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Screening of Cationic Compounds as an Absorption Enhancer for Nasal Drug Delivery

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Several cationic compounds were screened as potential nasal absorption enhancers to increase intranasal absorption of a model drug, fluorescein isothiocyanate labeled dextran (MW 4.4 kDa, FD-4), without nasal membrane damage in rats. Their effects were compared with those of classical enhancers. Various cationic compounds (poly-L-arginines with different molecular weights (MW 8.9, 45.5 and 92.0 kDa, poly-L-Arg (10), (50) and (100), respectively), L-arginine (L -Arg), L-lysine (L-Lys), and cetylpyridinium chloride (CPCL) were evaluated. Of the cationic compounds, poly-L-Arg and CPCL greatly enhanced the intranasal absorption of FD-4, as did chitosan, a cationic polysaccharide which has been reported to show a great effect on the transnasal delivery of peptide and protein drugs. The enhancing intensity by poly-L-Arg was dependent on its molecular weight. Rank order of the enhancing ratio, calculated from the AUC ratio for the enhancer treatment against the untreatment, was 0.5% poly- L-Arg (100) ≅ 0.5% sodium dodecylsulfate ≅ 0.5% CPCL > 0.5% poly-L-Arg (50) > 0.5% sodium deoxycholate ≅ 0.5% sodium taurodihydrofusidate > 0.5% polyoxyethylene-9-lauryl ether ≅ 0.5% lysophosphatidylcholine > 0.5% chitosan ≅ 0.5% poly-L-Arg (10) ≥ 10% L -Arg ≅ 10% L-Lys > 0.5% sodium glycocholate ≅ 0.5% sodium taurocholate ≅ 0.5% EDTA. Only the poly-L-Args represented almost the same degree of hemolysis of cationic compounds com-

pared with pH 7.0 phosphate buffered saline in the rat erythrocyte lysis experiment. The enhancing ratio by classical enhancers correlated with leaching of protein, phospholipids and LDH from isolated rabbit nasal mucosa. CPCL also fell on the regression lines between the enhancing ratio and their degree of leaching from classical enhancers. In contrast, the enhancing intensities by poly-L-Arg (10), (50) and (100) were greatly shifted from the regression line: the amount of leaching was markedly low in spite of a great enhancement of FD-4 absorption. These findings suggest that of the assessed enhancers only the poly-L-Args enhance the transnasal delivery of high molecular substances without severe damage to the nasal mucosal membrane. Poly-L-Arg is therefore a promising candidate having a good balance between enhancing activity and safety for nasal peptide and protein delivery.