



FACULTY OF PHARMACEUTICAL SCIENCES

Functional drugability of MOR-opioid peptides through desirability

Sylvia Van Dorpe¹, Olga Jedlickova¹, Antita Adriaens², Tim Waelbers², Simon Vermeire², Ingeborgh Polis², Kathelijne Peremans² and Bart De Spiegeleer^{1,*}

¹ Faculty of Pharmaceutical Sciences, Ghent University, DruQuaR group, Harelbekestraat 72, 9000 Gent

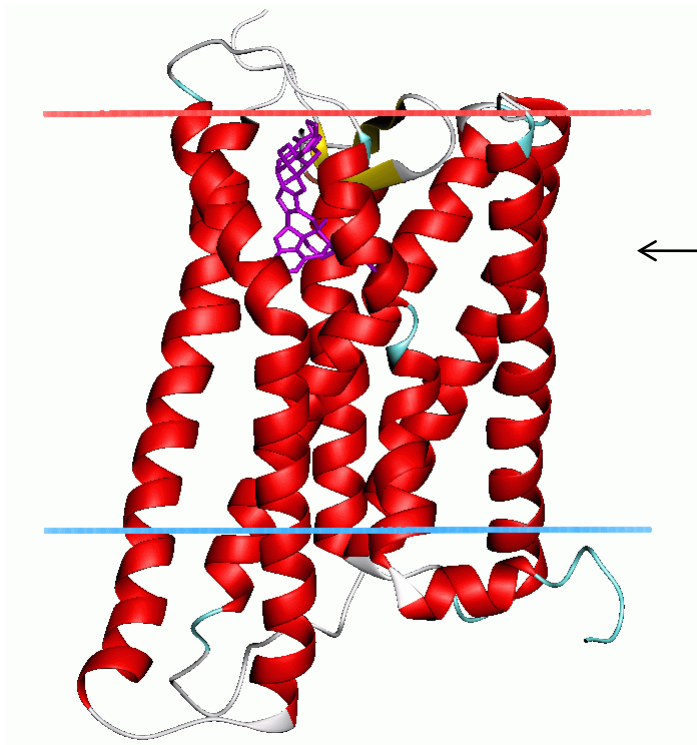
² Faculty of Veterinary Medicine, Ghent University, Salisburylaan 133, 9820 Merelbeke

*Corresponding author: Tel.: +32 9 264 8100; Fax: +32 9 264 8193,
E-mail: Bart.DeSpiegeleer@UGent.be

Outline

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2. Opioid peptides
3. BBB
4. BBB transport study
5. Metabolic stability study
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8. Desirability
9. Desirability results
10. Conclusion

1. Opioid receptors

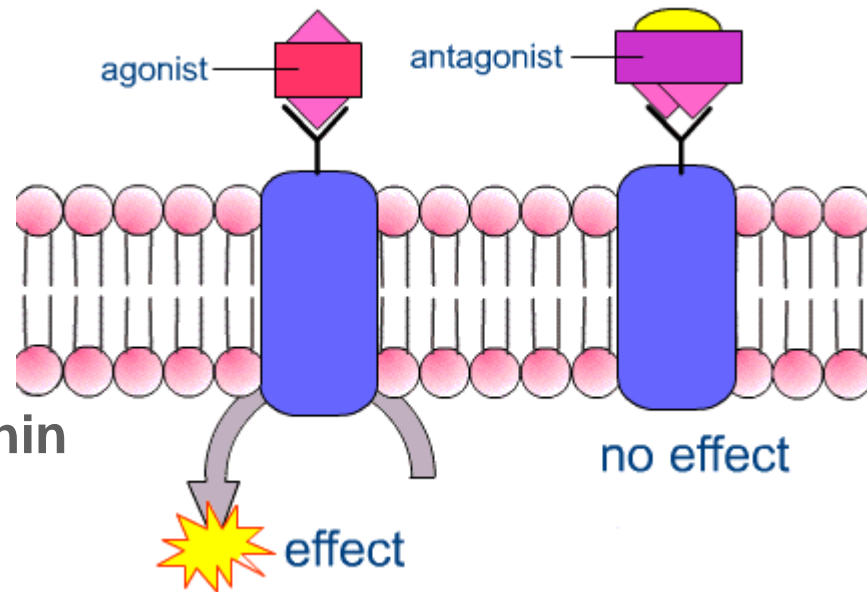


Opioid Receptor (OR)	Subtype
μ	μ_1 μ_2 μ_3
δ	δ_1 δ_2
κ	κ_1 (κ_{1a} , κ_{1b}) κ_2 κ_3
ORL	ORL ₁

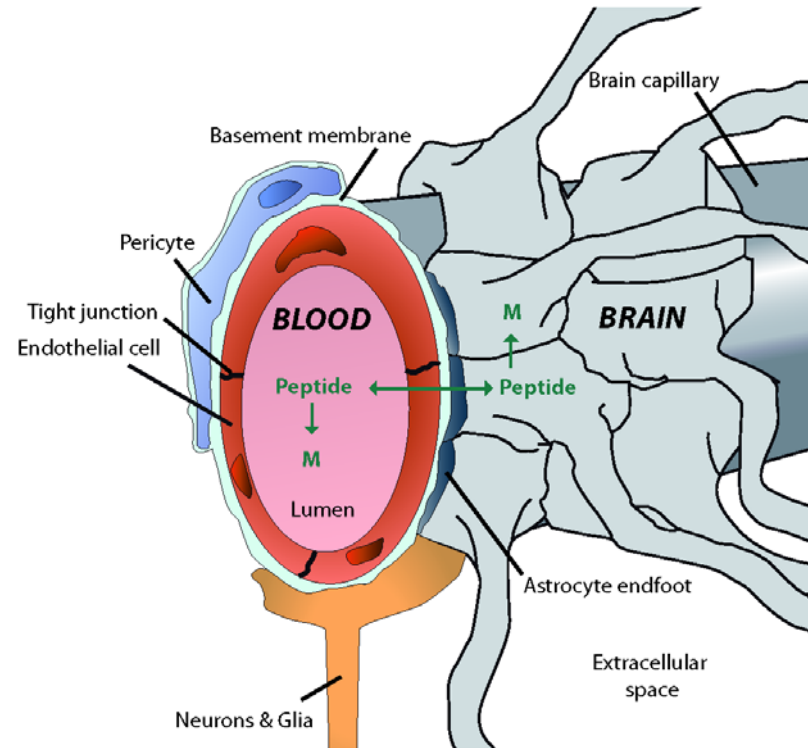
2. Opioid peptides

YPWF-NH ₂	EM-1
YPFF-NH ₂	EM-2
YrF-Sar	TAPS
YaFF-NH ₂	TAPP
YaGF(Me)G-OH	DAMGO
YaFGYPS-NH ₂	Dermorphin

CTAP	fCYwRT-Pen-T-NH ₂
CTOP	fCYw-Orn-T-Pen-T-NH ₂



3. Blood-brain barrier (BBB)



4. BBB transport study

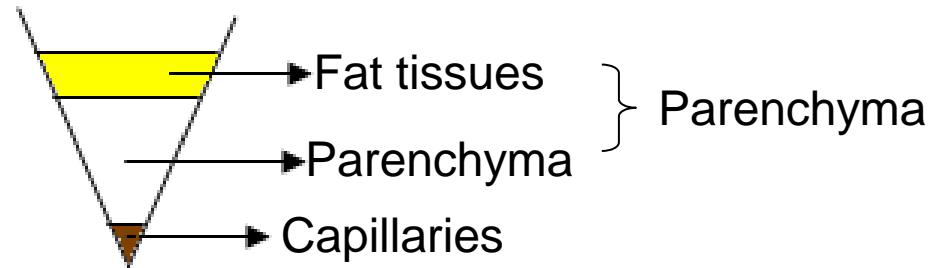
INFLUX

A. Multiple time regression

- IV injection
- Blood & brain collection

B. Capillary depletion

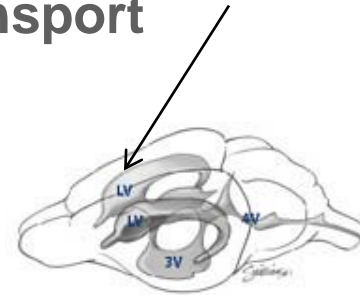
- Distribution EC vs. parenchyma
- Density centrifugation (Dextran)



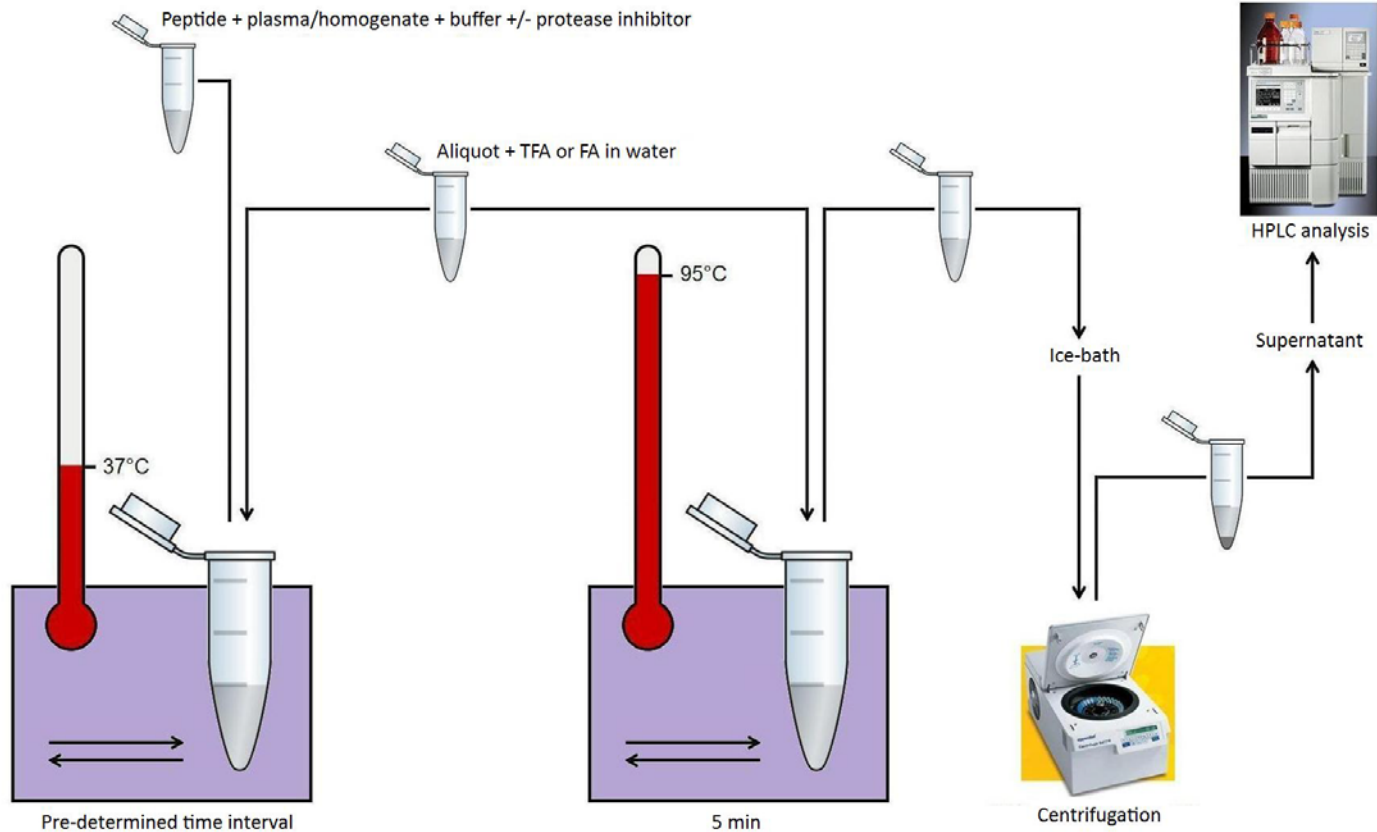
EFFLUX

Brain to blood transport

- ICV injection
- Brain collection
- Remaining activity



5. Metabolic stability study



6. Results

Peptide	Influx K_{in} ($\mu\text{l}/(\text{g} \times \text{min})$)	Efflux $T_{1/2}$ (min)	Met Stab m brain $T_{1/2}$ (min)	Met Stab m plasma $T_{1/2}$ (min)
Dermorphin	2.18	No efflux	1112	574
EM-2	1.14	21.98	88	4
TAPP	1.12	2.82	942	482
EM-1	1.06	14.69	205	7
DAMGO	0.40	10.66	2887	265
CTOP	0.24	No efflux	1499	381
TAPS	0.18	No efflux	1821	790
CTAP	No influx	No efflux	119	60

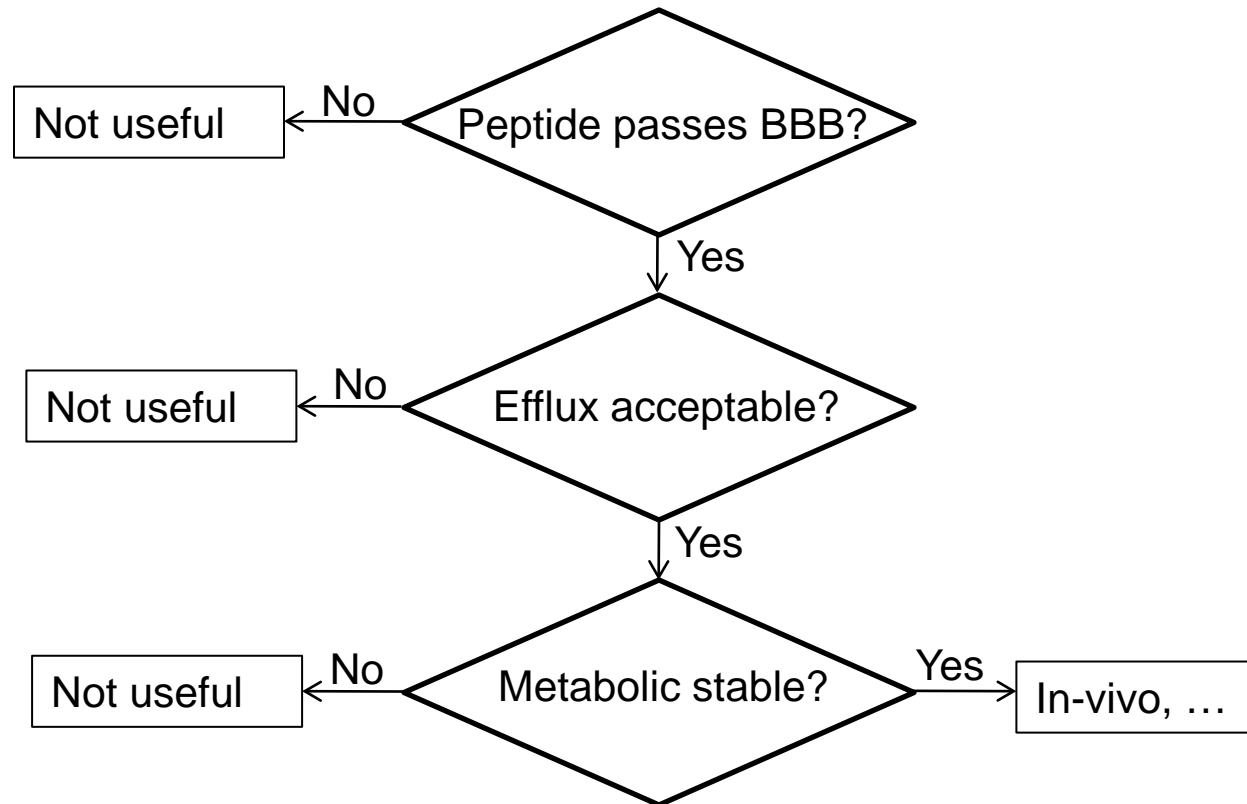
7. Decision flow chart

Dermorphin

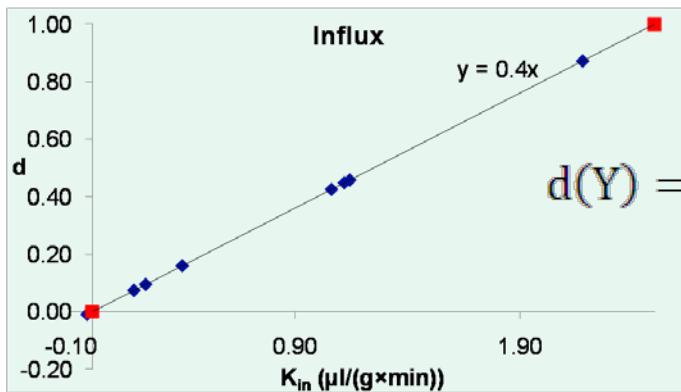
Yes: $K_{in} = 2.18 \mu\text{l/g}\times\text{min}$

Yes: no efflux

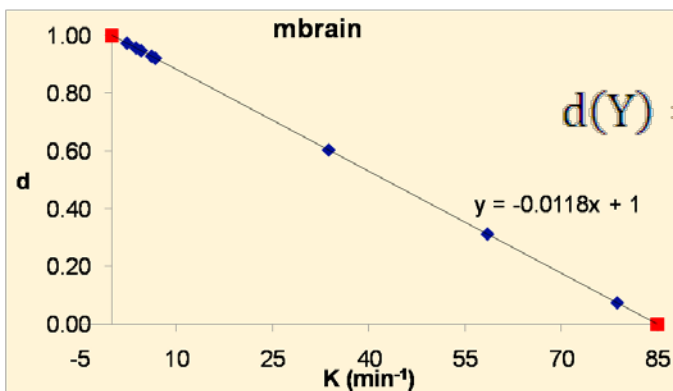
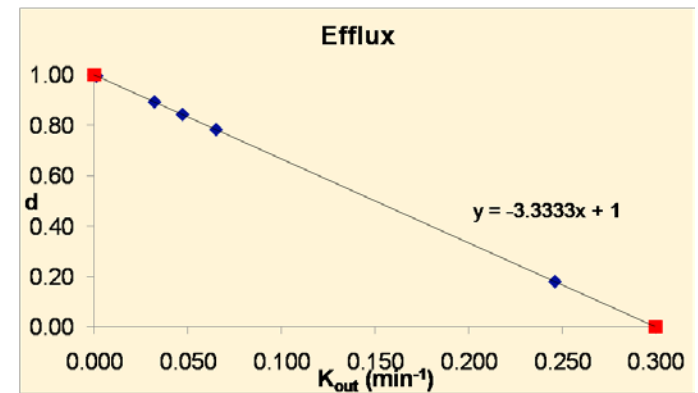
Stable: $T_{1/2} = 1112 \text{ min (brain)}$
 $T_{1/2} = 574 \text{ min (plasma)}$



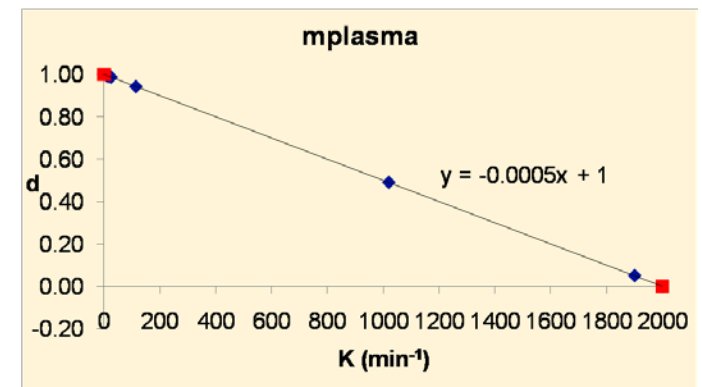
8. Desirability



$$d(Y) = \frac{Y_i - 0.9Y_{min}}{1.1Y_{max} - 0.9Y_{min}}$$



$$d(Y) = \frac{1.1Y_{max} - Y_i}{1.1Y_{max} - 0.9Y_{min}}$$



9. Desirability results

$$D = \sqrt[n]{\prod_{i=1}^n d_i^{p_i}}$$

($p_i = 1$)

Peptide	D-value	Ranking
Dermorphin	0.925	1
EM-1	0.580	2
DAMGO	0.578	3
TAPP	0.555	4
CTOP	0.533	5
TAPS	0.502	6
EM-2	0.300	7
CTAP	0	8

10. Conclusion

1. Dermorphin
 2. EM-1
 3. DAMGO
 4. TAPP
 5. CTOP
 6. TAPS
 7. EM-2
 8. CTAP
- } $K_d = 0.2 - 0.5 \text{ nM}$
} $B_{\max} = 10^1 - 10^2 \text{ fmole/mg protein}$

Thank you for your attention!!!

