Oligoarginine prodrugs with self-cleavable peptide spacers for effective intestinal absorption

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A variety of cell penetrating peptides, including oligoarginine and HIV Tat peptide, are currently considered as an attractive tool for intracellular delivery of compounds with low membrane permeability, such as proteins, oligonucleotides and drugs. Although conjugation with oligoarginine is expected to increase penetration of low permeable drugs across the intestinal epithelial cells, our preliminary experiments indicated that conjugation with heptaarginine only slightly increased permeability of drugs. This raised the possibility that, once the conjugates are internalized, most are retained in the intracellular compartment presumably due to positive charge of oligoarginine. A novel self-cleavable spacer strategy might be a solution to this problem. In this study, we selected FITC-ethanolamine (FE) as a model drug, and developed FE-heptaarginines conjugated with a series of new spacers having different conversion half-lives ($T_{1/2}$ = 9-100 min), which were expected to release the parent drug after cellular uptake. These spacers are self-catalytically cleaved under physiological conditions via intramolecular cyclization reaction through imide formation. Transport experiments of FE-spacer-heptaarginine conjugates across Caco-2 cell monolayers showed that the conjugate having a conversion half-life of 9 min yield the transport rate of FE three times higher than that of unconjugated FE. Other conjugates with longer conversion half-lives exhibited slightly increased or similar transport rate compared with FE itself, suggesting that shorter conversion half-life might be a important factor for improving the permeability. These novel peptidic self-cleavable spacers are promising for development of safe and effective oligoarginine-based cargo-transporter (OACT) system to enhance the intestinal absorption of drugs with low permeability as well as intracellular delivery of compounds with low membrane permeability.