

Neuropeptidases

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Overview

The term 'neuropeptidases' refers to those enzymes that participate in the inactivation of synaptically released neuropeptides and therefore serve to turn off the generated peptide signal. In general, these enzymes are integral plasma membrane proteinases located as ectoenzymes. Some of the enzymes listed below are able to hydrolyze neuropeptides, but are either present as cytosolic enzymes or not present as ectoenzymes. Their physiological roles are therefore not fully established.

To date, only a relatively small group of CNS peptidases have been characterized as neuropeptide-inactivating ectoenzymes. The majority are zinc metalloenzymes for which specific and potent inhibitors have generally been developed. Some of these are found in abundance elsewhere, especially the renal brush border membrane, but others appear to be more specific to the nervous system, e.g. pyroglutamyl aminopeptidase II. Neprilysin (NEP) is the prototype neuropeptidase originally discovered in the CNS as an enkephalin-degrading activity and subsequently as a substance P-hydrolyzing enzyme. It is appropriately located on neuronal membranes especially in the striatonigral pathway. Thus, it can act in an analogous manner to that of acetylcholinesterase at cholinergic terminals. Like several other neuropeptidases, it is also present in cells of the immune system where it may hydrolyze immunoregulatory peptides. NEP is a broadly specific enzyme hydrolyzing a wide range of susceptible peptide substrates. Some other neuropeptidases appear to be much more substrate-specific. For example, pyroglutamyl amino-peptidase II appears to hydrolyze thyrotropin releasing hormone (TRH) exclusively.

Studies of changes in levels of neuropeptides in neurological disease have been limited in extent and no consistent pattern yet emerges. Likewise, factors regulating the expression of neuropeptidases both in the normal and the pathological state in the nervous system are little explored. Inhibitors of neuropeptidases are useful both as pharmacological tools in studies of neuropeptide physiology and also as potential therapeutic agents.

Selective inhibitors of these enzymes have, to date, been obtained from natural products (e.g. phosphoramidon as an NEP inhibitor) or designed by analogy with similar enzymes from bacterial or other sources (e.g. thermolysin). Dual peptidase inhibitors (e.g. of NEP and angiotensin converting enzyme (ACE)) are increasingly finding favor as potential new therapeutics. Design of NEP and neurolysin inhibitors, in particular, will be aided by their recent three-dimensional structures which have been solved. We can expect a rapid expansion of peptidase discovery in the coming years. For example, genome sequencing studies reveal that there are probably 8-10 NEP-like enzymes in the human genome and 24 in *Drosophila*. The chart below describes the best characterized neuropeptidases to date. This includes a novel homolog of angiotensin converting enzyme (ACEH), recently identified from genomic information, which is not inhibited by classical ACE inhibitors.

Neuropeptidases

NAME	ALTERNATE NAME	TYPICAL SUBSTRATES	PROTEINASE CLASS	TYPICAL INHIBITORS	SUBCELLULAR LOCALIZATION
ENDOPEPTIDASES					
Nepriylisin (EC 3.4.24.11)	Endopeptidase-24.11; neutral endopeptidase; enkephalinase; CALLA; CD10	Leu- (L 9133) and Met-Enkephalin (M 6638), ANP (A 1663 (h) , A 8208 (r)), ET-1 (E 7764), ET-2 (E 9012), ET-3 (E 9137), CCK (C 2175), NT (N 6383), SS (S 9129 , S 1763), SP (S 6883), NKA (N 4267), NKB (N 4143)	Metallo (Zn ²⁺)	Phosphoramidon (R 7385) Thiorphan (T 6031)	Plasma membrane
Thimet oligopeptidase (EC 3.4.24.15)	Endopeptidase-24.15; Endo-oligopeptidase A	AI (A 9650 (h) , A 2928 (s)), All (A 9525 (h)), BK (B 3259), LHRH (L 7134 (h) , L 4897 (s)), NT (N 6383), SS (S 9129 , S 1763), Nociceptin/Orphanin FQ (O 4011)	Metallo (Zn ²⁺)	CPP-Ala-Ala-Tyr-pAB CPE-Ala-Ala-Phe-pAB Phosphodiepryl 21	Soluble and (membrane ?) (nuclear ?)
Neurolysin (EC 3.4.24.16)	Endopeptidase-24.16; NT degrading endopeptidase; Oligopeptidase M	AI (A 9650 (h) , A 2928 (s)), All (A 9525 (h)), BK (B 3259), NT (N 6383), SP (S 6883), SS (S 9129 , S 1763)	Metallo (Zn ²⁺)	Phosphodiepryl 03 Pro-Ile Phosphodiepryl 22 Phosphodiepryl 33	Soluble, plasma membrane (mitochondrial ?)
Proline endopeptidase (EC 3.4.21.26)	Post-proline cleaving enzyme; TRH deamidating enzyme	AI (A 9650 (h) , A 2928 (s)), All (A 9525 (h)), BK (B 3259), LHRH (L 7134 (h) , L 4897 (s)), NT (N 6383), SP (S 6883)	Serine	Cbz-Pro-Prolinal	Soluble
AMINOPEPTIDASES					
Aminopeptidase N (L 6007 , L 9776 , L 5006) (EC 3.4.11.2)	Aminopeptidase M; CD13	Leu- (L 9133) and Met-Enkephalin (M 6638), γ - (E 6386) and β -endorphin (E 6261 (h) , E 0637 (b) , E 1142 (r))	Metallo (Zn ²⁺)	Amastatin (A 1276) Bestatin (B 8385) Actinonin (A 6671)	Plasma membrane
Aminopeptidase A (EC 3.4.11.7)	Aspartate or glutamyl aminopeptidase; BPI/6C3 antigen	AI (A 9650 (h) , A 2928 (s)), All (A 9525 (h))	Metallo (Zn ²⁺); Ca ²⁺ -activated	Amastatin (A 1276) EC33	Plasma membrane
Aminopeptidase B (EC 3.4.11.6)	Aminopeptidase MI	Leu- (L 9133) and Met-Enkephalin (M 6638), BK (B 3259)	Thiol Cl- activated	Arphamenine A (A 2302) Arphamenine B (A 2177)	Soluble (?)
Aminopeptidase P (EC 3.4.11.9)	Prolyl aminopeptidase	BK (B 3259), SP (S 6883), PYY (P 1306 (h) , P 5801 (p)), enterostatin NPY (N 5017 (h) , N 3266 (p) , N 6269 (sh))	Metallo (Zn ²⁺)	Apstatin (A 1395)	Plasma membrane GPI-anchored
Dipeptidylpeptidase IV (D 7052) (EC 3.4.14.5)	Post-proline dipeptidyl aminopeptidase; CD26	SP (S 6883), PYY (P 1306 (h) , P 5801 (p)), NPY (N 5017 (h) , N 3266 (p) , N 6269 (sh)), enterostatin	Serine	Diprotin A (I 9759) & B	Plasma membrane
Pyroglutamyl aminopeptidase II	TRH degrading enzyme	TRH (P 1319 , P 2161)	Metallo (Zn ²⁺)		Plasma membrane
Tripeptidyl peptidase III	CCK degrading enzyme	CCK (C 2175)	Serine	Butabindide	Plasma membrane, cytosol

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DIPEPTIDASE					
NAALA dipeptidase	NAAG hydrolase	NAAG (A 5930)	Metallo	Quisqualate (Q 2128)	Plasma membrane
CARBOXYPEPTIDASES					
Carboxypeptidase H (EC 3.4.17.10)	Carboxypeptidase E, enkephalin convertase	Enkephalin hexapeptides, dynorphin (1-13) (D 7017), BK (B 3259), atriopeptin II (A 9035)	Metallo (?)	GEMSA (50975) MGTA	Membrane; secretory vesicles
Carboxypeptidase N (EC 3.4.17.3)	Kininase I, arginine carboxypeptidase	Enkephalin hexapeptides, dynorphin (1-13) (D 7017), BK (B 3259), atriopeptin II (A 9035)	Metallo (Zn ²⁺)	MGTA	Soluble
Carboxypeptidase P (C 5396) (EC 3.4.17.-)	Prolylcarboxypeptidase; angiotensinase C	All (A 9525 (h)), enterostatin	Metallo (?)	EDTA (ED255) o-Phenanthroline (P 1294)	Plasma membrane
Peptidyl dipeptidase A (A 2580 , A 6778) (EC 3.4.15.1)	Angiotensin converting enzyme	AI (A 9650 (h) , A 2928 (s)), BK (B 3259), CCK (C 2175), gastrin (G 9020 (h) , G 1276 (r)), Leu- (L 9133) and Met-Enkephalin (M 6638)	Metallo (Zn ²⁺)	Captopril (C 4042) Lisinopril, Enalaprilat	Plasma membrane; soluble (plasma)
Angiotensin converting enzyme homolog (ACEH)	ACE2	AI (A 9650 (h) , A 2928 (s)), All (A 9525 (h)), des-Arg ⁹ -bradykinin, (Zn ²⁺), NT (N 6383)	Metallo	EDTA (ED255)	Plasma membrane

ABBREVIATIONS

AI: Angiotensin I
AI1: Angiotensin II
ANP: Atrial natriuretic peptide
BK: Bradykinin
CALLA: Common acute lymphoblastic leukemia antigen
CCK: Cholecystokinin
CD: Cluster differentiation antigen
CPE: Carboxy-phenyl ethyl
CPP: Carboxy-phenyl propyl
EDTA: Ethylenediaminetetraacetic acid
ET-1: Endothelin-1
ET-2: Endothelin-2
ET-3: Endothelin-3
GEMSA: Guanidinoethylmercaptosuccinic acid

GPI: Glycosylphosphatidylinositol
LHRH: Luteinizing hormone-releasing hormone
MGTA: 2-Mercaptomethyl-3-guanidinoethylpropranoic acid
NAAG: N-Acetyl-L-aspartyl-L-glutamate
NAALA: N-Acetylated a-linked acidic dipeptidase
NKA: Neurokinin A
NKB: Neurokinin B
NPY: Neuropeptide Y
NT: Neurotensin
PYY: Peptide YY
SP: Substance P
SS: Somatostatin
TRH: Thyrotropin releasing hormone

b: bovine
h: human
p: porcine
r: rat
s: salmon
sh: sheep