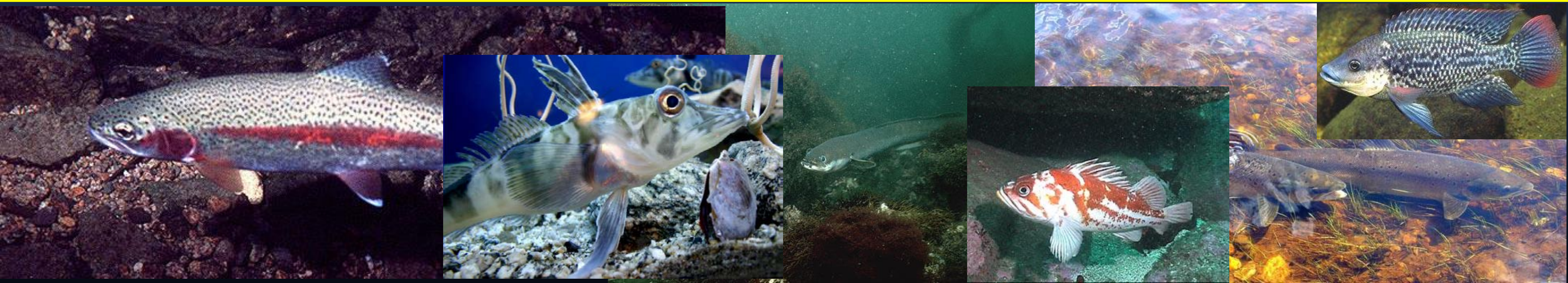
Genome size of 'model' vertebrates

	Haploid DNA content (pg)	Haploid genome size (Mb)	No. of chromosomes (*n*)
Mammals			
Human (*Homo sapiens*)	3.5	3000	23
Mouse (*Mus musculus*)	3.5	3000	20
Rat (*Rattus norvegicus*)	3.5	3000	21
Bird			
Chicken (*Gallus gallus*)	1.25	1200	39
Amphibians			
Xenopus laevis	3.2	3100	18
Xenopus tropicalis	1.78	1700	10
Fish			
Zebrafish (*Danio rerio*)	1.8	1700	25
Medaka (*Oryzias latipes*)	1.1	1100	24
Fugu (*Fugu rubripes*)		400	22

The chicken karyotype includes 30 microchromosomes in addition to nine macrochromosomes. *X. laevis* is a tetraploid whereas *X. tropicalis* is a diploid. The DNA content of Fugu has not been determined. References: chicken [44]; *Xenopus* [45]; zebrafish [46]; medaka [47] and Fugu [1,48].



The SLC family series in teleost fish

"Hot" in fish physiology and pathophysiology

- *Digestive/absorptive system*
- *Sensory system/brain*
- *Muscle and body skeleton*
- *Buoyancy and swim-bladder*
- *Osmoregulation*
- *Respiration and excretion*
- *Neuroendocrine system*
- *Immune system*
- *Skin and pigmentation*

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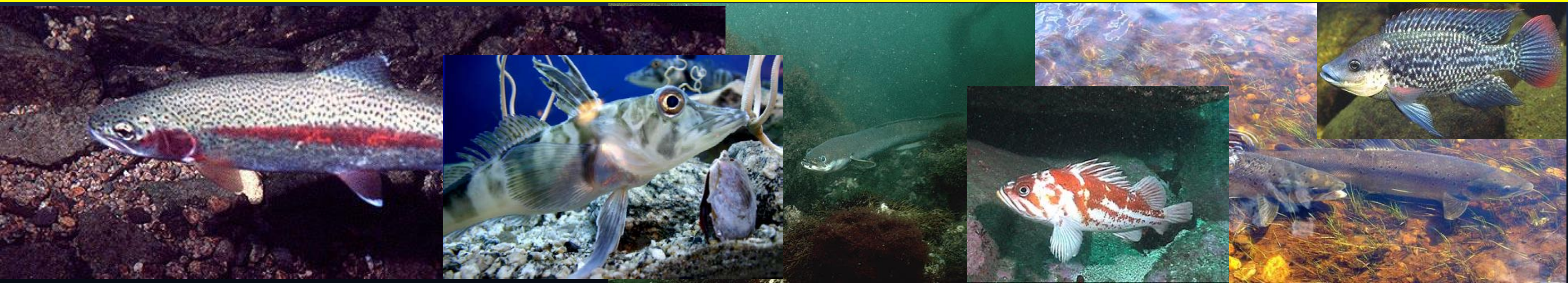
Peptide transport(ers) in teleost fish



SLC15: the proton oligopeptide cotransporter family

Human Gene Name	Protein Name	Predominant Substrates	Transport type / Coupling ions	Tissue distribution and cellular / subcellular expression	Human gene locus	Splice variants and their specific features
SLC15A1	PEPT1	Di- and tripeptides, protons	Cotransporter / H^+	Intestine, kidney apical, lysosomal membrane	13q33-q34	hPEPT1-RF shift of pH sensitivity profile
SLC15A2	PEPT2	Di- and tripeptides, protons	Cotransporter / H^+	Kidney, lung, brain, mammary gland, bronchial epithelium	3q13.3-q21	
SLC15A3	PHT2 hPTR3	Histidine, di- and tripeptides, protons	Cotransporter / H^+	Lung, spleen, thymus (faintly in brain, liver, adrenal gland, heart)	11q12.1	multiple, features unknown
SLC15A4	PHT1 PTR4	Histidine, di- and tripeptides, protons	Cotransporter / H^+	Brain, retina, placenta	12q24.32	multiple, features unknown

The HUGO Solute Carrier Family Series

Adapted from:
Daniel & Kottra, Pflügers Arch. 447:610-618 (2004)

400 dipeptides
8000 tripeptides

Not all di- and tripeptides are good substrates!

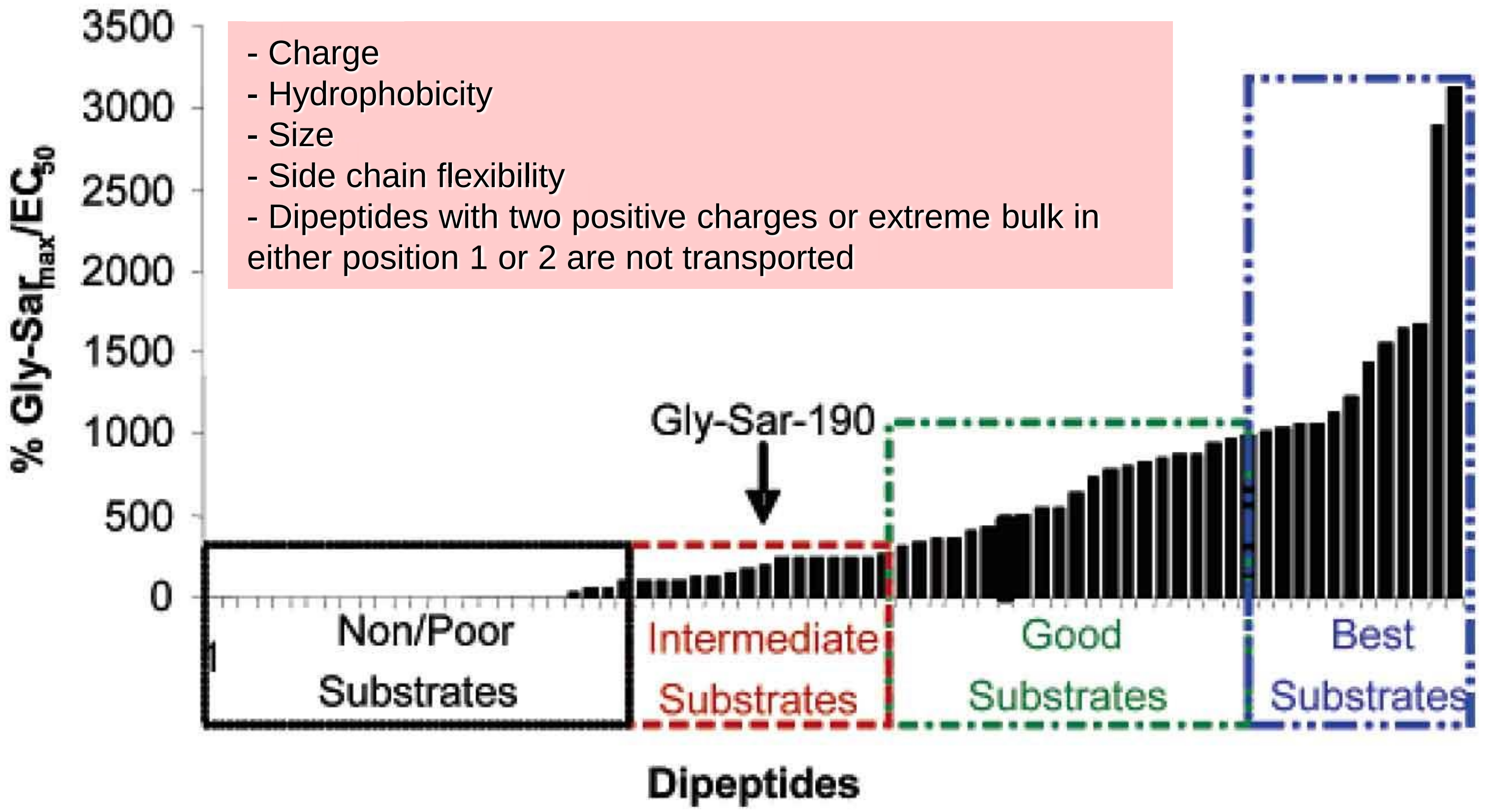


Figure 2. Classification of the dipeptides on the basis of the maximum depolarization achieved in a functional assay relative to the Gly-Sar response (%GS_{max}/EC_{50}). Best substrates >1000, good substrates = 300−1000, intermediate substrates = 100−300, and poor substrates = 0−100.

Adapted from:
Vig et al., J. Med. Chem. 49:3636-3644 (2006)

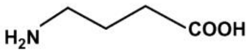
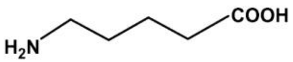
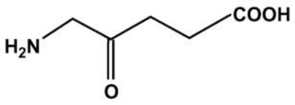
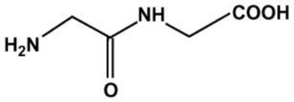
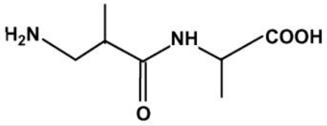
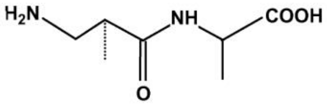
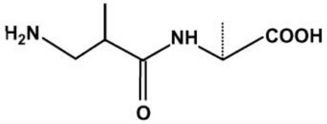
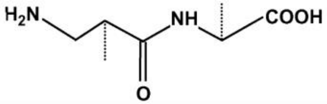
Table 1. PEPT1 Activity and Inhibition Data

no.	name	EC_{50} (mM) mean ± SD	$\%GS_{max}$ mean ± SD	$\%GS_{max}/EC_{50}$	IC_{50} (mM)	no.	name	EC_{50} (mM) mean ± SD	$\%GS_{max}$ mean ± SD	$\%GS_{max}/EC_{50}$	IC_{50} (mM)
1	Ac-Phe-di-iodo-Tyr	NC[a]	NA[b]		0.23	41	His-Gly	0.28 ± 0.03	128 ± 28	460	0.34
2	Ac-Phe-Tyr-NH_2	NC	NA		NA	42	His-His	0.37 ± 0.04	132 ± 33	350	0.40
3	Ala-Ala	0.08 ± 0.01	125 ± 19	1700	0.25	43	His-Trp	0.19	28	150	0.95
4	Ala-Asp	0.23 ± 0.04	124 ± 10	540	0.45	44	Leu-Leu	0.08 ± 0.03	108 ± 29	1400	0.17
5	Ala-Lys	0.22 ± 0.04	117 ± 16	540	0.28	45	Lys-Arg	NC	NA		7.20
6	Ala-Phe	0.08 ± 0.02	135 ± 34	1700	0.07	46	Lys-Glu	0.53 ± 0.05	121 ± 21	230	0.82
7	Ala-Trp	0.08[c]	64 ± 4	830	0.26	47	Lys-Gly	0.32 ± 0.06	130 ± 27	410	0.38
8	Ala-Tyr	0.06 ± 0.01	90 ± 23	1600	0.17	48	Lys-Lys	NC	NA		10.9
9	Arg-Arg	NC	NA		7.31	49	Lys-Pro	0.19 ± 0.03	138 ± 8	720	0.39
10	Arg-Gly	0.27 ± 0.06	136 ± 32	500	0.39	50	Lys-Trp	NC	NA		0.66
11	Arg-Lys	NC	NA		8.11	51	Lys-Val	0.14 ± 0.06	132 ± 6	960	0.25
12	Asp-Asp	0.99	99 ±11	100	0.63	52	Orn-Orn	NC	NA		NA
13	Asp-Gly	0.44	107 ± 15	240	0.81	53	Phe-Ala	0.11 ± 0.05	108 ± 20	1000	0.07
14	Asp-Trp	0.47 ± 0.36	22 ± 5	46	1.31	54	Phe-Ala-NH_2	0.85	39	50	2.99
15	Asp-Val	0.69 ± 0.28	78 ± 4	110	0.31	55	Phe-Gly	0.11 ± 0.00	120 ± 11	1100	0.17
16	Gln-Gln	0.10 ± 0.02	77 ±12	790	0.15	56	Phe-Phe	0.03 ± 0.02	105 ± 19	3100	0.08
17	Gln-Glu	0.42 ± 0.08	97 ± 4	230	0.51	57	Phe-Tyr	0.03 ± 0.01	78 ± 14	2900	0.02
18	Glu-Glu	1.00 ± 0.17	111 ± 3	110	0.62	58	Pro-Asp	>5	104 ± 30		9.16
19	Glu-Gly	0.51 ± 0.05	122 ± 10	240	0.39	59	Pro-Glu	>5	65 ± 14		12.3
20	Glu-Lys	0.31 ± 0.15	83 ± 12	270	0.72	60	Pro-Gly	NC	42 ± 27		>16
21	Gly	NC	NA	NC	NC	61	Pro-Leu	0.25 ± 0.06	76 ± 4	300	0.62
22	Gly-Arg	0.52 ± 0.05	55 ± 20	100	1.82	62	Pro-Lys	NC	NA		>16
23	Gly-Asp	0.55 ± 0.28	124 ± 16	230	0.38	63	Pro-Pro	0.70 ± 0.16	116 ± 31	170	0.80
24	Gly-Glu	1.10 ± 0.41	113 ± 12	100	0.65	64	Pro-Ser	1.6 ± 0.10	31 ± 25	20	>16
25	Gly-Gly	0.48 ± 0.18	112 ± 18	230	0.82	65	Ser-Ser	0.14 ± 0.02	108 ± 9	770	0.13
26	Gly-Gly-Gly	0.58 ± 0.06	109 ± 10	190	1.07	66	Trp-Ala	0.10 ± 0.02	98 ± 18	1000	0.26
27	Gly-Gly-Gly-Gly	NC	15		NA	67	Trp-Gly	0.26 ± 0.05	92 ± 10	350	0.73
28	Gly-Gly-Gly-NH_2				NA	68	Trp-Trp	NC	NA		0.25
29	Gly-His	0.40 ± 0.06	128 ± 31	320	0.81	69	Trp-Tyr	NC	NA		0.08
30	Gly-Leu	0.17 ± 0.11	103 ± 18	620	0.07	70	Trp-Val	0.05 ±0.02	58 ± 5	1100	0.09
31	Gly-Leu-Gly	0.21 ± 0.05	113 ± 29	530	0.24	71	Tyr-Ala	0.10 ±0.05	102 ± 21	1110	0.11
32	Gly-Leu-Phe	0.28 ± 0.07	83 ± 7	290	0.98	72	Tyr-Gly	0.24 ±0.06	99 ± 18	420	0.33
33	Gly-Lys	0.75 ± 0.37	78 ± 5	100	1.25	73	Tyr-Gly-NH_2	NC	NA		NA
34	Gly-Phe	0.13 ± 0.01	111 ± 17	830	0.17	74	Tyr-Tic-NH_2	NC	NA		NA
35	Gly-Phe-NH_2	NC			NA	75	Tyr-Trp	NC	46 ± 8		0.10
36	Gly-Pro	0.13 ± 0.03	111 ± 27	870	0.33	76	Tyr-Tyr	0.06 ± 0.01	69 ± 12	1200	0.06
37	Gly-Sar	0.54 ± 0.20	101 ± 7	190	1.16	77	Tyr-Tyr-NH_2	NC	NA		9.11
38	Gly-Trp	0.33 ± 0.08	23 ± 7	70	0.52	78	Val	NC	NA	NC	NC
39	Gly-Tyr	0.14 ± 0.01	125 ± 27	870	0.12	79	Val-Trp	0.04 ± 0.01	37 ± 21	950	0.10
40	Gly-Tyr-NH_2	NC	NA		NA	80	Val-Val	0.07 ± 0.02	74 ± 14	1000	0.21
						81	Val-Val-Val	0.21 ± 0.04	99 ± 28	480	0.23

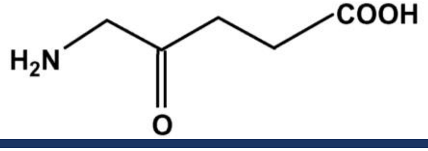
[a] NA = No activity. [b] NC = Not calculable. [c] At places, the standard deviation is not provided. This may be due to either compounds causing insufficient activation of PEPT1 for parameter calculation or not enough repeats (n = 2) for few of the compounds.

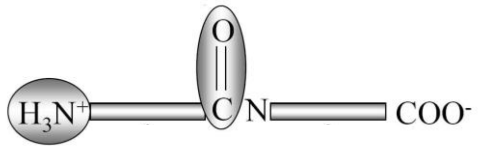
The key structural and conformational elements in PEPT1 substrates and how they affect substrate affinity and electrogenic transport

This series of model compounds has been analyzed with respect to substrate affinity and electrogenic transport under identical experimental conditions in *Pichia pastoris* cells and *Xenopus* oocytes expressing PEPT1. Apparent substrate affinities are derived from competition experiments with the model compounds in P. pastoris cells with a radioactive dipeptide serving as substrate. Inward currents generated by the compounds in *Xenopus* oocytes expressing PEPT1, determined by the two-voltage-clamp technique, are used to express the maximal transport rate. The test compounds have been applied under substrate saturation conditions and maximal transport currents are expressed as I_{max} in percent of that elicited by 10 mM Gly-L-Gln serving as a control in the same batch of oocytes. The comparison shows the most critical structural elements in substrates such as the intramolecular distance between the centers of the amino- and carboxy-terminal head groups and the central carbonyl function. Moreover, the stereoselective recognition of substrate side chains is demonstrated on basis of alanyl-peptides with D- and L-residues at different positions in the dipeptide.

compound	structure	apparent affinity [mM]	transport currents (I_{max} % of control)
4-aminobutyric acid		> 50	0
5-aminopentanoic acid		1.14 ± 0.06	100
5-amino-4-oxo-pentanoic acid		0.27 ± 0.04	100
Gly-Gly		0.20 ± 0.02	100
L-Ala-L-Ala		0.16 ± 0.03	100
D-Ala-L-Ala		0.80 ± 0.06	70
L-Ala-D-Ala		6.12 ± 0.34	30
D-Ala-D-Ala		> 25	0

The key structural and conformational elements in PEPT1 substrates and how they affect substrate affinity and electrogenic transport

compound	structure	apparent affinity [mM]	transport currents (I_{max} % of control)
5-amino-4-oxo-pentanoic acid		0.27 ± 0.04	100



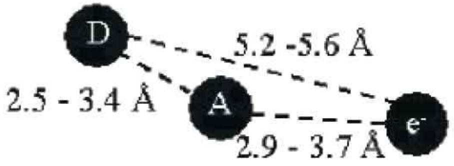
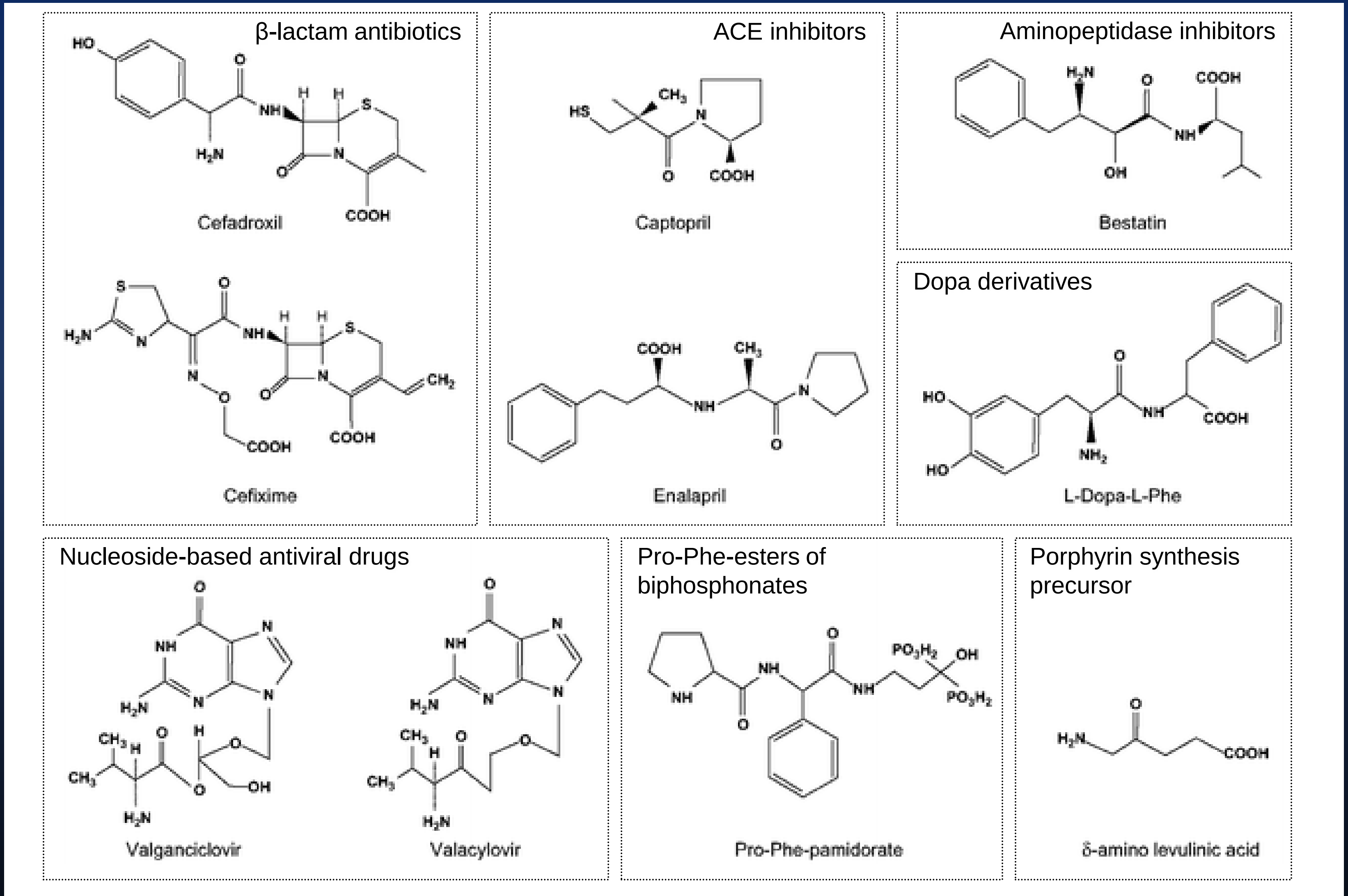


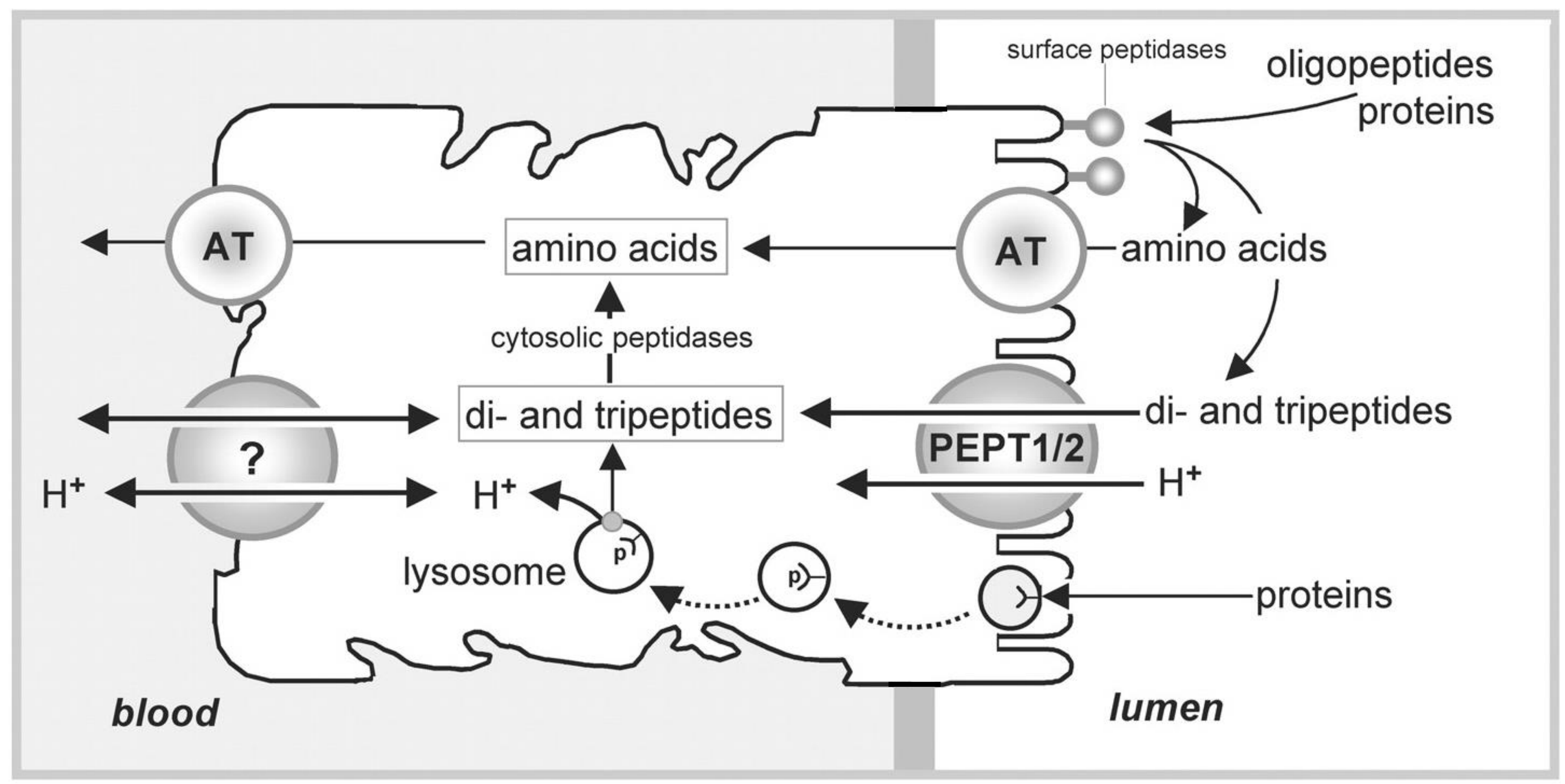
Figure 1. The 3D structure of **14** and the three-point recognition model for PEPT1 (D = Donor, A = Acceptor and e⁻ = high electron density).

Adapted from:
Gebauer et al., J. Med. Chem. 46:5725-5734 (2003)

Molecular structures of selected pharmacologically important compounds that serve as substrates of PEPT1



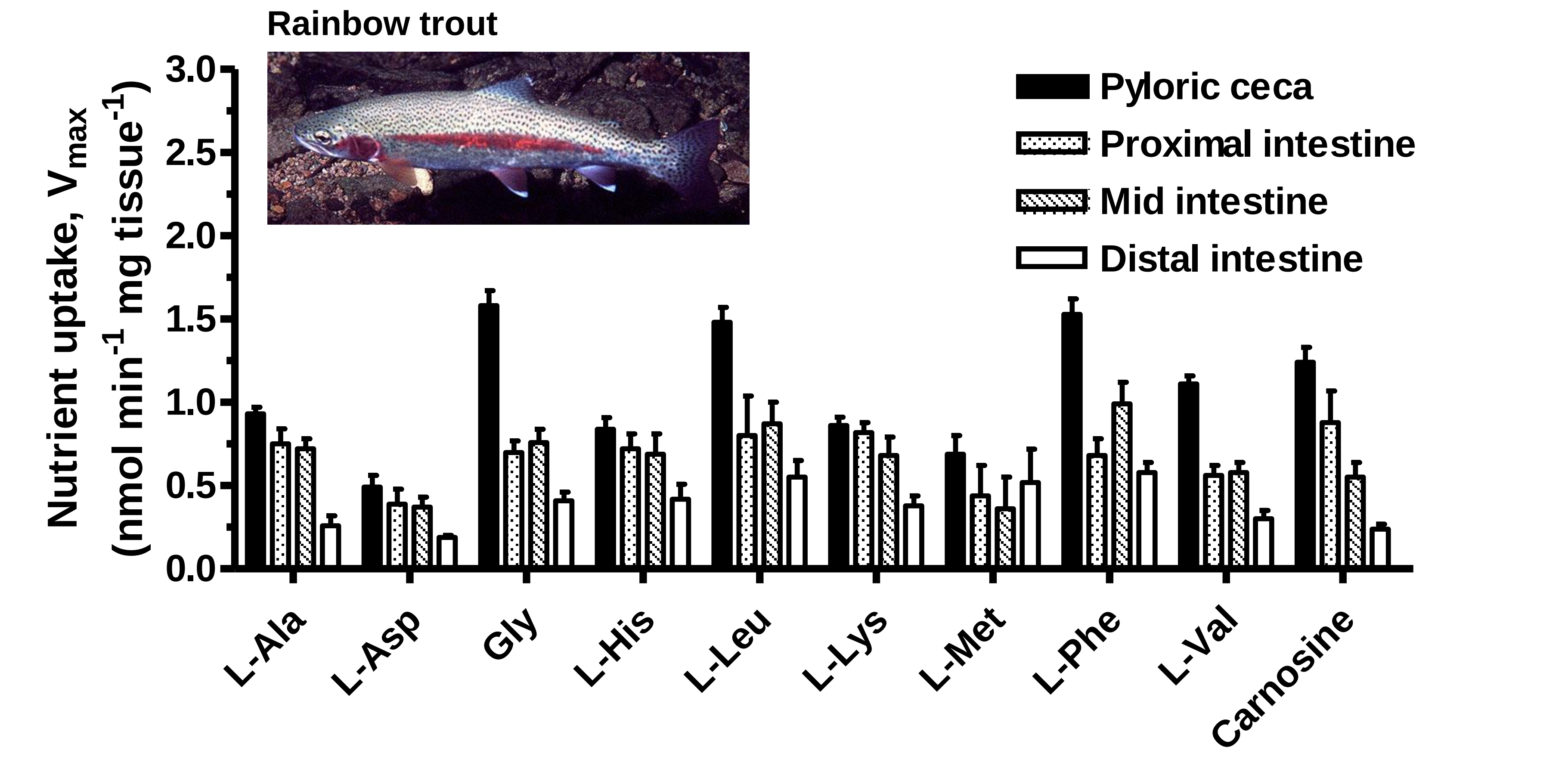
A simplified model for di- and tripeptide transport in epithelial cells



p, proteins; AT, amino acid transporter(s)

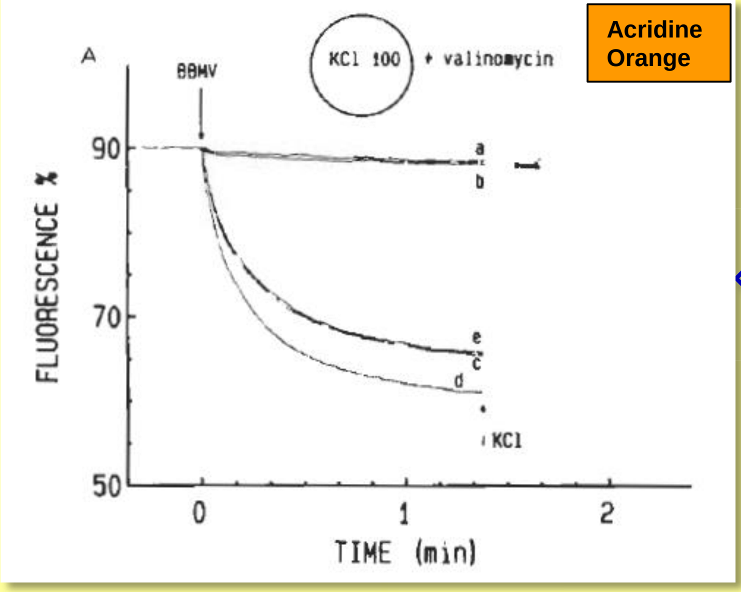
Adapted from:
Daniel & Rubio-Aliaga, Am. J. Physiol. Renal Physiol. 284:F885 (2003)

Uptake of nine amino acids and the dipeptide β-Ala-L-His (carnosine) in rainbow trout gut



Data adapted from:
Buddington & Diamond, Am. J. Physiol. 252:G65 (1987)

Carrier-mediated transport of peptides in fish intestine



Species	Tissue (Method)	Substrate	K_m (mM)	Reference
European eel (*A. anguilla*)	Whole intestine (BBMV)	Gly-L-Pro	1.27 ± 0.01	Maffia et al. (1997) *Am. J. Physiol.* 272:R217
			1.32 ± 0.10	Maffia et al. (1997) *Am. J. Physiol.* 272:R217
			1.04 ± 0.31	Verri et al. (2000) *J. Exp. Biol.* 203:2991
			1.43 ± 0.53	Verri et al. (2008) *Aquacult. Nutr.* 14:341
			1.68 ± 1.01	Verri et al. (2008) *Aquacult. Nutr.* 14:341
		D-Phe-L-Ala	0.74 ± 0.16	Verri et al. (2000) *J. Exp. Biol.* 203:2991
			1.19 ± 0.52	Verri et al. (2000) *J. Exp. Biol.* 203:2991
		Gly-Gly	12.36 ± 3.13	Verri et al. (1992) *Biochim. Biophys. Acta* 1110:123
			1.81 ± 0.49	Verri et al. (2000) *J. Exp. Biol.* 203:2991
			1.59 ± 0.40	Verri et al. (2008) *Aquacult. Nutr.* 14:341
			2.49 ± 0.84	Verri et al. (2008) *Aquacult. Nutr.* 14:341
		Gly-L-Ala	0.97 ± 0.42	Verri et al. (2000) *J. Exp. Biol.* 203:2991
		Gly-L-Asn	2.59 ± 0.73	Verri et al. (2000) *J. Exp. Biol.* 203:2991
		Gly-Sar	1.75 ± 0.47	Verri et al. (2000) *J. Exp. Biol.* 203:2991
		L-Pro-Gly	0.87 ± 0.36	Verri et al. (2000) *J. Exp. Biol.* 203:2991
Mozambique tilapia (*O. mossambicus*)	Whole intestine (BBMV)	Gly-L-Phe	9.8 ± 3.5	Reshkin & Ahearn (1991) *Am. J. Physiol.* 260:R563
	Upper one-half intestine (BBMV)	Gly-Sar	0.56 ± 0.08	Thamotharan et al. (1996) *Am. J. Physiol.* 270:R939
Antarctic icefish (*C. hamatus*)	Whole intestine (BBMV)	Gly-L-Pro	0.806 ± 0.161	Maffia et al. (2003) *J. Exp. Biol.* 206:705
Mozambique tilapia (*O. mossambicus*)	Upper one-half intestine (BBMV)	Gly-Sar	13.27 ± 3.80	Thamotharan et al. (1996) *Am. J. Physiol.* 270:R948
Atlantic salmon (*S. salar*)	Pyloric ceca (everted sleeves)	Gly-L-Pro	0.5 ± 0.4	Bakke-McKellep et al. (2000) *Fish Physiol. Biochem.* 22:33
	Mid intestine (everted sleeves)		1.5 ± 0.4	Bakke-McKellep et al. (2000) *Fish Physiol. Biochem.* 22:33
	Distal intestine (everted sleeves)		ND	Bakke-McKellep et al. (2000) *Fish Physiol. Biochem.* 22:33
	Proximal intestine (everted sleeves)	Gly-Sar	8.579 ± 5.327	Nordrum et al. (2000) *Comp. Biochem. Physiol. B* 125:317
			13.120 ± 6.620	Nordrum et al. (2000) *Comp. Biochem. Physiol. B* 125:317
			1.370 ± 0.118	Nordrum et al. (2000) *Comp. Biochem. Physiol. B* 125:317
Rainbow trout (*O. mykiss*)	Proximal intestine (everted sleeves)	Gly-Sar	9.774 ± 8.736	Nordrum et al. (2000) *Comp. Biochem. Physiol. B* 125:317
			0.747 ± 0.051	Nordrum et al. (2000) *Comp. Biochem. Physiol. B* 125:317
			5.270 ± 1.41	Nordrum et al. (2000) *Comp. Biochem. Physiol. B* 125:317

Peptide transport(ers) in the zebrafish