Characterization of macrocyclic peptide drug interactions with bile salts and biorelevant colloids in the context of oral delivery

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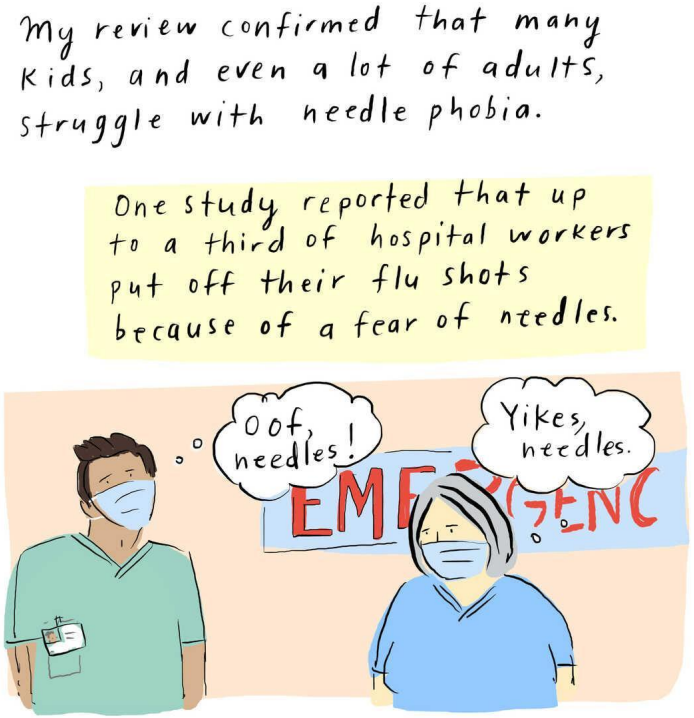
Oral peptide delivery – why?



Patient Preference

Needle phobias – up to 2 in 3 children & 1 in 4 adults

Increased medication compliance

No requirement for specialized equipment or trained professionals

Manufacturing

Easier scale-up & manufacturing of solid oral dosage forms

Lower manufacturing costs

Oral semaglutide (Rybelsus®) example:

- 100-fold higher peptide dose & daily vs. weekly administration required for PO vs. SC drug products
- Additional costs for PO drug product are cost-effective given the greater QoL when taking a tablet vs. injection[1]
- FDA label updates: Jan 2023 – Rybelsus® as first line Tx for T2DM & March 2025 – cardiovascular risk reduction (under review)[2,3]
- 2024 annual sales $3.4 billion USD[3]

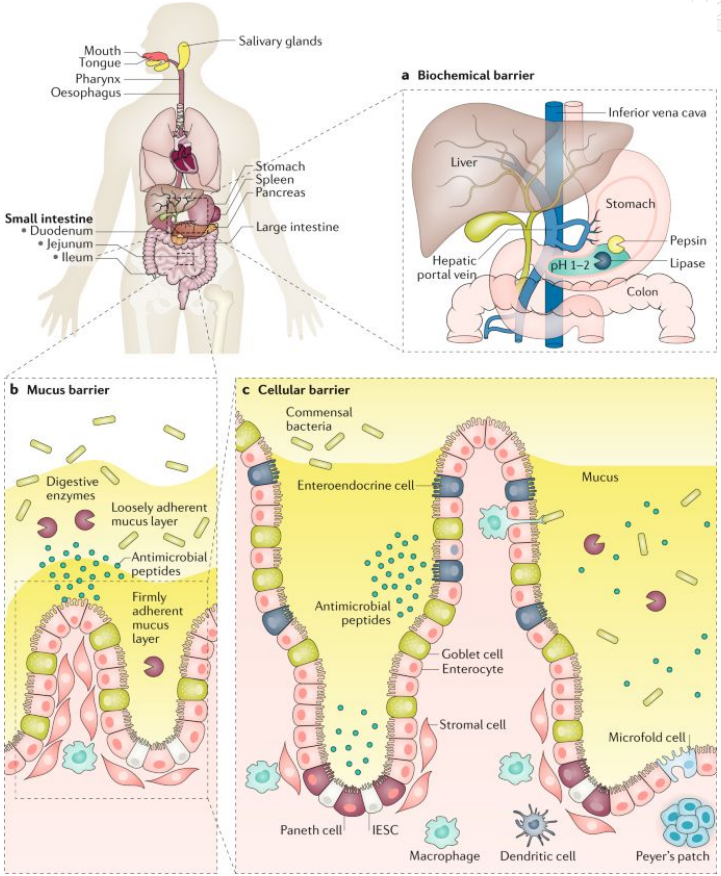
[1] Abramson *et al.* J Pharm Sci 2019; 108 pp. 3138-3145; [2] https://www.pharmavoice.com/news/weight-loss-market-oral-glp1-novo-lilly/717148/ [3] https://www.fiercepharma.com/pharma/fda-accepts-novo-nordisks-application-expand-label-oral-glp-1-rybelsus

Oral peptide delivery – what are the major challenges?

- Peptides & small proteins violate Lipinski's Rule of 5:[1]
  - **Molecular mass <500 Da**
  - cLogP <5
  - **HBD ≤5 & HBA ≤10**
- **Low membrane permeability** limits oral bioavailability, OR

  Low aqueous solubility limits oral bioavailability
- Susceptible to **proteolytic degradation** – pepsin, pancreatic enzymes, intestinal brush border enzymes
- Inter- & intra-individual variability in gastrointestinal physiology has an outsized impact on oral absorption = **high PK variability**

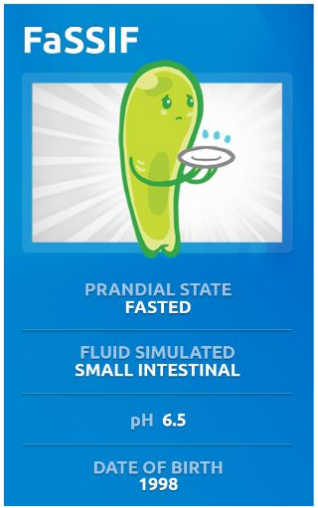
What is the impact of bile salt & phospholipid on oral peptide delivery?



[1] Lipinski *et al.* ADDR 1997; 23 pp. 3-25; Brown *et al.* Nature Reviews Materials 2020; 5 127-148

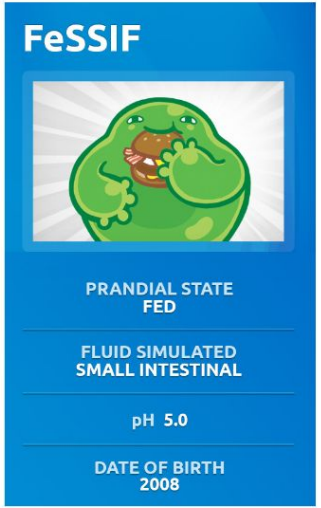
Oral small molecule drug delivery – the impact of bile salts on solubility is well understood

- Endogenous bile salts/phospholipids in the gastrointestinal environment solubilize poorly water-soluble small molecule drugs & increase their oral absorption/bioavailability
- Drug solubility & formulation performance is routinely measured in commercially available human biorelevant media – FaSSIF & FeSSIF



COMPOSITION

Component	Concentration (mM)
Taurocholate	3
Phospholipids	0.75
Sodium	148
Chloride	106
Phosphate	29



COMPOSITION

Component	Concentration (mM)
Taurocholate	15
Phospholipids	3.75
Sodium	319
Chloride	203
Acetic acid	144

Peptides…

…are not small molecules…

…nor are they large molecules!

Peptides are a unique modality, and we should not consider them as “large” small molecules or “small” large molecules

In general, we do not have a good understanding of the impact of bile salts on peptide drug absorption & the preclinical/clinical translatability of this phenomena

Cyclosporine A (BCS Class II “like” peptide – low solubility/high permeability) & bile salts

- Cyclosporine A PO F decreased from **5.4% to 1.6%** with bile duct cannulation when dosed as an aqueous suspension to rats[1]
- Coadministration of Sandimmune® ± tauroursodeoxycholate (bile salt) to rats = higher absorption[2]
- Co-administration of cholic acid/dehydrocholic acid (bile salt) improved cyclosporine A PO F in healthy volunteers & kidney transplant patients[3]

Bile increases cyclosporine A oral absorption

Cyclosporine A

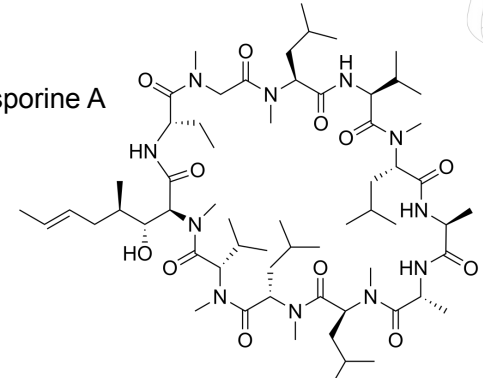


Table 1. Pharmacokinetic Parameters of CsA after Oral Administration of the Aqueous Suspension Containing CsA or Its DM-β-CyD or Sandimmune (Equivalent to 10 μg/kg CsA) to Bile Duct-Cannulated or -Noncannulated Rats

System	AUC (μg · h/ml)	C_{max} (μg/ml)	T_{max} (h)	MRT (h)	F (%)
Non-cannulated rat					
Drug alone	1.62	0.33	3.00	4.62	5.43
With DM-β-CyD	7.58	0.92	5.00	5.41	24.8
Sandimmune	6.90	0.82	4.00	6.60	22.6
Cannulated rat					
Drug alone	0.49	0.10	2.80	4.43	1.6
With DM-β-CyD	2.88	0.57	2.60	4.15	9.4

Each value represents the mean of 4—5 rats.

[1] Miyake *et al.* Biol Pharm Bull 1999; [2] Balandraud-Pieri *et al.* Drug Met Dist 1997; [3] Lindholm *et al.* Br J Clin Pharmacol 1990

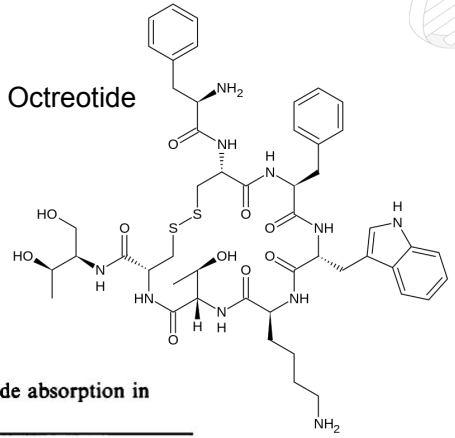
Octreotide (BCS Class III "like" peptide – high solubility/low permeability) & bile salts

Table 1 Pharmacokinetic parameters of octreotide after administration at different sites of rat small intestine

Administration site	AUC_{0-2h} ($ng\,h^{-1}\,ml^{-1}$)	C_{max} ($ng\,ml^{-1}$)	t_{max} (h)	*Absorption efficiency* (%)
Duodenum	4.39 ± 2.05	3.20 ± 1.54	0.5 ± 0.1	1.56
Proximal jejunum	8.89 ± 2.63	7.10 ± 1.75	0.4 ± 0.1	3.16
Ileum	0.52 ± 0.09	2.37 ± 1.17	0.7 ± 0.3	0.19
i.v. reference	14.04 ± 1.16	23.27 ± 1.31	0.1 ± 0.0	100

In anaesthetized rats after administration of 50 μg octreotide in 0.5 ml saline at different sites in the small intestine; reference animals received an i.v. dose of 2.5 μg octreotide (mean values ± s.d.; n = 6).

Octreotide



Octreotide absorption increased 6-fold in the absence of bile = bile decreases oral absorption

Table 2 Effect of bile on intestinal octreotide absorption in rats

Animal model	AUC_{0-2h} ($ng\,h^{-1}\,ml^{-1}$)	C_{max} ($ng\,ml^{-1}$)	t_{max} (h)
Control rats	2.26 ± 1.13	2.23 ± 1.34	1.2 ± 0.6
Sham operated	5.10 ± 6.17	4.14 ± 3.68	0.5 ± 0.2
Bile-duct cannulated	12.94 ± 4.66	8.73 ± 3.06	1.2 ± 0.5

In different rat models after administration of 50 μg octreotide (mean values ± s.d.; n = 6).

Besides cyclosporine A research & the above 1992 study from Sandoz Pharma on octreotide, the impact of bile salts & bile salt-phospholipid mixed micelles on oral peptide drug delivery has not been reported in the literature

Fricker *et al.* Br J Pharmacol 1992; 105 pp. 783-786

Bile salt & phospholipid concentrations *in vivo* – humans

- High inter- and intra-individual variability in bile salt levels in healthy volunteers[1]
  - Median duodenal concentration = 3.3 mM (range 2.5-5.9 mM)[2]
  - Median jejunal concentration = 2.5 mM (range 1.5-5.5 mM)[2]
- Mean phospholipid concentration in fasted human intestinal fluid = 0.3 ± 0.5 mM (range 0.003-2.7 mM)[1]
- Three main bile salts = taurocholate, glycocholate & glycodeoxycholate (glycine conjugates are predominant)

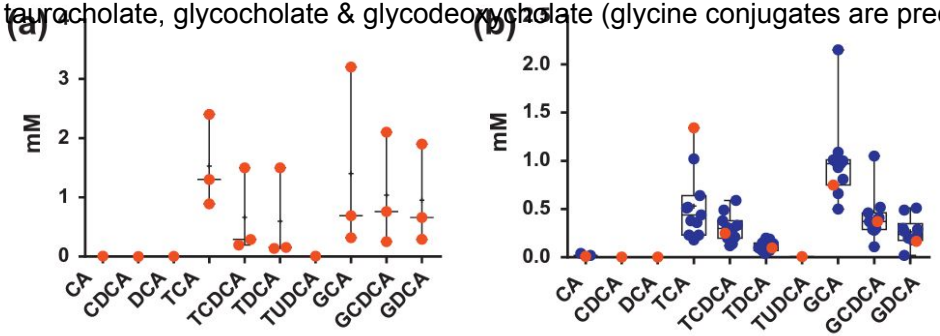


Fig. 5. Bile salt composition in human (a) duodenum and (b) jejunum. CA: cholic acid; CDCA: chenodeoxycholic acid; DCA: deoxycholic acid; TCA: taurocholic acid; TCDCA: taurochenodeoxycholic acid; TDCA: taurodeoxycholic acid; TUDCA: Tauroursodeoxycholic acid; GCA: glycocholic acid; GCDCA: glycochenodeoxycholic acid; GDCA: glycodeoxycholic acid. Box–whisker plots show minimum and maximum values, as well as 25, 50 and 75 percentile. The cross indicates the mean value. Each data point represents a group of participants (n = 1–10 colored red, n = 11–20 colored blue) reported in one publication. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

[1] Fuchs & Dressman J Pharm Sci 2014; [2] Bergstrom et al. Eur J Pharm Sci 2014

Bile salt & phospholipid concentrations *in vivo* – rats

- Rats have a continuous flow of bile – highest during the night and decreases sharply in the morning[1]
- Bile flow in rodents is 2-20 times greater, per unit of liver weight, than in dogs and humans
- Glycine conjugates are predominant in humans; taurine conjugates are predominant in rats (and rats make muricholic acids i.e., hydroxylated at 6ß position)

Table 1
Overview of studies evaluating pH and levels of bile acids, phospholipids and osmolality in the GI tract of fasted rats. Human values as recently reviewed by Bergström et al. [14] are included for comparison.

Parameter		Rat (fasted)	Human (fasted)[d]
pH	Stomach	1.4–1.9[a], 3.9[b], 4.3 (forestomach)[c], 4.0 (glandular stomach)[c], germ free rats: 3.8 (forestomach)[c], 5.7 (glandular stomach)[c].	1.7–3.3
	Proximal small intestine	6.7–7.0[a], 5.9–6.1[b], 7.1[c]	5.6–7.8
	Distal small intestine	6.9–7.4[a], 5.9[b], 8.0[c]	-
Bile acids (mM)	Stomach	< 5[a]	0–0.8
	Proximal small intestine	51[a]	1.4–5.9
	Distal small intestine	102[a]	–
Phospholipids (mM)	Stomach	hardly detected[a]	0.029
	Proximal small intestine	1.5–5.5[a]	0.1–0.6
	Distal small intestine	hardly detected[a]	–
Osmolality (mOsm/kg)	Stomach	–	119–221
	Proximal small intestine	–	137–300
	Distal small intestine	–	–

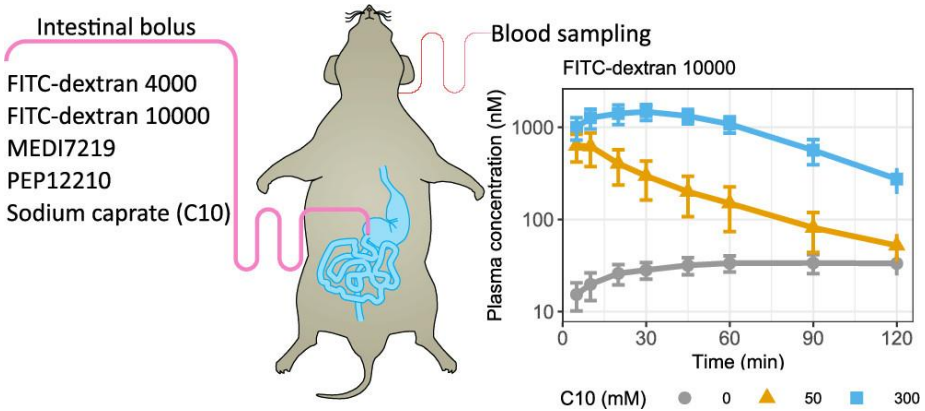
References: a: [15], b: [16], c: [17] and d: [14].

[1] Holm et al. Int J Pharm 2013; [2] Christfort et al. Eur J Pharm Biopharm 2019

Preclinical rat PK models – to cannulate the bile duct or not?

Intraduodenal or intrajejunal route of administration commonly used to assess peptide + permeation enhancer (PE) absorption in rats

- Conscious vs unconscious rat models utilized
- Bile duct cannulation (BDC) employed by some institutions e.g., AstraZeneca papers[1]
  - If bile has a **positive effect** on peptide absorption = BDC may **underestimate** peptide bioavailability
  - If bile has a **negative effect** on peptide absorption = BDC may **overestimate** peptide bioavailability

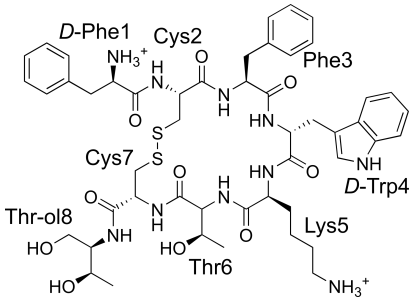


[1] Berg et al. Mol Pharm 2022

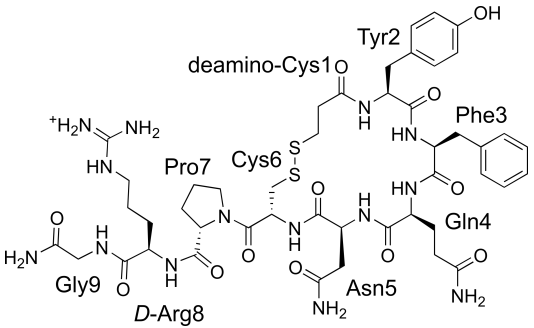
Research hypotheses

- Primary hypothesis: that water-soluble macrocyclic peptide (MCP) drugs will interact with bile salt micelles & bile salt-phospholipid mixed micelles in solution
- Secondary hypothesis: that hydrophobic interactions between aromatic amino acid residues and bile salts/phospholipids drive the interaction between octreotide & biorelevant colloids in solution

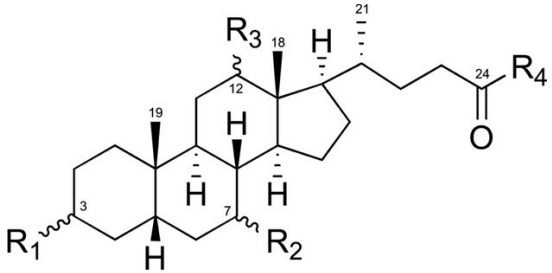
Octreotide
MW 1019 Da
Aqueous solubility >10 mg/mL
BCS Class III
Oral bioavailability ~0.7% (+ PE)

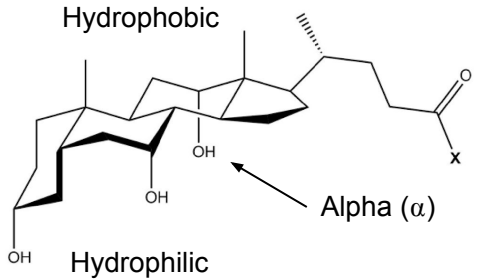


Desmopressin
MW 1069 Da
Aqueous solubility >50 mg/mL
BCS Class III
Oral bioavailability ~0.1% (no PE)



Biologically relevant bile salts

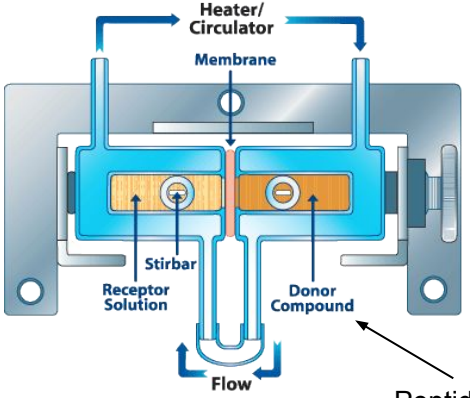




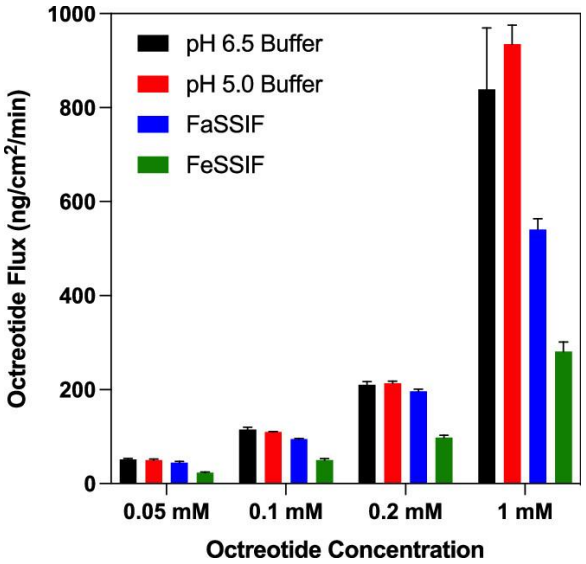
						Measured CMC (mM)
Cholate (NaC)	OH(α)	OH(α)	OH(α)	O^-	trace	10.3 ± 0.1
Taurocholate (NaTC)	OH(α)	OH(α)	OH(α)	$NHCH_2CH_2SO_3^-$	10	9.1 ± 0.4
Glycocholate (NaGC)	OH(α)	OH(α)	OH(α)	$NHCH_2COO^-$	30	9.8 ± 0.5
Taurodeoxycholate (NaTDC)	OH(α)	H	OH(α)	$NHCH_2CH_2SO_3^-$	10	1.5 ± 0.0
Glycodeoxycholate (NaGDC)	OH(α)	H	OH(α)	$NHCH_2COO^-$	15	1.8 ± 0.1
Taurochenodeoxycholate (NaTCDC)	OH(α)	OH(α)	H	$NHCH_2CH_2SO_3^-$	5	1.7 ± 0.0
Glycochenodeoxycholate (NaGCDC)	OH(α)	OH(α)	H	$NHCH_2COO^-$	30	2.1 ± 0.1

FaSSIF & FeSSIF bile salt-phospholipid mixed micelles decrease octreotide flux

3.5 kDa regenerated cellulose dialysis membrane



Peptide ± FaSSIF/FeSSIF

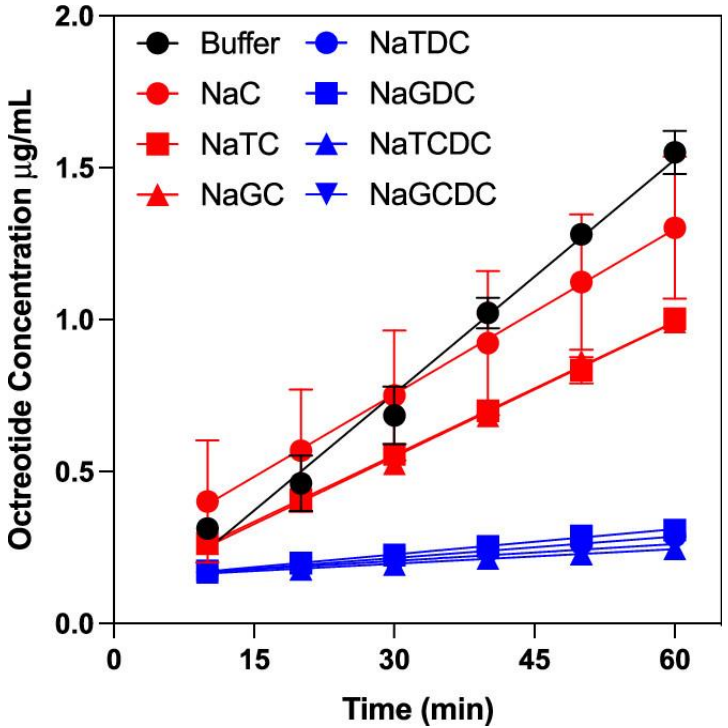


FaSSIF, composed of 3 mM NaTC/0.75 mM PL in pH 6.5 phosphate buffer, decreased octreotide flux by 7-37%

FeSSIF, composed of 15 mM NaTC/3.75 mM PL in pH 5.0 acetate buffer, decreased octreotide flux by 53-70%

Dening et al. Mol Pharm 2021; Dening et al. J Pharm Sci 2024

Pure bile salt micelles (15 mM) decrease octreotide flux

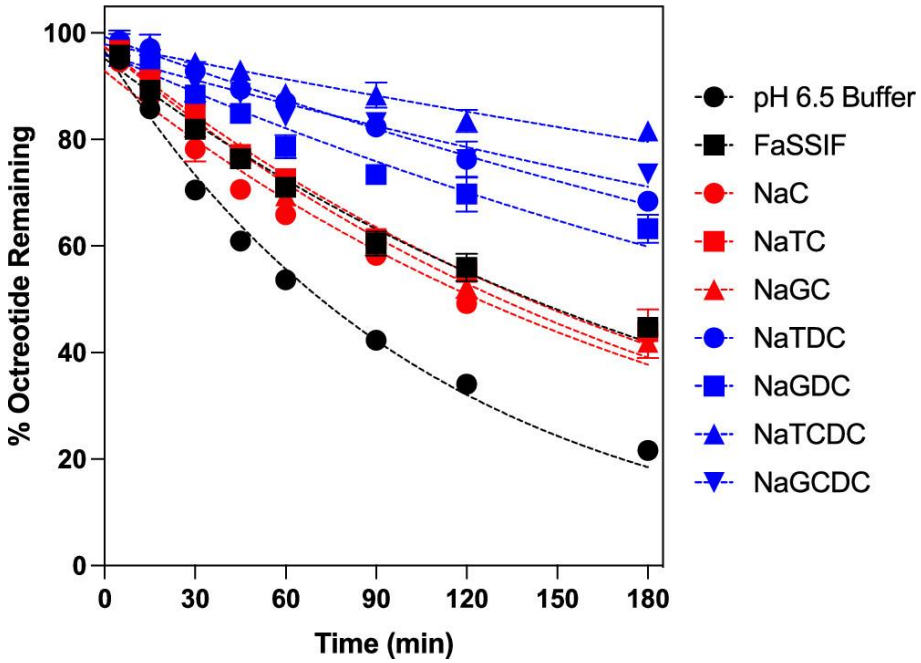


Trihydroxy bile salt (NaC, NaTC, NaGC) micelles decreased octreotide membrane flux by ~30-40%

Dihydroxy bile salt (NaTDC, NaGDC, NaTCDC, NaGCDC) micelles decreased octreotide membrane flux by ~90%

Dening et al. Mol Pharm 2021; Dening et al. J Pharm Sci 2024

Biorelevant colloids protect octreotide from enzymatic degradation



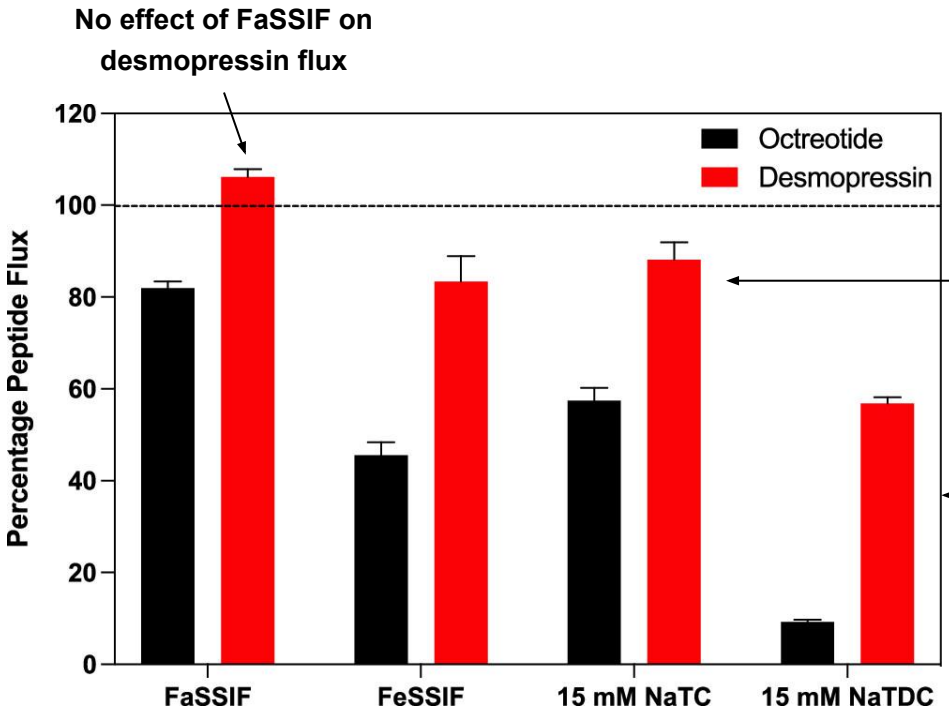
Dihydroxy bile salt (NaTDC, NaGDC, NaTCDC, NaGCDC) micelles increased octreotide $T_{1/2}$ to ~4-10 h

Trihydroxy bile salt (NaC, NaTC, NaGC) micelles increased octreotide $T_{1/2}$ to ~140 min *e.g.*, similar to FaSSIF

FaSSIF increased octreotide $T_{1/2}$ from 75 min (buffer) to 153 min in the presence of 10 mg/mL pancreatin

Dening et al. Mol Pharm 2021; Dening et al. J Pharm Sci 2024

Bile salt micelles & bile salt-phospholipid mixed micelles also decrease desmopressin flux



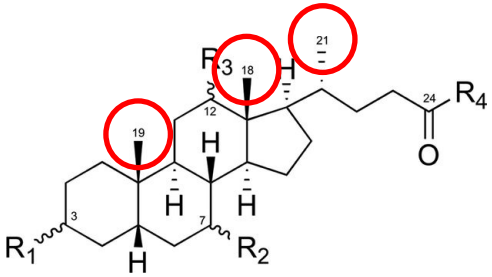
Desmopressin interacts with bile salt micelles & bile salt/phospholipid mixed micelles to a lesser extent than octreotide

For both peptides, dihydroxy bile salts have a larger effect than trihydroxy bile salts

Dening et al. Mol Pharm 2021; Dening et al. J Pharm Sci 2024

Characterizing trihydroxy vs. dihydroxy bile salt micelles – ^{1}H DOSY NMR

Dihydroxy bile salt micelles have a much larger effect on octreotide membrane flux & enzymatic stability than trihydroxy bile salt micelles – why?



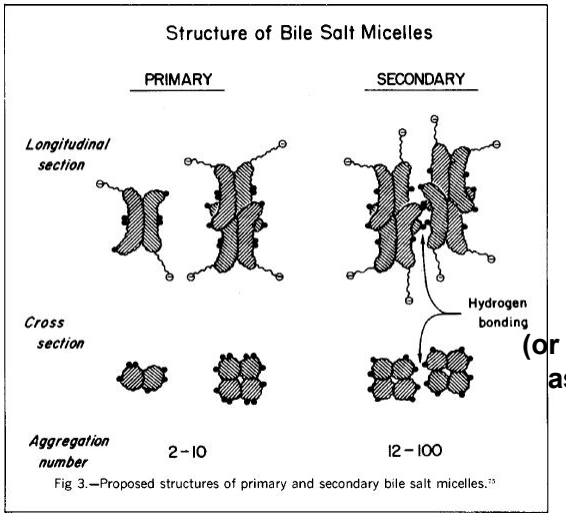


Fig 3.—Proposed structures of primary and secondary bile salt micelles.[75]

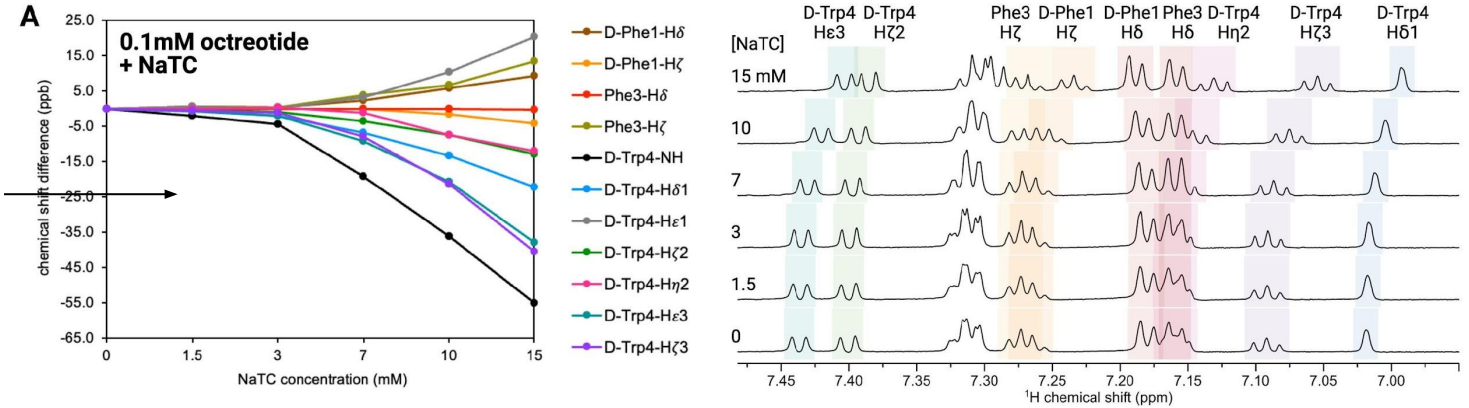
(or hydrophobic association)

Bile Salt	Diffusion Coefficient (x 10^{-10} m^2/s)	Hydrodynamic Radius (nm)	CMC (mM)
NaC	2.96 ± 0.04	0.8 ± 0.0	10.3 ± 0.1
NaTC	3.39 ± 0.05	0.7 ± 0.0	9.1 ± 0.4
NaGC	3.43 ± 0.04	0.7 ± 0.0	9.8 ± 0.5
NaTDC	1.79 ± 0.01	1.4 ± 0.0	1.5 ± 0.0
NaGDC	1.85 ± 0.01	1.3 ± 0.0	1.8 ± 0.1
NaTCDC	1.44 ± 0.03	1.7 ± 0.0	1.7 ± 0.0
NaGCDC	1.52 ± 0.01	1.6 ± 0.0	2.1 ± 0.1

Carey & Small Arch Int Med 1972; 130 pp. 506-527; Dening et al. Mol Pharm 2021; Dening et al. J Pharm Sci 2024

Interactions of octreotide's individual amino acid residues with bile salts – ^{1}H NMR

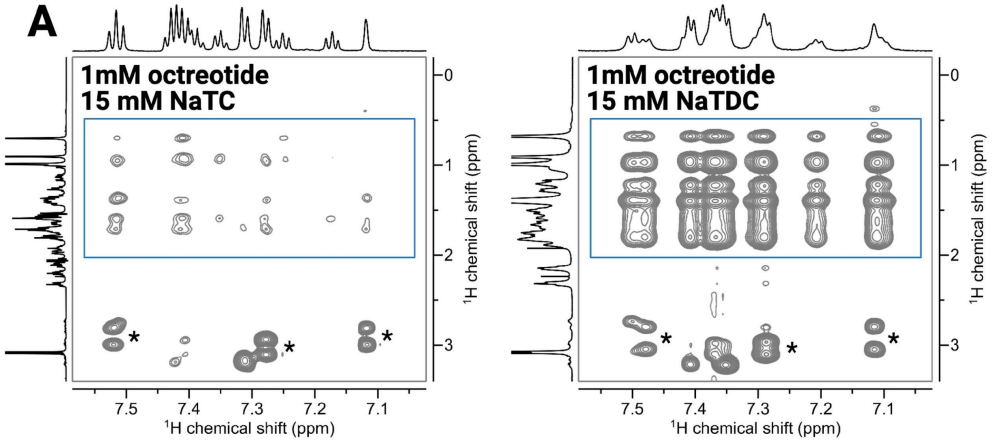
Individual aromatic protons perturbed to different extent(s)



Peak broadening & larger chemical shift perturbations in the presence of dihydroxy bile salts – consistent with flux observations

Dening et al. Mol Pharm 2021; Dening et al. J Pharm Sci 2024

Octreotide and desmopressin interaction with bile salts – ^{1}H NMR



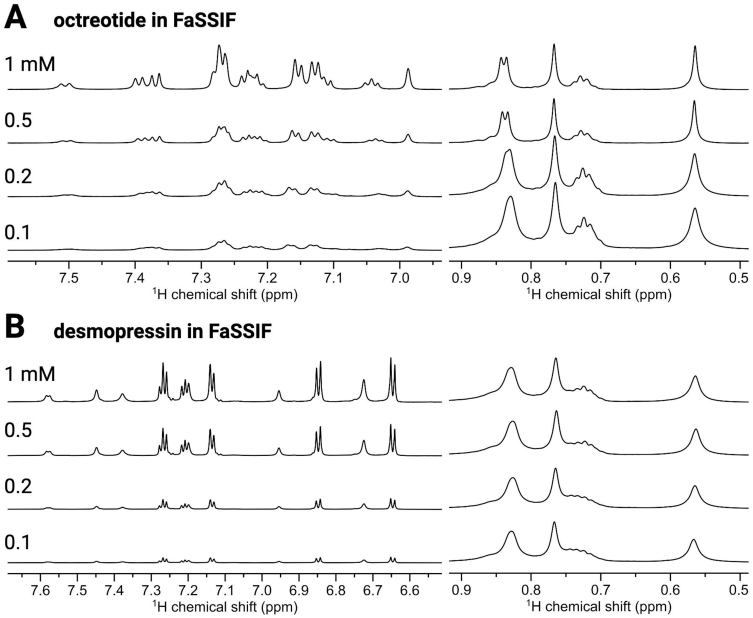
Significant cross-correlations between octreotide's aromatic protons & NaTDC protons (minor cross-correlations with NaTC protons)

Cross-correlations between desmopressin's aromatic protons & NaTDC (but not NaTC) protons; weaker relative to octreotide

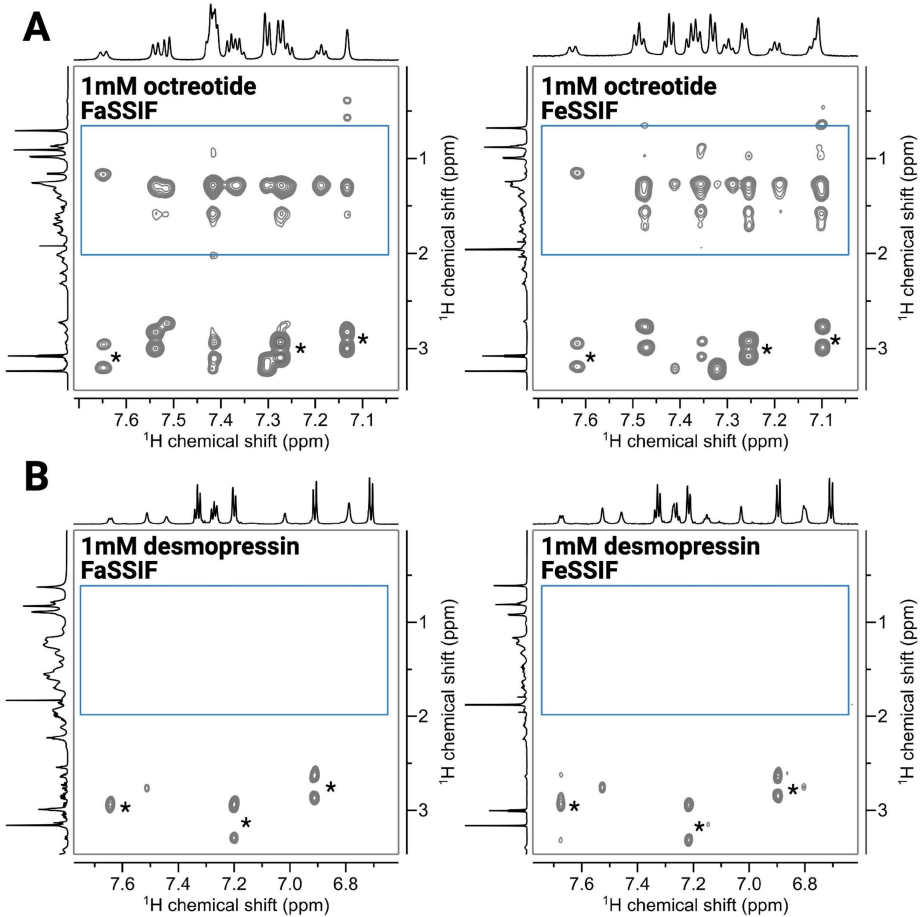
Dening et al. Mol Pharm 2021; Dening et al. J Pharm Sci 2024

Octreotide & desmopressin interaction with FaSSIF colloids – ^{1}H NMR

Octreotide perturbs FaSSIF colloids & induces colloidal restructuring at increasing concentrations



Desmopressin does not interact with FaSSIF colloids – no spectral changes observed



Dening et al. Mol Pharm 2021; Dening et al. J Pharm Sci 2024

Alanine scan of octreotide – can we get a better understanding of the contributions of each individual residue?

Table 2
Peptide sequences with single amino acid mutations indicated in bold. Cys2 and Cys7 residues are connected via a disulfide bond for all peptides, and unless otherwise indicated, all amino acids have L-configuration.

Peptide Name	Sequence	MW (Da)
Octreotide	D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-ol	1019.2
[Ala1]	**Ala**-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr-ol	943.2
[Ala3]	D-Phe-Cys-**Ala**-D-Trp-Lys-Thr-Cys-Thr-ol	943.2
[Ala4]	D-Phe-Cys-Phe-**Ala**-Lys-Thr-Cys-Thr-ol	904.1
[Leu4]	D-Phe-Cys-Phe-**Leu**-Lys-Thr-Cys-Thr-ol	946.2
[Phe4]	D-Phe-Cys-Phe-**Phe**-Lys-Thr-Cys-Thr-ol	980.2
[Ala5]	D-Phe-Cys-Phe-D-Trp-**Ala**-Thr-Cys-Thr-ol	962.2
[Ala6]	D-Phe-Cys-Phe-D-Trp-Lys-**Ala**-Cys-Thr-ol	989.2
[Ala8]	D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-**Ala**-ol	989.2

D-Trp4 (hydrophobicity value = 97) hypothesized to be a key residue: mutated to Ala (41), Leu (97) & Phe (100)

Dening et al. Mol Pharm 2021; Dening et al. J Pharm Sci 2024

Alanine scan of octreotide – what is the contribution of each residue to the interaction with FaSSIF colloids?

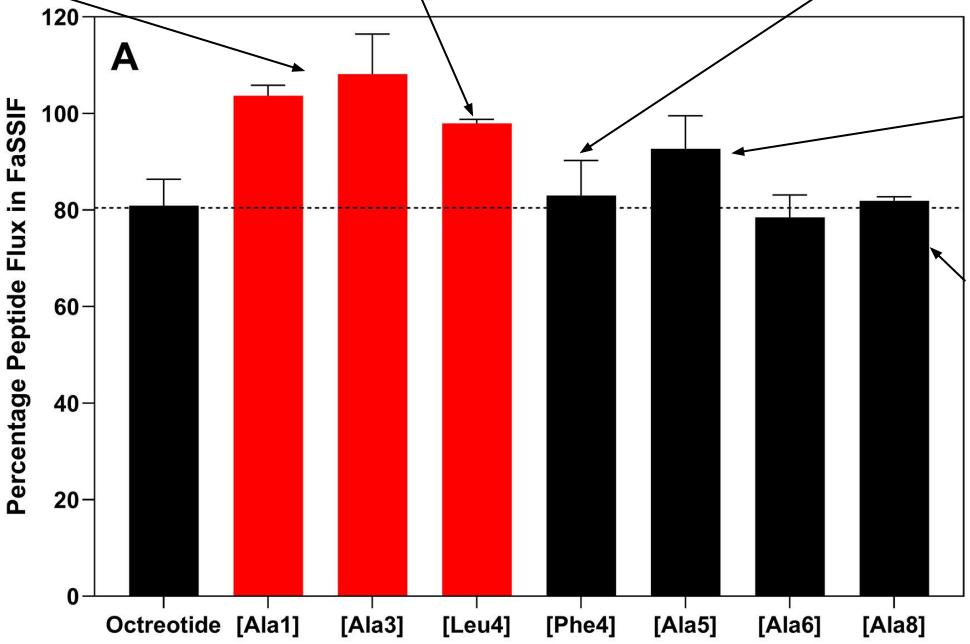
***D*-Phe-Cys-Phe-*D*-Trp-Lys-Thr-Cys-Thr-ol**

Replacing D-Phe1 or Phe3 residues with Ala decreases FaSSIF interaction

Replacing D-Trp4 residue with non-aromatic Leu decreases FaSSIF interaction

Replacing D-Trp4 residue with aromatic Phe does not affect FaSSIF interaction

Octreotide flux in FaSSIF = 81% relative to buffer control



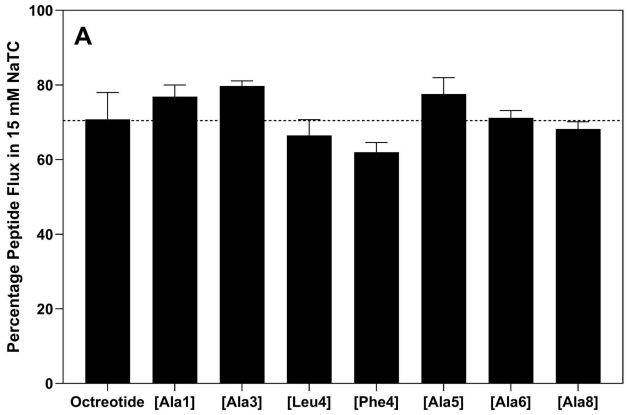
Replacing Lys5 residue with Ala decreases FaSSIF interaction (not significant; $p>0.05$)

Replacing Thr6 & Thr8-ol with Ala does not affect FaSSIF interaction

Data supports that aromatic residues & Lys drive the interaction between octreotide and bile salt/phospholipid mixed micelles

Dening et al. Mol Pharm 2021; Dening et al. J Pharm Sci 2024

Alanine scan of octreotide – what is the contribution of each residue to the interaction with bile salt micelles?



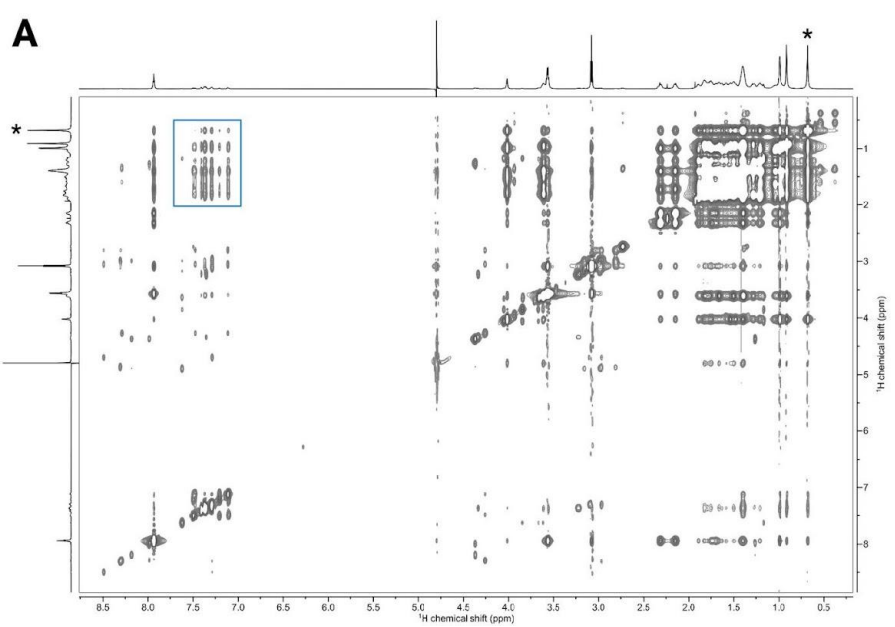
No significant difference in membrane flux between octreotide & each mutated peptide in 15 mM NaTC media – single amino acid mutations do not disrupt peptide-NaTC micelle interactions

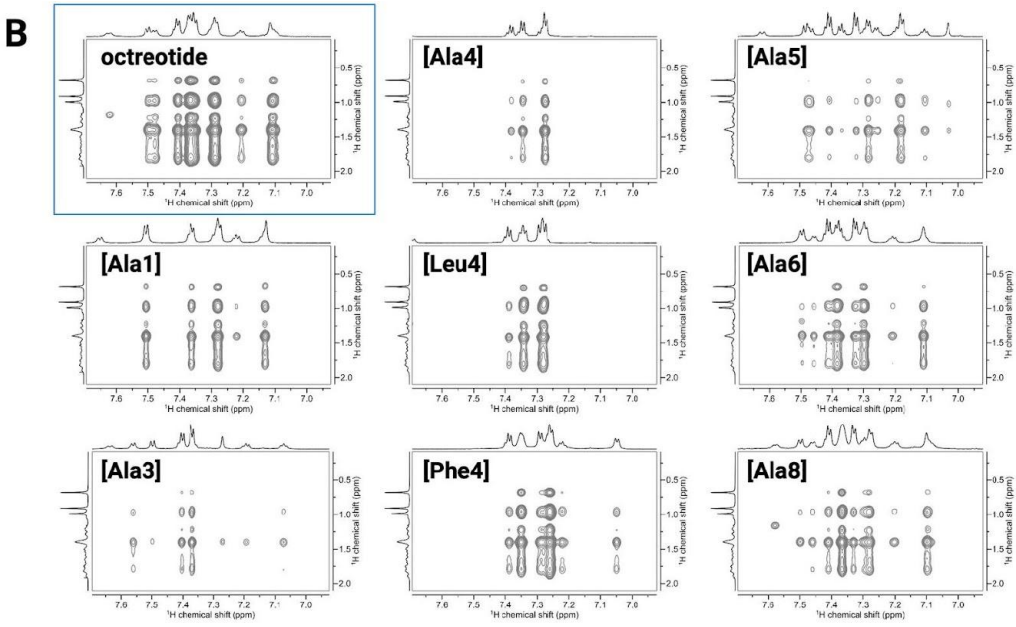
Mutating aromatic or basic amino acid residues decreased the interaction with NaTDC micelles

Dening et al. Mol Pharm 2021; Dening et al. J Pharm Sci 2024

Interactions of individual amino acid residues with bile salts – ^{1}H NMR

All mutated peptides exhibited weaker cross-correlations with NaTDC compared to octreotide





Dening et al. Mol Pharm 2021; Dening et al. J Pharm Sci 2024

To further complicate matters…bile salts also act as membrane PEs

Table 1 Absorption of octreotide in rats

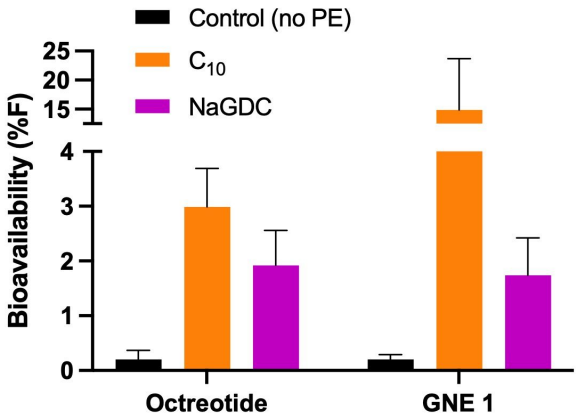
Substance/ composition	*AUC* 0–5 h (ng h ml^{-1})	C_{max} (ng ml^{-1})	*Absorption efficiency* (0–5 h) %
Octreotide i.v.	6.25 ± 1.25	5.84	100
Octreotide i.j.	0.82 ± 0.08	0.34	0.26
i.j. + 1% ursodeoxycholate	14.73 ± 7.21	9.78	4.71
i.j. + 1% chenodeoxycholate	63.19 ± 5.93	32.14	20.22
i.j. + 2% ursodeoxycholate	15.39 ± 1.63	9.56	4.92
i.j. + 2% chenodeoxycholate	56.72 ± 9.95	30.41	18.15

Data represent means ± s.e.mean; $n = 5$; i.v. = intramesenteric administration; i.j. = intrajejunal administration.

Table 2 Absorption of octreotide in human subjects

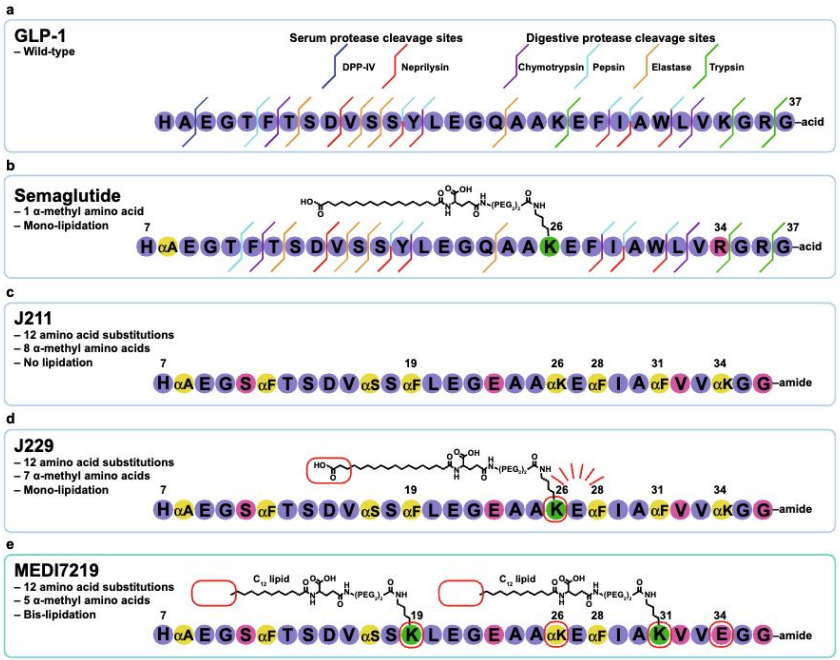
Composition	*Octreotide* (4 mg) + *NA^+-UDCA* (100 mg) (p.o.)	*Octreotide* (4 mg) + *Na^+-CDCA* (100 mg) (p.o.)	*Octreotide* (100 μg) (i.v.)
AUC (ng h ml^{-1})	0.63 ± 0.20	6.10 ± 2.69**	10.78 ± 0.92
F (%)	0.13 ± 0.03	1.26 ± 0.41	100 (reference)
C_{max} (ng ml^{-1})	0.13 ± 0.03	1.45 ± 0.64**	7.92 ± 0.59
T_{max} (h)	3.0 ± 0.47	2.7 ± 0.53	0.5 ± 0.00
$t_{\frac{1}{2},z}$ (h)			1.9 ± 0.16

Data represent mean ± s.e.mean; $n = 10$; p.o. = by mouth; i.v. = intravenous; AUC = area under the plasma concentration-time curve extrapolated to infinity; F = absolute bioavailability in percentage of the dose defined as: $F = (AUC_{p.o.} \times Dose_{i.v.})/(AUC_{i.v.} \times Dose_{p.o.}) \times 100$; C_{max} = maximum plasma concentration, T_{max} = time of C_{max}; $t_{\frac{1}{2},z}$ = terminal half-life for elimination; Na^+-UDCA = sodium ursodeoxycholate; Na^+-CDCA = sodium chenodeoxycholate. Significantly different from Na^+-UDCA-group, $^{**}P < 0.01$, Wilcoxon matched-pairs signed-ranks test.



Fricker et al. Br J Pharmacol 1996

MEDI7219 – a stable GLP-1 RA peptide designed for oral delivery is bioavailable up to 15% + bile salt as a PE



Amino acid substitutions to protect against proteases (natural & alpha-Me) & optimize solubility (Gln to Glu)

High potency required to enable low clinical dose

0-15% F in dogs achieved

Table 2. Formulations prepared for optimization of immediate-release tablet formulation. Cohorts indicate different animal studies. Cohort 1 corresponds to Figure 2A and cohort 2 corresponds to Figure 2B. CDC = chenodeoxycholate; PG = propyl gallate; PK = pharmacokinetic.

Formulation	Permeation Enhancer Content (mg)	Peptide Content (mg)	Permeation Enhancer Ratio (Na CDC:PG)	Absolute Oral Bioavailability, F, (%)	PK Variability at C_{max} (%)
		Cohort 1			
1	50	10	2:1	0.3	110
2	50	10	1:2	1.8	63
3	300	10	1:2	6.3	74
4	300	10	2:1	4.8	35
5	300	1	1:2	10.1	26
6	300	1	2:1	5.0	42
7	50	1	2:1	0.1	36
8	50	1	1:2	0.0	67
9	150	5	1:1	3.2	97
10	150	3	1:2	11.1	100
		Cohort 2			
11	150	10	1:2	13.5	94
12	300	3	1:3	7.5	89
13	300	10	1:2	7.5	119
14	450	3	1:2	7.5	81
15	300	3	1:2	15.5	86
16	300	3	1:1	6.6	74

Pechenov et al. Nat Sci Rep 2021; Tyagi et al. Pharmaceutics 2023

Key takeaways

- Water-soluble macrocyclic peptide drugs interact with endogenous bile salt ± phospholipid micelles in solution
- Aromatic amino acid residues play a key role in driving the interaction between octreotide and biorelevant colloids
- Desmopressin also interacts with biorelevant colloids, but to a lesser extent than octreotide (no Trp residue)
- Dihydroxy bile salt micelles have a much larger effect on peptide solution behavior than trihydroxy bile salt micelles – is commercial FaSSIF/FeSSIF media that only incorporates trihydroxy bile salt appropriate for peptide drugs?

What is the net impact of biorelevant colloids on oral peptide drug absorption and bioavailability?

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