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Pre-clinical pharmacokinetics of selected Quorum Sensing Peptides

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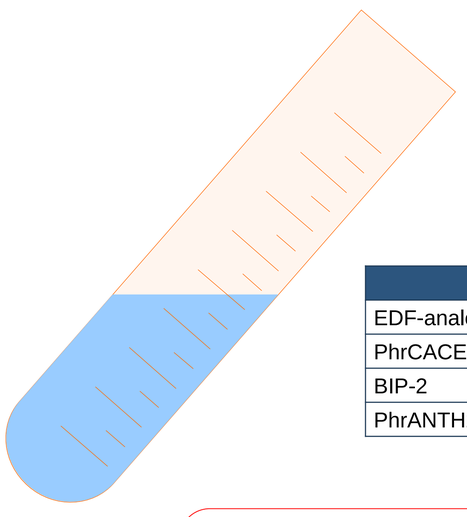
INTRODUCTION & OBJECTIVE

Human beings live in a co-evolutionary association with microorganisms. The collection of these microorganisms is termed the microbiome. Bacteria are able to communicate with each other by quorum sensing molecules. An important group of these molecules are the oligopeptides, mainly produced by Gram-positive bacteria. These quorum sensing peptides (QSP) are able to interact with human eukaryotic cells [1,2]. The pharmacokinetic properties of these peptides are still to be explored.

RESULTS & DISCUSSION



In vitro cell medium & human plasma stability

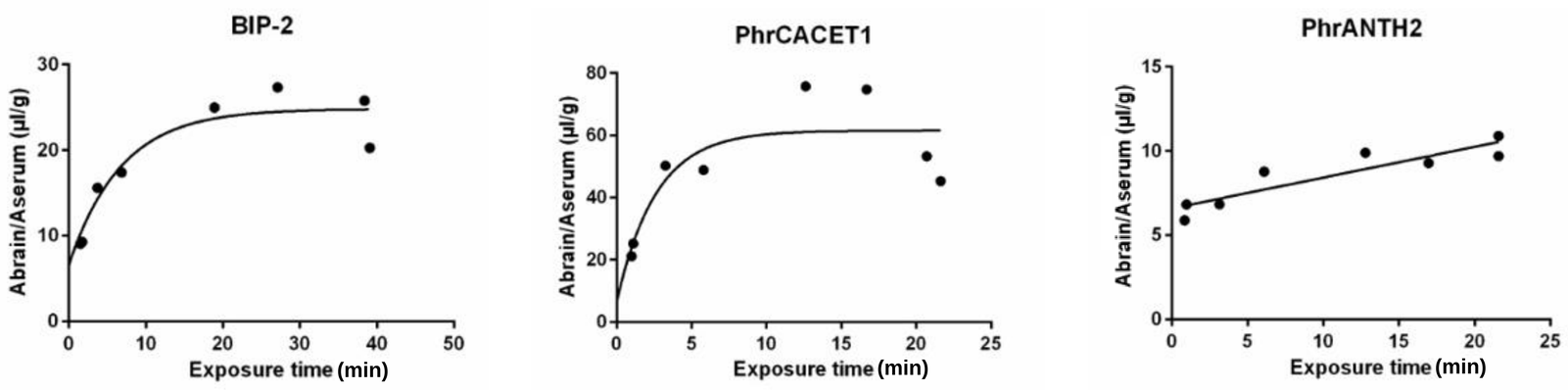
Methods: HPLC-UV and UHPLC-PDA quantification

Peptide	Sequence	Cell medium half-life (hours)	Human plasma half-life (minutes)
EDF-analogue	NWN	42.03	268.2
PhrCACET1	SYPGWSW	9.89	23.6
BIP-2	GLWEDDLLYNINRYAHYIT	26.91	320.7
PhrANTH2	SKDYN	18.39	56.4

QSP are sufficiently stable in cell medium and human plasma to exert biological functions

Methods: *In vivo* (mice) multiple time regression (MTR), efflux and capillary depletion (CD).

BBB penetration

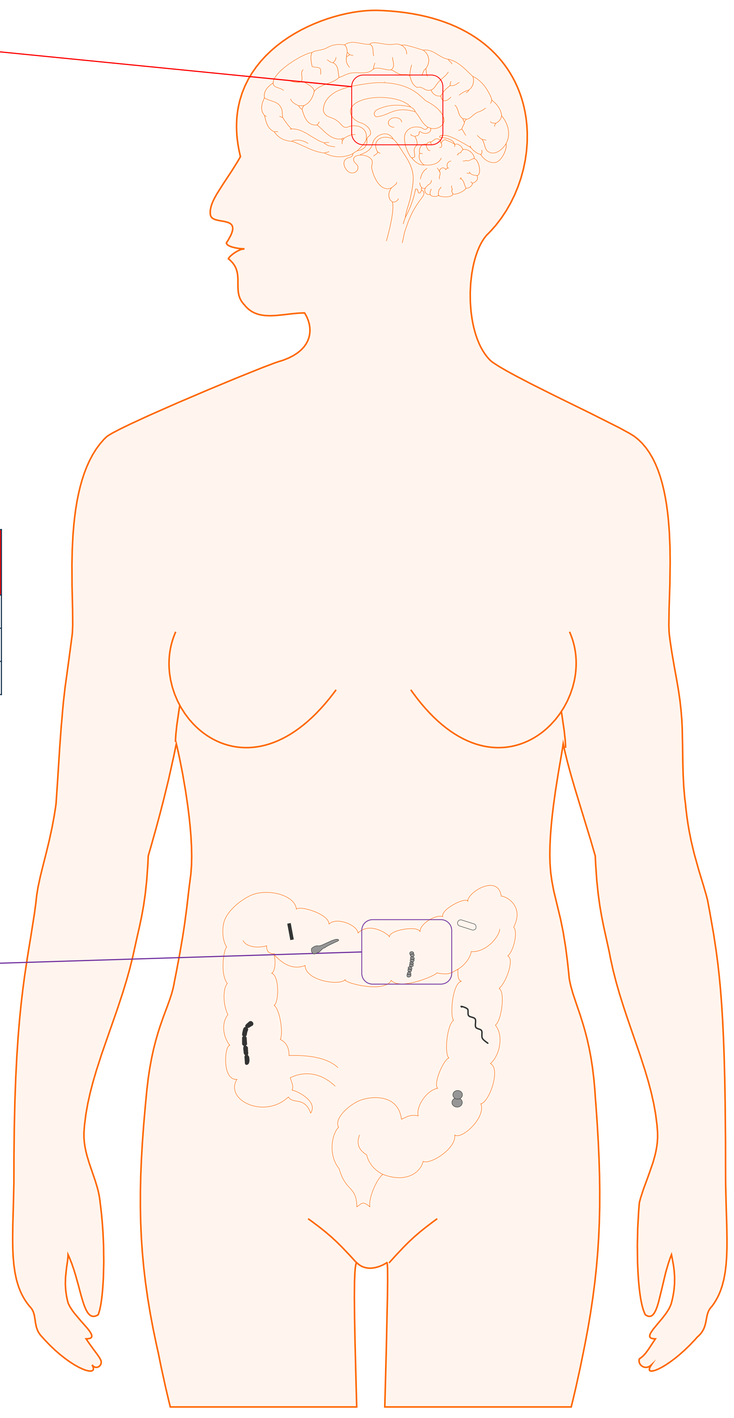


Peptide (^{125}I-)	K_{in} (µl/g x min)[a]	Initial brain distribution volume (µl/g)[a]		Parenchymal fraction (%)	Capillary fraction (%)	k_{out} (min^{-1})[a]
		V_0 (vascular)	V_g (tissue)			
BIP-2	2.68 ± 0.66	(6.59)[b]	18.22 ± 1.43	76.9	23.1	-0.06 ± 0.02
PhrCACET1	20.87 ± 7.97	(6.59)[b]	54.90 ± 5.75	84.9	15.1	-0.02 ± 0.04
PhrANTH2	0.18 ± 0.03	6.59 ± 0.47	NA[c]	79.4	20.6	-0.05 ± 0.07

[a] mean ± 1 standard error
[b] NA (V_0): in the biphasic model, V_0 was set to be equal to the V_0 of Phranth2 *i.e.* 6.59 µl/g
[c] NA (V_g): not applicable

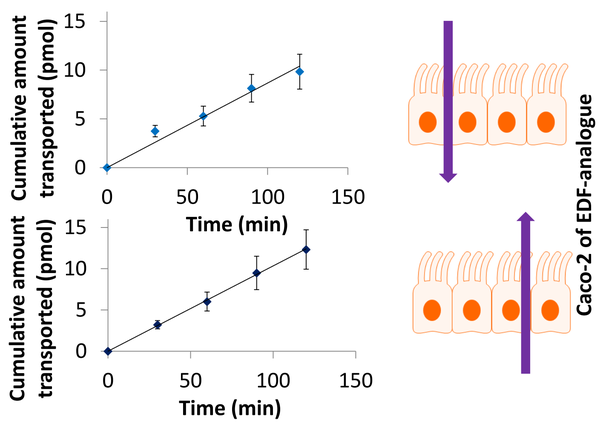
Some QSP are able to cross the blood-brain barrier and reach the brain parenchyma while no significant efflux appears

→ LINK WITH CENTRAL NERVOUS DISORDERS?



Methods: Caco-2 transport studies and HPLC/ESI-MS quantification.

Intestinal permeability



Some QSP cross the intestinal barrier (Caco-2 cell) and reach the blood circulation

→ EFFECT AT DISTANT SITES OF THE BODY?

CONCLUSIONS

Quorum sensing peptides are sufficiently stable in human plasma to exert biological functions. Moreover, they are able to cross the intestinal barrier and thus can have a possible effect at distant sites of the body. Due to the permeability of some QSP through the blood-brain barrier, these peptides can even affect the central nervous system and act as mediators of the gut-brain axis.

REFERENCES

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[2] Wynendaele E, *et al.* (2015). Crosstalk between the microbiome and cancer cells by quorum sensing peptides. Peptides 64: 40-48.
[3] Wynendaele E, *et al.* (2015). Quorum Sensing Peptides Selectively Penetrate the Blood-Brain Barrier. PLoS ONE 10(11): e0142071.