limited number of functional groups from the backbone. Exploring new polymers of high drug loading capacity and brain-targeting ability is important in order to meet the increasing needs for CNS disease treatment. The objective of this work was to apply dendrimers as carrier to deliver CNS drugs and explore the buccal mucosa as an alternative adsorption site for administration of dendrimer-based CNS nanomedicines.

Methods: Opioid peptide DPDPE was chosen as a model CNS drug and coupled to the surface of polyamidoamine (PAMAM) dendrimer G4.5 along with polyethylene glycol (PEG) by using EDC/NHS coupling chemistry. The permeability of PAMAM dendrimers G3.0, 3.5, G4.0, and G4.5 across the porcine buccal mucosa was also investigated. To enable the quantitative analysis of permeants across the buccal mucosa with fluorometry, carboxylate-terminated PAMAM dendrimer G3.5, G4.5, and DPDPE-G4.5-PEG were fluorescently labeled with 5-(aminoacetamido) fluorescein (AAF), and amine-terminated PAMAM dendrimers G3.0, and G4.0 were labeled with fluorescein isothiocynate (FITC). Benzylamine and FITC-dextran (MW=4000 Da, FD-4) were used as positive control and negative control, respectively.

The mean particle size and zeta potential of the prepared dendrimer derivatives was measured at room temperature using Malvern Zetasizer Nano S. Fluorescently labeled dendrimer derivatives were characterized and quantified using fluorescence spectrophotometry.

A vertical Franz diffusion cell mounted with buccal mucosa membrane of porcine cheek tissues was used for permeability studies. Dendrimer derivatives in solution were loaded into the donor chamber. At given time point up to 5 h, samples from the receiver chamber were collected and analyzed. Dendrimer loaded PEGdA/gelatin sIPN and PEG-only hydrogel disks were also used for in vitro permeation study.

Results/Discussion: The synthesis of PEG-G4.5-DPDPE was confirmed by ^{1}H-NMR spectroscopy. Fluorescently labeled dendrimers were characterized with fluorescence spectroscopy. Stand curves of fluorescence intensity versus mass were established.

The cumulative flux curves of all model permeants displayed a linear range, indicating steady state transport via the paracellular route. The permeability coefficients were then calculated from the curves. Although the permeability coefficients of all tested dendrimer derivatives were relatively low, the dendrimer derivatives were capable of permeating through the porcine buccal mucosa at detectable transport rates.

Coadministration of bile salt NaGDC to enhance transbuccal permeation of dendritic nanoparticles was investigated. According to our evaluation, the coadministered NaGDC at 10 mM indeed enhanced transbuccal permeation of FD-4 and dendrimer derivatives. The enhancement ratios of the permeability coefficients of G4.5-AAF, PEG-G4.5 (AAF)-DPDPE, and FD-4 were 47.5, 2.3, and 4.6, respectively. The low permeability enhancement ratio of PEG-G4.5 (AAF)-DPDPE by NaGDC may indicate that the intra- and extra-cellular distribution of PEG-G4.5 (AAF)-DPDPE was close to an optimal intra- and extra-cellular distribution for maximally enhanced transport.

The mucoadhesive sIPN platform was used to formulate buccal patches for delivery of dendrimer-based nanomedicines. The results showed that encapsulated dendritic nanoparticles were released from the gel disk and permeated through the buccal mucosa at a detectable rate. The dendrimer derivatives can be released from sIPN disks through particle diffusion and scaffold degradation. Impressively, G4.5-AAF and PEG-G4.5 (AAF)-DPDPE encapsulated by sIPN gained enhanced transbuccal transport across the buccal mucosa as compared to the dendritic nanoparticles in solution.

Conclusions: PAMAM dendrimers and CNS drug-carrying PEGylated PAMAM dendrimer were found to be able to permeate through the porcine buccal mucosa. Coadministration of sodium glycodeoxycholate significantly enhanced the permeation of dendrimer derivatives. Furthermore, dendrimer derivatives loaded into PEGdA/gelatin sIPNs were capable of diffusing out of the gel disks and permeating through the mucosa membrane with enhanced permeability. The results suggest that transbuccal delivery can be further explored as an alternative route for administration of dendrimer-based CNS nanomedicines.

Acknowledgements: NIH (R21NS063200).