

A

aa, amino acid.

AA, antamanide.

Aad, α -amino adipic acid.

β -Aad, β -amino adipic acid.

AAP, antimicrobial animal peptides.

Aart, a designed Cys2-His2 \rightarrow zinc finger protein (190 aa, M_r 21.4 kDa). It was designed and constructed based on the application of zinc-finger domains of predetermined specificity to bind a 22-base-pair duplex DNA. The aart protein was expressed in *E. coli* as a C-terminal fusion to maltose-binding protein (MBP). The fusion protein contained a factor Xa protease cleavage site for the MBP tag. Aart complexed with its DNA target was crystallized followed by X-ray analysis. Aart binds its DNA target with picomolar affinity. The 1.96 Å structure of Aart was described in 2006 [B. Dreier et al., *J. Biol. Chem.* **2001**, 276, 29466; J. W. Crotty et al., *Acta Crystallogr.* **2005**, F61, 573; D. J. Segal et al., *J. Mol. Biol.* **2006**, 363, 405].

AatRS, amino acyl tRNA synthetase.

A β , amyloid- β .

Ab, antibody.

A₂bu, 2,4-diaminobutyric acid.

Abderhalden, Emil (1877–1950), professor of physiology (1908–1910) at Berlin, of biochemistry (1911–1945) at Halle/S. (Germany), and of physiological chemistry (1946/47) at Zurich (Switzerland). From 1931–1950 Prof. Abderhalden was Presi-

dent of the German Academy of Natural Scientists Leopoldina in Halle/S. In 1902, Abderhalden had joined \rightarrow Emil Fischer's group and worked on protein hydrolysates and proteolytic enzymes which led, in 1904, to *Habilitation*. Further scientific activities were mainly directed towards the chemistry of proteins and physiological chemistry of metabolism [J. Gabathuler (Ed.), *Emil Abderhalden, Sein Leben und Werk*, Ribaux, St. Gallen, **1991**].

Abrin, a highly toxic protein isolated and crystallized from the red seeds of *Abrus precatorius*. It consists of an A-chain (M_r \sim 30 kDa) and a B-chain (M_r \sim 35 kDa), joined by disulfide bridges. The A-chain is a highly specific *N*-glucosidase acting as ribosome-inactivating protein (RIP), whereas the B-chain is a glycoprotein responsible for anchoring at the cell surface. One of the carbohydrate chains forms a bridge between two neighboring molecules, whereas another sugar chain covers the surface of the B-chain. A disulfide-cleaving system of the cell releases the A-chain, which enters the cell by endocytosis. RIP cleaves a single adenine residue from the rRNA, resulting in inhibition of protein synthesis followed by cell death. Similar action and structure are possessed by \rightarrow ricin. The A-chain coupled with a monoclonal antibody directed against a tumor antigen is used in drug targeting [J. Y. Lin et al., *J. Formosan Med. Assoc.* **1969**, 68, 32; J. Y. Lin et al., *Nature* **1970**, 227, 292; A. J. Cumber et al., *Methods Enzymol.* **1985**, 112, 207; T. H. Tahirov et al., *J. Mol. Biol.* **1995**, 250, 354].

Abu, α -aminobutyric acid.

Abz, aminobenzoic acid.

Abzyme, *catalytic antibody*, a monoclonal antibody with catalytic activity. An antibody raised against a transition-state analogue of a particular reaction can catalyze that reaction. The first abzyme to be generated was capable of catalyzing the hydrolysis of esters. Abzymes have been described that catalyze, e.g., acyl transfer, C–C bond cleavage, β -elimination, and C–C bond formation. From X-ray analyses it could be concluded that antibodies bind peptides of various length in elongated grooves using hydrogen bonding, van der Waals forces, and ionic contacts for recognition. Abzymes are also an interesting choice for \rightarrow abzyme-catalyzed peptide synthesis [L. Pauling, *Am. Sci.* **1948**, 36, 51; W. P. Jencks, *Catalysis in Chemistry and Enzymology*, McGraw-Hill, New York, **1969**; R. A. Lerner et al., *Science* **1991**, 252, 659; D. Hilvert et al. in: *Bioorganic Chemistry: Peptides and Proteins*, S. M. Hecht (Ed.), Oxford University Press, Oxford, **1998**].

Abzyme-catalyzed synthesis, the application of catalytic antibodies as catalysts for formation of the peptide bond. If an abzyme could bind a substrate already in the transition-state conformation, it might act as an enzyme catalyzing the reaction to which the transition-state conformation is predisposed. Analogues of the transition state were used as haptens to induce abzymes (catalytic antibodies) with the correct arrangement of catalytic groups. At present, the main disadvantage of the abzyme approach is the requirement of a large number of abzyme catalysts to accommodate the wide specificity pattern of amino acids in coupling reactions. However, these first interesting results in this field provide an impetus for producing

further generations of abzymes capable of catalyzing the ligation of longer, unprotected fragments, combined with a general strategy for the development of sequence-specific abzyme ligases [R. Hirschmann et al., *Science* **1994**, 265, 234; J. R. Jacobson, P.G. Schultz, *Proc. Natl. Acad. Sci. USA* **1994**, 91, 5888; D. W. Smithrud et al., *J. Am. Chem. Soc.* **1997**, 119, 278; S. N. Savinov et al., *Bioorg. Med. Chem. Lett.* **2003**, 13, 1321].

Ac, acetyl.

ACE, angiotensin-converting enzyme.

ACE 2, angiotensin-converting enzyme 2.

ACE inhibitors, pharmaceuticals for the treatment of hypertension, congestive heart failure, and myocardial infarction. Different types of synthetic ACE inhibitor have been designed. Synthetic ACE inhibitors are grouped by their ligand for the active site of the \rightarrow angiotensin converting enzyme (ACE). The major representative of this group is \rightarrow captopril bearing a sulfhydryl moiety, whereas \rightarrow enalapril and lisinopril have a carboxyl moiety, and fosinopril a phosphorous group. The beneficial effects of this group of ACE inhibitors in hypertension and heart failure result primarily from suppression of the renin-angiotensin-aldosterone system. Inhibition of ACE causes a decrease in plasma angiotensin II (\rightarrow angiotensins) level, which leads to decreased vasopressor activity and to a small decrease in aldosterone secretion. However, these synthetic ACE inhibitors are known to have strong adverse side effects, such as cough, skin rashes, and angioedema. Attempts to use \rightarrow angiotensin-converting enzyme 2 and its proteolysis product angiotensin-(1–7) for the regulation of blood pressure are under investigation. Naturally occurring \rightarrow ACE inhibitory peptides have been reported to

have potential as antihypertensive components in functional foods or nutraceuticals. However, the development of ACE inhibitors was greatly influenced by natural products, e.g., by special members of the \rightarrow bradykinin-potentiating peptides. The 9-peptide *teprotide*, <Glu-Trp-Pro-Arg-Pro-Gln-Ile-Pro-Pro-OH (BPP_{9a}, SQ20, 881) was the most active ACE inhibitor *in vivo*, whereas the 5-peptide <Glu-Lys-Trp-Ala-Pro-OH (BPP_{5a}, SQ20, 475) showed *in vitro* the highest activity. The proposed binding of BPP_{5a} to the active site of ACE led to the rational design of the first marketed, orally active ACE inhibitor \rightarrow captopril [M. A. Ondetti et al., *Biochemistry* **1971**, *10*, 4033; M. A. Ondetti et al., *Science* **1977**, *196*, 441; D. W. Cushman et al., *Biochemistry* **1977**, *16*, 5484; M. L. Cohen, *Annu. Rev. Pharmacol. Toxicol.* **1985**, *25*, 307; G. Lawton et al., in: *Advances in Drug Research*, B. Testa (Ed.), Volume 23, p. 161, Academic Press, New York, **1992**; T. F. T. Antonius, G. A. Macgregor, *J. Hypertens.* **1995**, *13*, S11].

ACE inhibitory peptides, naturally occurring peptides derived, for example, from the venoms of the Brazilian pit viper *Bothrops jararaca* and other snakes, known as \rightarrow bradykinin-potentiating peptides, have significantly influenced the development of synthetic \rightarrow ACE inhibitors based on rational drug design. Surprisingly, peptides from the enzymatic partial hydrolysis of proteins, such as milk, maize, gelatin, soybean, wheatgerm, serum, hemoglobin, porcine and chicken muscle have a potential as antihypertensive compounds in functional foods and nutraceuticals. It is interesting to note that some of these peptides not only show ACE inhibitory activity *in vitro*, but also exhibit *in-vivo* antihypertensive activity in spontaneously hypertensive rats [H. Kato, T. Suzuki, *Experientia* **1969**, *25*, 694; *Biochemistry* **1971**, *10*, 972;

L. Verduysee et al., *J. Agric. Food Chem.* **2005**, *53*, 8106].

Acetaldehyde/chloranil test, a monitoring method for the control of complete coupling reaction in \rightarrow solid-phase peptide synthesis [T. Voikovskiy, *Peptide Res.* **1995**, *8*, 236].

Acetamidomethyl group (Acm), a type of thiol protecting group with an *N*-acyl *N,S*-acetal moiety, compatible with both Boc and Fmoc chemistry. The Acm group is completely stable towards acidolysis, and is cleaved with mercury(II) salts at pH 4, thallium(III) trifluoroacetate, or iodine. Oxidizing agents such as iodine simultaneously induce disulfide formation. Structural analogues of the Acm group are the chloroacetamidomethyl group, the isobutyrylamidomethyl group, and the \rightarrow trimethylacetamidomethyl group.

Achatin, a 4-peptide isolated from the ganglia of the African giant land snail *Achatina fulica*. The neuroexcitatory peptide *achatin I* (H-Gly-D-Phe-Ala-Asp-OH) contains a D-amino acid (\rightarrow dermorphin, \rightarrow deltorphins, \rightarrow fulicin) in position 2, whereas *achatin-II* with the L-isomer in the same position shows neither physiological nor pharmacological activities. Because of Na⁺, *achatin I* induced a voltage-dependent inward current on the giant neuron. It has been assumed that D-Phe in *achatin-I* is a prerequisite for forming a 15-membered ring with a unique turn conformation structure, which may be the active conformation suitable for interactions with the receptor. The characterization of a cDNA encoding a precursor polypeptide of *achatin-I* have been described [Y. Kamatani et al., *Biochem. Biophys. Res. Commun.* **1989**, *160*, 1015; T. Ishida et al., *FEBS Lett.* **1992**, *307*, 253; H. Satake et al., *Eur. J. Biochem.* **1999**, *261*, 130].

AchR, acetylcholine receptor.

Acm, acetamidomethyl.

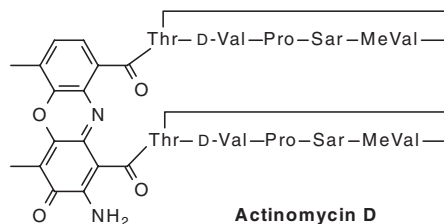
ACP, acyl carrier protein.

ACTH, acronym of adrenocorticotrophic hormone, → corticotropin.

Actin, a contractile protein occurring in many eukaryotic cell types. Actin and → myosin are the major components of the muscle. Both proteins account for 60–70% and 20–25% of the total muscle protein, respectively. Actin and its filaments are the major components of the cytoskeleton in eukaryotic cells. Besides thymomyosin and → troponin, actin is the major constituent of thin filaments. The fibrous *F-actin* forms the core of the thin filament and is formed under physiological conditions by polymerization of the globular *G-actin* ($M_r \sim 42$ kDa; 375 aa). The regulation of the polymerization/depolymerization of F-actin is essential for cytokinesis, cell mobility, and the control of cell shape and polarity. The monomeric G-actin consists of two domains, each of which is divided into two subdomains. G-actin normally binds one molecule of ATP, which is hydrolyzed during polymerization to F-actin, and the resulting ADP remains bound to the F-actin monomer unit. ATP and ADP bind in a cleft between the two domains. The F-actin helix (diameter 100 Å) has 2.17 actin monomers per left-handed helix turn (13 subunits in six turns) and a rise per turn of 60 Å. The monomeric unit of each F actin is capable of binding a single myosin S 1 fragment [R. A. Milligan et al., *Nature* **1990**, 348, 217; P. Shterline, J. C. Sparrow, *Protein Profiles* **1994**, 1, 1; P. Shterline et al., *Actin*, Oxford University Press, New York, **1998**; J.-W. Chu, G. A. Voth, *Proc. Natl. Acad. Sci. USA* **2005**, 102, 13111].

Actinohivin (AH), a sugar-binding anti-human immunodeficiency virus protein produced by an actinomycete *Longispora al-bida* gen. nov, sp. nov. AH consists of 114 aa and is composed of highly conserved three-tandem repeats. Each repeat unit is built of 38 aa containing a Gln-Xaa-Trp motif at the C-terminus. It has been reported that AH inhibits the infection of susceptible cells by various strains of T-lymphocyte (T)-tropic and macrophage (M)-tropic HIV types 1 and 2, and both T- and M-tropic syncytium formation via AH binding to the high-mannose-type saccharide chains of HIV gp120. The three tandem-repeat structure of AH is essential for potent anti-syncytium formation activity and gp120-binding [H. Chiba et al., *J. Antibiot.* **2001**, 54, 818; *Biochem. Biophys. Res. Commun.* **2004**, 316, 203; A. Takahashi et al., *Arch. Biochem. Biophys.* **2005**, 437, 233].

Actinomycins, peptide antibiotics produced by various strains of *Streptomyces*. Actinomycins are orange-red bacteriostatic and cytostatic, but highly toxic, chromopeptides. The chromophore *actinocin*, 2-amino-4, 6-dimethyl-3-oxo-phenoxazine-1,9-dicarboxylic acid, is linked to two five-membered peptide lactones by the amino groups of two threonine residues. The various naturally occurring and synthetic actinomycins differ mostly in the amino acid sequence of the lactone moieties. *Actinomycin D* is one of the well-known actinomycins with known 3D structure. Actinomycin D is a useful antineoplastic agent that binds tightly to ds-DNA, and in this manner strongly inhibits both transcription and DNA replication. It presumably interferes as an intercalating agent with the passage of RNA polymerase and DNA polymerase, respectively. Actinomycin D is used as a cytostatic in the treatment of the rare types of cancer, e.g.,



Wilms' carcinoma, chorion carcinoma, and Hodgkin's disease [A. B. Mauger, *Topics Antibiot. Chem.* **1980**, *5*, 223].

Active ester, R-CO-XR', an amino acid or peptide ester bearing an electron-withdrawing substituent XR' that promotes the nucleophilic attack of the amino component during the formation of a peptide bond. The acylating power of an ester moiety increases with the ability of its leaving group X^- to depart, which in turn is related to the strength of the acid HXR'. A very large number of different types of active esters have been described, but only some of these, e.g., thiophenyl-, pentafluorophenyl- and 4-nitrophenyl esters, have been used much. New types of active ester are mechanistically based on intramolecular base catalysis. Efforts to minimize racemization have led to studies of neighboring effects (anchimeric assistance) which led to the development of active esters capable of discriminating effectively between aminolysis and racemization first indicated by 8-quinolyl ester and *N*-hydroxypiperidinyl ester. The same situation applies to other active esters of high practical importance, such as derivatives of *N*-hydroxysuccinimide (HOSu), 1-hydroxybenzotriazole ((HOBt), and the 7-aza analogue of HOBt, commonly referred to as 1-hydroxy-7-azabenzotriazole (HOAt; the correct name is 1-hydroxy-1,2,3-triazolo[5,4-*b*] pyridine) [H.-D. Jakubke et al., *Chem. Ber.* **1967**, *106*, 2367;

M. Bodanszky, in: *The Peptides: Analysis, Synthesis, Biology*, Volume 1, E. Gross, J. Meienhofer (Eds.), Academic Press, New York **1979**, 105].

Activins, members of the transforming growth factor- β protein family, originally discovered in the follicular fluid from ovaries and in leukemic cells. They stimulate the release of \rightarrow follitropin. *Activin A* is a homodimer of the β -chains of \rightarrow inhibin-A, whereas *activin B* consists of the β -chains of inhibin-A and inhibin-B. Activin is involved in the regulation of a couple of biological events, ranging from early development to pituitary function. It has numerous functions in both normal and neoplastic cells. Several different cells synthesize activin and have a specific binding site for this protein. It has been described that the activin-binding protein in rat ovary is \rightarrow follistatin. Another activin-binding protein in biological fluids is \rightarrow α_2 -macroglobulin. cDNAs coding for an activin receptor were cloned in order to obtain more information on the cellular mechanisms of activin actions. The resulting cDNAs code for a receptor protein consisting of 494 aa comprising a ligand-binding extracellular domain, a single membrane-spanning domain, and an intracellular kinase domain with predicted Ser/Thr specificity. Recently, regulated production of activin A and activin B throughout the cycle of seminiferous epithelium in the rat have been described [T. Nakamura et al., *Science* **1990**, *247*, 836; L. S. Mathews, W. W. Vale, *Cell* **1991**, *65*, 973; P. G. Knight et al., *J. Endocrinol.* **1996**, *148*, 267; Y. Okuma et al., *J. Endocrinol.* **2006**, *190*, 331].

Activity-dependent neurotrophic peptides (ADNP), peptides derived from the neuroprotective protein, named *activity-dependent neuroprotective factor (ADNF)*. ADNF ($M_r \sim 14$ kDa; pI 8.3) is a glia-derived

protein and is neuroprotective at femtomolar concentrations. Besides ADNF, even the related peptide fragment ADNP-14, VLGGGSALLR¹⁰SIPA, protects neurons from multiple neurotoxins. From structure-activity studies it follows that ADNP-9, SALLRSIPA, shows greater potency and a broader effective concentration range (10^{-16} – 10^{-13} M) compared with ADNF and ADNP-14 in preventing cell death with tetrodotoxin treatment of cerebral cortical cultures [D. E. Brenneman, I. Gozes, *J. Clin. Invest.* **1996**, *97*, 2299; D. E. Brenneman et al., *Pharmacol. Exp. Ther.* **1998**, *285*, 619].

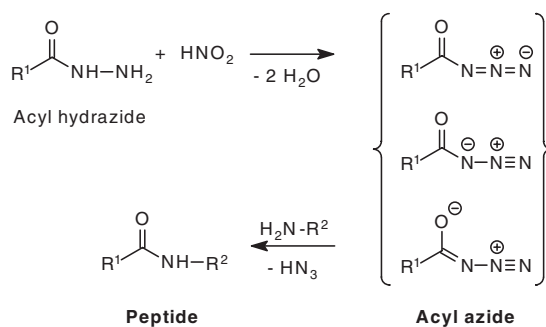
Aculeacins, antifungal peptides affecting glucan synthesis. Aculeacins A to G are produced by *Aspergillus aculeantus*. The peptides A through D, F, and G show good *in-vitro* activity against *C. albicans* and *Saccharomyces cerevisiae*, but reduced the growth of only a few filamentous fungi [K. Mizuno et al., *J. Antibiot.* **1977**, *30*, 297].

Acyl azide method, one of the oldest coupling methods in peptide synthesis, introduced by Theodor Curtius in 1902. Starting compounds are amino acid or peptide hydrazides (R-CO-NH-NH₂), easily accessible from the corresponding esters by hydrazinolysis, which are transformed into azides (R-CO-N₃) by *N*-

nitrosation at -10°C . The azide is extracted from the aqueous layer with ethyl acetate, washed, dried and reacted with the amino component. The azide method is still important, especially for segment condensations, because of its low tendency towards racemization [J. Meienhofer, in: *The Peptides: Analysis, Synthesis, Biology*, Volume 1, E. Gross, J. Meienhofer (Eds.), Academic Press, New York, **1979**, 197].

Acyl enzyme, an intermediate in the catalytic mechanism of serine proteases, such as trypsin and chymotrypsin. After the serine protease has bound a peptide substrate to form the Michaelis complex, Ser¹⁹⁵ (in the case of chymotrypsin) nucleophilically attacks the peptide bond in the rate-determining step, forming a transition-state complex, known as a tetrahedral intermediate. The latter decomposes to the acyl enzyme, an extremely unstable intermediate, that bears the acyl moiety at the hydroxy group of Ser¹⁹⁵. The acyl enzyme intermediate is deacylated by water during proteolysis, or the attacking nucleophile is an amino component in case of kinetically controlled \rightarrow enzymatic peptide synthesis.

O-Acyl isopeptide method, an approach to the efficient synthesis of peptides containing \rightarrow difficult sequences via the *O*-*N*

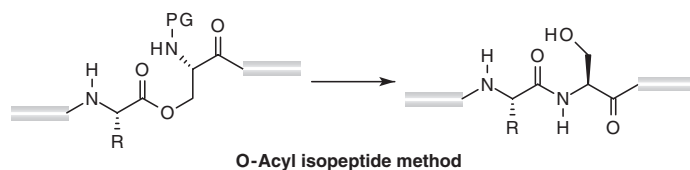


intramolecular acyl migration reaction of *O*-acyl isopeptides. Such intermediates have also been termed \rightarrow click peptides or \rightarrow switch peptides. The sequence-specific formation of stable β -strands that aggregate and consequently prevent further deprotection or acylation reactions in SPPS is a major problem in peptide synthesis. Depending on the amino acid sequence present in the target peptide, the synthetic accessibility may be hampered or even rendered impossible. Such \rightarrow difficult sequences require special consideration when planning a synthesis. Besides the introduction of \rightarrow backbone amide protecting groups or serine/threonine derived \rightarrow pseudo-prolines building blocks, the application of the *O*-acyl isopeptide method provides appropriate measures for obtaining difficult sequences. It relies on an *O*-*N*-intramolecular acyl migration at serine or threonine residues in strategic positions. During the peptide synthesis, a serine or threonine residue protected at *N* $^\alpha$ is incorporated, involving the β -hydroxy functionality and giving rise to a depsipeptide bond (*O*-acyl isopeptide). Such a single isopeptide moiety prevents the undesired formation of secondary structures. The method allowed, e.g., the synthesis of the Alzheimer's disease-related \rightarrow amyloid β peptide (1-42) [*A* β (1-42)]. The water soluble *A* β (1-42) isopeptide precursor with Gly²⁵-Ser²⁶ replacement by the corresponding β -depsipeptide undergoes, upon Ser²⁶ *N* $^\alpha$ deprotection, an *O*-*N* acyl migration forming the target *A* β (1-42). Because of this property, the names \rightarrow click peptide and \rightarrow

switch peptide have been coined. As there is a protecting group at the *N* $^\alpha$ of the isopeptide bond, the *O*-*N* acyl migration can not only be triggered by acidolytic cleavage of the *N* $^\alpha$ -Boc group, but also, e.g., by the photolysis of photolabile *N* $^\alpha$ -protecting groups. Such compounds will certainly facilitate the investigation of, e.g., β -sheet formation. Besides *A* β (1-42), other difficult sequences such as the Jung-Redemann 10-peptide and 26-peptide, H-(VT)₁₀NH₂ and the 37-peptide of the FEP28 WW-domain have been synthesized [Y. Sohma et al., *Biopolymers* **2007**, *88*, 253; M. Mutter et al., *Angew. Chem. Int. Ed.* **2004**, *43*, 4172; L. Carpino et al., *Tetrahedron Lett.* **2004**, *45*, 7519].

***O*-Acylisourea**, a reactive intermediate of the \rightarrow carbodiimide method.

Acyl halides, derivatives of amino acids in which the hydroxy group in the carboxyl group is replaced by a halogen atom. Acyl halides are reactive compounds suitable as acylating agents. First, Fmoc-protected amino acid chlorides have been used as stable derivatives for rapid peptide coupling reaction without the danger of racemization. However, their general application is somewhat limited, as not all Fmoc-protected amino acid derivatives are accessible. In contrast, Fmoc-protected amino acid fluorides do not suffer from such limitations. Further advantages of fluorides relative to the chlorides include their greater stability towards water, including moisture in the air, and their relative lack of conversion to the corresponding oxazolones on treatment with tertiary



organic bases. The Fmoc-protected amino acid fluorides are suited both for solution peptide synthesis and for SPPS [L. A. Carpino et al., *J. Org. Chem.* **1986**, *51*, 3732; L. A. Carpino et al., *Acc. Chem. Res.* **1996**, *29*, 268; L. A. Carpino et al., *Tetrahedron Lett.* **1998**, *39*, 241].

Acyltransfer, the transfer of an acyl group R-CO- between two molecules in the course of a reaction as takes place, for example, in a serine protease-catalyzed cleavage of a peptide bond (\rightarrow acyl enzyme).

AD, Alzheimer's disease.

Ada, adamantyl.

Adaptins, accessory proteins thought to bind the membrane-spanning receptors for those specific proteins that the coated vesicle clathrin sequester.

Adhesion molecules, proteins responsible for interactions between cells and their environment, especially, the extracellular matrix and other cells. Several different molecules act as cell adhesion receptors such as \rightarrow integrins, intercellular adhesion molecules (ICAM), leukocyte LFA-1, Mac-1 and p150/95 molecules, the fibronectin receptor complex (\rightarrow fibronectin), tenascin, and the position-specific (PS) antigens of *Drosophila*.

Adipokinetic hormones (AKH), peptide hormones belonging to the \rightarrow AKH/RPCH peptide hormone family. As early in the 1960s, it was observed that extracts of the corpus cardiacum (CC) from either the American cockroach or the migratory (*Locusta migratoria*) and desert locust show metabolic effects such as elevation of the blood sugar trehalose or of the blood lipids (adipokinetic or hyperlipemic effect). In 1976, the complete sequence of the locust's AKH, today denoted as *Locmi-AKH-I*, pGlu-Leu-Asn-Phe-Thr-Pro-Asn-

Trp-Gly-Thr-NH₂, was elucidated. Insecta contain up to three AKH peptides (isoforms) as demonstrated by the other two peptides produced by the African migratory locust: *Locmi-AKH-II*, pGlu-Leu-Asn-Phe-Ser-Ala-Gly-Trp-NN₂, and *Locmi-AKH-III*, pGlu-Leu-Asn-Phe-Thr-Pro-Trp-Trp-NH₂. The mobilization of substrates for high-energetic phases is the major function of AKH in insects. AKH are involved in the regulation of the level of circulating metabolites such as lipids, carbohydrates and proline by activating phosphorylases or lipases in the fat body cells. However, AKH peptides play also a multifunctional role and exert pleiotropic actions. For example, in certain insects (firebug, cricket) AKH show an effect on the locomotory activity, and are also involved in the immune response of locusts. Beside the members listed above, a huge number of AKHs such as Phymo-AKH (from *Phymateus morbillosus*), Emppe-AKH (from *Empusa pennata*), Manto-CC (*Mantophasmatodea*), and others (Psein-AKH, Grybi-AKH) are known. Recently, a novel member in a water boatman (*Heteroptera*, *Corixidae*), named Corpu-AKH, and its bioanalogue in a saucer bug (*Heteroptera*, *Naucoridae*), code-name Anaim-AKH, have been described. Interestingly, a glycosylated AKH, denoted Carma-HrTH (hypertrehalosemic hormone)-I, synthesized in the CC of the stick insect, is characterized by a unique modification. The hexose moiety is thought to be linked by C-glycosylation to the C-2 atom of the indole ring of tryptophan. On the other hand, Trifa-CC isolated of an extracts of CC from the protea beetle, *Trichostetha fascicularis*, is the first report of a phosphorylated invertebrate neuropeptide [J. V. Stone et al., *Nature* **1976**, *263*, 207; L. Schoofs et al., *Peptides* **1997**, *18*, 145; M. J. Lee et al., *Regul. Pept.* **1997**, *69*, 69; G. Gäde, *Annu. Rev. Entomol.* **2004**, *49*,

93; G. Gäde et al., *Biochem. Biophys. Res. Commun.* **2005**, 330, 598; G. Gäde et al., *Biochem. J.* **2006**, 393, 705; G. Gäde et al., *Peptides* **2007**, 28, 594].

Adiponectin, adipocyte complement-related protein of 30 kDa (ACRP30), *adipoQ*, adipose most abundant gene transcript 1 (*apM1*), gelatin-binding protein of 28 kDa (*GBP28*), an adipose-tissue-derived protein with important effects in glucose and lipid homeostasis. The molecular structure of adiponectin is characterized by an N-terminal collagen-like domain and a C-terminal globular domain with similarities to the complement factor C1q. It assembles into homotrimers, and higher-order oligomeric structures resulting by interactions between the collagen-like domains. The production and/or secretion of adiponectin is regulated by various mechanisms; e.g., it is increased by both IGF-1 and insulin in white adipose tissue. The synthesis and secretion of adiponectin are decreased by TNF- α , β -adrenergic agonists, glucocorticoids, and cAMP. With AdipoR1 and AdipoR2 two receptors for adiponectin have been cloned. AdipoR1 occurs primarily in skeletal muscle, whereas AdipoR2 is primarily produced in hepatic tissues. It may act also directly on bone, since receptors are found in osteoblasts and these cells also secrete adiponectin [L. Shapiro, P. E. Scherer, *Curr. Biol.* **1998**, 12, 335; A. H. Berg et al., *Trends Endocrinol. Metab.* **2002**, 13, 84; H. S. Berner et al., *Bone* **2004**, 35, 842; U. Meier, A. M. Gressner, *Clin. Chem.* **2004**, 50, 1511].

Adoc, 1-adamantylloxycarbonyl.

Adrenocorticotropin hormone (ACTH), \rightarrow corticotropin.

Adrenocorticotropin, \rightarrow corticotropin.

Adrenomedullin (AM), YRQSMNNFQG¹⁰ LRSFGCRFGT²⁰CTVQKLAHQI³⁰YQFTD KDKDN⁴⁰VAPRSKISPQ⁵⁰GYa (disulfide bond: C¹⁶-C²¹), a vasoactive 52-peptide amide which is a member of the \rightarrow calcitonin/calcitonin gene-related peptide family and shares 24% sequence homology with \rightarrow calcitonin gene-related peptide (CGRP). AM was first discovered in human pheochromocytoma tissue in 1993, and later found in the normal adrenal medullae, kidneys, lungs, and blood vessels. AM has been reported to be synthesized and secreted by various types of cell, such as vascular endothelial and smooth muscle cells, cardiomyocytes, macrophages, fibroblasts, neurons, glial cells, and retinal pigment epithelial cells. In humans, its gene is situated in a single locus on chromosome 11p15.4. The amino acid sequence is highly conserved across species. The gene contains four exons separated by three introns and codes for a longer preprohormone of 185 aa, which is processed post-translationally, originating AM and *proadrenomedullin N-terminal 20-peptide (PAMP)*. Both peptides participate in many physiological functions, including vasodilatation, bronchodilatation, neurotransmission, regulation of hormone secretion, brain functions, renal homeostasis, and antimicrobial activities. Apart from vasodepressive effects in mammals, caused by decreasing peripheral vascular resistance, AM shows diuretic and bronchodilatory effects and plays a regulatory role on aldosterone and ACTH (\rightarrow corticotropin) release. In renal failure, hypertension, heart failure, pregnancy loss, and septic shock plasma, the AM level has been found to be increased. The biological actions of AM are mediated through the calcitonin receptor-like receptor (CRLR) complexed with \rightarrow receptor activity-modifying proteins (RAMPs),

especially via both CRLR/RAMP2 and CRLR/RAMP3 receptors, respectively (\rightarrow calcitonin/calcitonin gene-related peptide family). Plasma AM concentration is increased in patients with cardiovascular diseases. It has been shown that the source of increased AM levels in cardiac failure is the heart. AM has hypotensive, diuretic and natriuretic properties that are in common with \rightarrow natriuretic peptides; however, the role of AM in cardiac pathologies is less clear. Sequence analysis of the *Fugu rubripes* genome led to the identification of three AM orthologues characterized by a 31 aa C-terminal domain sharing 50, 38, and 35% sequence identity with hAM in the mature area. The sequence N-terminal to the cystine ring varies greatly among species. Recently, it has been reported that AM and PAMP might be potent inducers of angiogenesis which is required for the maintained growth of solid tumors [K. Kitamura et al., *Biochem. Biophys. Res. Commun.* **1993**, *192*, 553; C. J. Charles et al., *Am. J. Hypertens.* **1999**, *12*, 166; S. J. Wimalawansa, *Crit. Rev. Neurobiol.* **1997**, *11*, 167; M. Jougasaki, J. C. Burnett, Jr., *Life Sci.* **2000**, *66*, 855; T. Eto et al., *Regul. Pept.* **2003**, *112*, 61; M. T. Rademaker et al., *Regul. Pept.* **2003**, *112*, 51; C. L. Chang et al., *Peptides* **2004**, *25*, 1633; A. Martinez, *Cancer Lett.* **2006**, *236*, 157].

Adrenorphin, \rightarrow metorphamide.

Advanced glycation end products (AGEs), a heterogeneous group of non-enzymatically glycosylated and oxidized proteins or lipids. AGEs are present and accumulated in many different cell types, and affect extracellular and intracellular structure and function. Microvascular and macrovascular complications are caused through the formation of crosslinks between molecules in the basement membrane of the extracellular matrix. AGEs are prevalent in the

diabetic vasculature, and contribute to the development of atherosclerosis. The concentrations of AGEs are altered in the body, particularly in relation to changes occurring with age. AGEs contribute to amyloidosis in \rightarrow Alzheimer's disease, and AGEs formation is also stimulated by oxidative stress, e.g., in uremia. A decrease in renal function increases circulating AGE concentrations by reduced clearance [M. P. Vitek et al., *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 4766; R. Singh et al. *Diabetologia* **2001**, *44*, 129; J. M. Bohlender et al., *Am. J. Renal Physiol.* **2005**, *289*, F645; A. Goldin et al., *Circulation* **2006**, *114*, 597].

Aequorin, a calcium-sensitive photoprotein originally obtained from the jellyfish *Aequorea victoria*. This bioluminescent jellyfish produces a greenish luminescence from the margin of its umbrella using aequorin and a chromophore-bearing \rightarrow green fluorescent protein (GFP). Aequorin is a Ca^{2+} -binding protein ($M_r \sim 21$ kDa), and undergoes an intramolecular reaction on binding Ca^{2+} , yielding a blue fluorescent protein in the singlet excited state, transferring its energy by resonance to GFP. Aequorin consists of four helix-loop-helix "EF-hand" domains, of which three can bind Ca^{2+} . It also contains coelenterazine as its chromophoric ligand. The addition of Ca^{2+} causes decomposition of the protein complex into apoaequorin, coelenteramide and CO_2 , accompanied by the emission of light. Regeneration of apoaequorin into active aequorin takes place in the absence of Ca^{2+} by incubation with coelenterazine, oxygen, and a thiol agent. Aequorin is widely used as a probe to monitor intracellular levels of Ca^{2+} . The crystal structure of recombinant aequorin at 2.3 Å resolution shows a globular molecule containing a hydrophobic core cavity accommodating the ligand

coelenterazine-2-hydroperoxide [O. Shimomura et al., *J. Cell. Comp. Physiol.* **1962**, 59, 223; H. Morise et al., *Biochemistry* **1974**, 13, 2656; M. Brini et al., *J. Biol. Chem.* **1995**, 270, 9896; J. F. Head et al., *Nature* **2000**, 405, 291].

Aeruginosins, a main class of → cyanobacterial peptides characterized by a derivative of hydroxyphenyl lactic acid (Hpla) at the *N*-terminus, 2-carboxy-6-hydroxyoctahydroindole (Choi) and the arginine derivative agmatine at the *C*-terminus. The aeruginosins 98-A and B from the blue-green alga *Microcystis aeruginosa* act as trypsin inhibitors [M. Murakami et al., *Tetrahedron Lett.* **1995**, 36, 2785].

Aet, aminoethyl.

Affinity chromatography, a special variant of adsorption chromatography in which the adsorbent is biospecific. A molecule, known as the ligand, that specifically binds, for example to the protein of interest, is covalently attached to an inert porous matrix, e.g., agarose gel, glass beads, cellulose, polyacrylamide, crosslinked dextrans. The impure protein solution is passed through this stationary phase and the desired protein with selective affinity to the ligand is retained, while other proteins and substances are immediately eluted. The bound substance can then be recovered in highly purified form by changing the elution conditions such that the desired protein is released from the stationary phase. Specific interactions between, e.g., antibodies and antigens, enzymes and their inhibitors, nucleic acids of complementary sequences, lectins and polysaccharides, receptors and hormones, avidin and biotin can be utilized [P. Cuatrecasas et al., *Proc. Natl. Acad. Sci. USA* **1968**, 61, 636].

Ag, antigen.

AG3, AYSSGAPPMP¹⁰PF, an inorganic-binding peptide (→ silver-binding peptides) that specifically and selectively binds to silver. AG3 was immobilized on the surface of protonated poly(ethylene terephthalate) (PET) film which was prepared for biomimetic synthesis of silver particles *in vitro*. Silver crystallites have been formatted on the surface of the AG3-PET film showing various shapes 1 to 4 μm in size [Z. Xu et al., *J. Inorg. Biochem.* **2005**, 99, 1692].

AGaloc, tetra-*O*-acetyl-β-*D*-galactopyranosyloxycarbonyl.

AGE, advanced glycation end product.

Agloc, tetra-*O*-acetyl-*D*-glucopyranosyloxycarbonyl.

Agonist, a term given for analogues of native peptide hormones that trigger the hormone signal in the same manner.

Agouti protein, a 131 aa protein encoded by the murine agouti gene and expressed in the skin. During hair growth, agouti acts to regulate coat coloration, and abnormal expression of the agouti protein causes the yellow phenotype. The agouti protein is a paracrine signaling molecule that regulates coat coloration via competitive antagonism of α-MSH (→ melanocortin peptides) binding to its receptor (→ melanocortin receptors, MCR). The antagonistic action of agouti protein prevents the α-MSH-mediated increase in intracellular cAMP that results in the cell switching from the production of black pigment, eumelanin, to yellow pigment, phaemelanin. Pharmacologically, agouti is a high-affinity, competitive antagonist of the melanocortin peptides at melanocortin receptors MC1R, MC3R, MC4R, and the adrenocortical ACTH (→ corticotropin) receptor, MC2R, respectively [D. Lu et al., *Nature* 1994, 371,

Agouti-related protein (AGRP)

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799; D. M. Dinulescu, R. D. Cone, *J. Biol. Chem.* **2000**, 275, 6695].

Agouti-related protein (AGRP), a 132 aa protein first identified by database searches for molecules with homology to → agouti protein in 1997. AGRP is expressed predominantly in the adrenal gland, hypothalamus, and at low levels in the lung, testis, and kidney. AGRP has been physiologically implicated in the regulation of food intake, body weight, and energy homeostasis. It is acting as a brain melanocortin-4 (MC4R) and melanocortin-3 (MC3R) receptor (→ melanocortin receptor) antagonist. It has been reported that AGRP has additional targets in the hypothalamus and/or physiologically functions through a mechanism in addition to competitive antagonism of α-MSH at the brain melanocortin receptors. AGRP is a orexigenic (appetite-stimulating) peptide that promotes food intake and is coexpressed with another potent orexigenic neuropeptide, → neuropeptide Y. The human AGRP gene is relatively short, spanning 1.1 kb on chromosome 16q22. Most investigations on the *in-vivo* function of AGRP have used C-terminal AGRP peptide sequences that mimic the effect of the full-length protein. Human AGRP-(87–132): CVRLHESCLG¹⁰QQVPCCDPCA²⁰TCYCRFFNAF³⁰CYCRKLG⁴⁰TAM⁴⁰NPC⁵⁰SRT (disulfide bonds: C¹–C¹⁶/C⁸–C²²/C¹⁵–C³³/C¹⁹–C⁴³/C²³–C³¹), a synthetic 46-peptide was capable of binding the melanocortin receptors MC3R, MC4R, and MC5R, thus, inhibiting binding of α-MSH. NMR structure analysis of AGRP-(87–132) revealed an inhibitor cysteine-knot structure which makes possible contact with the MC3R and MC4R with two loops which are present in this structure. The appetite-boosting AGRP-(87–132) may be both an important

tool for elucidating the mechanism of obesity, and a potentially interesting drug target in combating obesity and related co-morbidities [M. M. Ollman et al., *Science* **1997**, 278, 135; J. R. Shutter et al., *Genes Dev.* **1997**, 17, 75; R. D. Rosenfeld et al., *Biochemistry* **1998**, 37, 16041; E. J. Bures et al., *Biochemistry* **1998**, 37, 12172; C. Haskell-Luevano, E. K. Monck, *Regul. Pept.* **2001**, 99, 1].

AGRP, agouti-related protein.

Ahx, 2-aminohexanoic acid (norleucine).

εAhx, 6-aminohexanoic acid.

AHZ, β-alanyl-histidinato zinc.

Aib, α-aminoisobutyric acid (α-methyl-alanine).

AIDS, acquired immunodeficiency syndrome.

alle, allo-isoleucine (2*S*,3*R* in the L-series).

Aimoto thioester approach, a polypeptide synthesis method characterized by converting an S-alkyl thioester moiety in the presence of a silver salt into an active ester derived from HOBt or HODhbt, followed by segment condensation of partially protected segments [S. Aimoto, *Biopolymers* **1999**, 51, 247].

Akabori Conference, called in honor of Shiro Akabori, a series of conferences with Japanese and German peptide chemists held every two years, alternating between the two countries, founded by Erich Wunsch and Shumpei Sakakibara.

Akabori method, an approach to C-terminal amino acid end group analysis of peptides using hydrazine. By treatment of the peptide under investigation with anhydrous hydrazine for 90–100 h at 90°C in the presence of an acidic ion-exchange resin, only the C-terminal amino acid residue

is released as free amino acid, whereas all other amino acids are converted into hydrazides. The resulting C-terminal free amino acid can be identified chromatographically [S. Akabori et al., *Bull. Chem. Soc. Japan* **1956**, *29*, 507].

Akabori, Shiro (1900–1992), professor of organic chemistry at Osaka University (1939–1966), known as the father of peptide chemistry in Japan, with outstanding international achievements in peptide research, inter alia → Akabori method. From 1960 onwards, and even after his retirement in 1966, Professor Akabori continuously served the scientific community for over 20 years as president of the Protein Research Foundation Japan.

AKH, adipokinetic hormone.

AKH/RPCH peptide hormone family, *adipokinetic hormone/red pigment-concentrating hormone family*, peptide hormones produced in the neurosecretory organs of crustacean and insects, and named after the first fully characterized members and their most prominent functions. These include the aggregation of pigment in the epidermal cells of crustaceans by the → red pigment-concentrating hormone (Pando-RPCH), whereas the → adipokinetic hormones (AKH) in insects regulate the levels of circulating metabolites such as lipids, carbohydrates and proline by activating phosphorylases or lipases in the fat body cell. The resulting substrates can subsequently be used during intense muscular work, e.g., flight, swimming, or running. At present, only Pando-RPCH have been found in a relatively large number of crustaceans, whereas about 40 analogues (isomers), including Panbo-RPCH, have been isolated from all major orders of insects. The members of this peptide hormone family consist of 8 to 10 amino acid residues

bearing both a blocked N-terminus (pyroglutamate residue) and C-terminus (amide) respectively. They are characterized by aromatic amino acids at position four (Phe or Tyr) and eight (Trp). Besides the well-known members of this family, some AKH/RPCH peptides are produced in the brain and not in the retrocerebral corpora cardiaca (CC), for example in the migratory locust and the African malarial mosquito. In addition to the modified termini of the peptides, additional post-translational modifications comprise C-glycosylations at Trp and phosphorylation at Thr residues [G. Gäde, *Z. Naturforsch.* **1996**, *51*, 333; G. Gäde, H. G. Marco, in: *Studies in Natural Product Chemistry (Bioactive Natural Products)*, Atta-ur-Rahmann (Ed.), Vol. 33, pp. 69–139, Elsevier Science Publishers, The Netherlands, **2005**].

Al, allyl

Ala, alanine

Alanine (Ala, A), α -aminopropionic acid, $\text{H}_3\text{C-CH}(\text{NH}_2)\text{-COOH}$, $\text{C}_3\text{H}_7\text{NO}_2$, M_r 89.09 Da, a proteinogenic amino acid.

Alanine scan, systematic substitution of each amino acid residue of a native peptide by a simple amino acid such as alanine. A first step in structure–activity relationship studies.

β -Ala, β -alanine

β -Alanine (β -Ala), β -aminopropionic acid, a naturally occurring non-proteinogenic amino acid occurring, e.g., in → carnosine, → anserine, and coenzyme A.

Alamethicin, a member of the → peptaibols produced by the fungus *Trichoderma viride*. This is one of the most extensively investigated member of the long peptaibol antibiotics. Alamethicin consists of a natural microheterogeneous peptaibol mixture

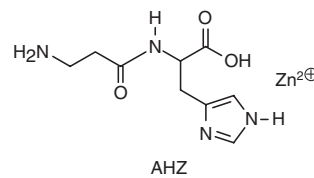
β -Alanyl-histidinato zinc (AHZ)

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of which 23 members have been sequenced up to 2004. All alamethicins are 19-peptides blocked at the *N*-terminus by an acetyl moiety, and at the *C*-terminus by the 1,2-aminoalcohol L-phenylalaninol (Fol). The acidic alamethicins bear a Glu¹⁸ residue, whereas this building block is replaced by Gln¹⁸ in the neutral alamethicins. The alamethicins are classified into two groups. The major group is called F50 and is composed of neutral peptides (Gln¹⁸), whereas the minor group, termed F30, consists of acidic peptides (Glu¹⁸). Only the F30/6 analogue bears two acidic amino acids (Glu⁷, Glu¹⁸), while in all other alamethicins Gln⁷ is conserved. The alamethicins are rich (7–10 aa) on the strongly helicogenic, non-coded α -aminoisobutyric acid (Aib), and contain two well-spaced proline residues in positions 2 and 14. A major component of the natural alamethicin mixture is the F50/5 analogue with the following sequence: Ac-Aib-Pro-Aib-Ala-Aib-Ala-Gln-Aib-Val-Aib¹⁰-Gly-Leu-Aib-Pro-Val-Aib-Aib-Glu-Gln-Phe-ol, the total synthesis of which in solution by an easily tunable segment condensation approach was described in 2004. Besides this approach, more than 20 other synthesis variants of alamethicin have been reported. Alamethicin is amphiphilic, but of high overall hydrophobicity. It is known to generate voltage-dependent pores in biological membranes, and to insert spontaneously into lipid bilayers. Some more or less convincing models have been postulated. From the crystal structure it could be revealed that alamethicin is preferentially α -helical, with a bend in the helix axis at Pro¹⁴. This structure is in agreement with an early model for the mode of action, in which a certain number (6–12) of molecules form aggregates, like the staves of a barrel. However, there are also other models for channel formation. One model, based on a voltage-

dependent flip-flop of α -helix dipoles, postulates that the membrane-inserted helices attract each other when oriented in anti-parallel fashion. In contrast to the flip-flop model, another model assumes that the gating charge transfer is involved in the opening-closing mechanisms. The mechanisms of membrane permeability by alamethicin remain the subject of debate [R. Nagaray, P. Balaram, *Acc. Chem. Res.* **1981**, *14*, 356; E. Benedetti et al., *Proc. Natl. Acad. Sci. USA* **1982**, *79*, 7951; R. O. Fox, F. M. Richards, *Nature* **1982**, *300*, 325; H. Brückner, H. Graf, *Experientia* **1983**, *39*, 528; G. Boheim et al., *Biophys. Struct. Mech.* **1983**, *9*, 181; D. T. Edmonds, *Eur. Biophys. J.* **1985**, *13*, 31; H. Wenschuh et al., *J. Org. Chem.* **1995**, *60*, 405; M. S. P. Sansom, *Mol. Biol.* **1991**, *55*, 139; J. Kirschbaum et al., *J. Peptide Sci.* **2003**, *9*, 799; C. Peggion et al., *Biopolymers (Pept. Sci.)* **2004**, *76*, 485].

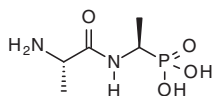
β -Alanyl-histidinato zinc (AHZ), a zinc-chelated dipeptide for the exogenous administration of zinc. The zinc delivery potential of AHZ is more effective on bone metabolism than zinc sulfate. In-vitro studies have established that AHZ causes complete inhibition of the decrease of bone calcium in a bone tissue culture system, as well as in the formation of osteoclast-like cells in mouse marrow culture [M. Yamaguchi, *Gen. Pharmacol.* **1995**, *26*, 1179].



β -Alanyl-histidinato zinc

Alaphosphin, L-alanyl-L-1-aminoethylphosphonic acid, a \rightarrow phosphopeptide acting as an antibacterial agent. It selectively inhibited peptidoglycan biosynthesis in both

Gram-negative and Gram-positive bacteria. Alaphosphin was selected from a range of phosphonopeptides for studies in humans on the basis of its antibacterial activity, pharmacokinetics, and stability against intestinal and kidney proteases. *In vitro*, it proved active against the majority of about 50 strains of *Serratia marcescens* [J. G. Allen et al., *Antimicrob. Agents Chemother.* **1979**, *15*, 684; F. R. Atherton et al., *Antimicrob. Agents Chemother.* **1979**, *15*, 696; W. H. Traub, *Chemotherapy* **1980**, *26*, 103].



Alaphosphin

Albomycins, natural siderophores and antibiotics first isolated from *Streptomyces griseus* and named grisein in 1947. Some years later, another microbial iron-transport compound, named albomycin, was isolated from *Streptomyces subtropicus* which had the same structure as grisein. In 1982, the structure of the albomycins was firmly established. The linear tripeptide built of N^5 -acetyl- N^5 -hydroxy-L-ornithine is the hexadentate, octahedral ligand for ferric ion responsible for intracellular transport of iron. The albomycins are used for treatment of iron metabolism disorders [G. Benz et al., *Angew. Chem. Int. Ed.* **1982**, *21*, 527; G. Benz, *Liebigs Ann. Chem.* **1984**, 1408].

Albumins, a group of water-soluble proteins occurring in body liquids, animal tissues and in some plant seeds. They are rich in both Glu and Asp (20–25%) as well as Leu and Ile (up to 16%). Albumins have a low molecular mass, are easily crystallizable, and their isoelectric points are in the weakly acid range. High concentrations of neutral salts are necessary for “salting

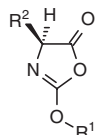
out.” Albumins have been used as a model protein for diverse biophysical, biochemical, and physico-chemical studies. *Serum albumins* ($M_r \sim 67.5$ kDa) are the most abundant of these proteins in blood plasma. These proteins have been one of the most investigated proteins for many years, and show interesting properties of binding a variety of hydrophobic ligands, e.g., fatty acids, warfarin, anesthetics, bilirubin, steroids, lysolecithin, and several dyes. Furthermore, a high binding capacity for Ca^{2+} , Na^+ , K^+ must be mentioned. Serum albumins comprise up to 60% of the dry mass of blood serum, corresponding to a concentration of 42 g L^{-1} , and provide about 80% of the osmotic pressure of blood. The single peptide chain of about 580 aa forms a secondary structure characterized by 67% of α -helix, six turns, and 17 disulfide bridges. The X-ray structure of *human serum albumin* (HSA) shows three domains I, II, and III, which confer to the protein a heart-shaped molecular form. Each domain consists of two subdomains, named IAB, IC, IIAB, IIC, IIIAB, IIIC, respectively. Interestingly, the domains exhibit a certain degree of binding specificity. Domain I, also named the warfarin binding site, binds predominantly indole derivatives, several dyes, long-chain fatty acids, and compounds with alicyclic ring structures, whereas domain II, termed the indole or benzodiazepine binding site, is specific for the binding of short-chain fatty acids, bilirubin, indole derivatives, several dyes, and steroids. Domain III is specific for indole derivatives, long-chain fatty acids, diazepam and other drugs. *Bovine serum albumin* (BSA) shows 76% sequence identity with HSA. BSA contains two tryptophan residues (W^{214} , W^{131}), while HSA has only one (W^{214}). The consequences are different spectroscopic properties of the two proteins. Bovine and human serum

albumin contain 16% nitrogen, and are used as standard proteins for calibration. Further important animal and plant albumins are \rightarrow lactalbumin, \rightarrow ovalbumin and \rightarrow ricin [J. R. Brown, P. Shockley, *Lipid-Protein Interactions*, Vol. 1, Wiley, New York, 1982; D. Carter, J. X. Ho, *Advances in Protein Chemistry*, Vol. 45, Academic Press, New York, 1994, p. 153; E. L. Gelano et al., *Biochim. Biophys. Acta* 2002, 1594, 84].

Alkanesulfonamide linker, \rightarrow safety-catch linker.

Alkene peptidomimetics, peptides, where an amide bond has been replaced to give E-alkene [M. M. Hahn et al., *J. Chem. Soc. Commun.* 1980, 234; M. Kranz, H. Kessler, *Tetrahedron Lett.* 1996, 37, 5359].

2-Alkoxy-5(4H)-oxazolones, azlactones, stereochemically labile intermediates that occur during coupling reactions and can cause \rightarrow racemization at the stereogenic center of an α -amino acid. The propensity toward oxazolone formation strongly correlates with the activation potential of the activating group X in the carboxy component, R^1 -CO-NH-CHR²-CO-X, and with the electronic properties of the N-acyl moiety R^1 -CO- [M. Goodman, L. Levine, *J. Am. Chem. Soc.* 1964, 86, 2918].



Oxazolone

Alkyl-type protecting groups, protecting groups for the amino function of amino acids during peptide synthesis based on alkyl moieties. The most popular protect-

ing group of the alkyl type is the \rightarrow triphenylmethyl (Trt) group.

All, allyl

Allatostatins (AST), a family of neuropeptides first isolated from the brain of the cockroach *Diploptera punctata*. There are three allatostatin families according to C-terminal sequence homology: (a) the *cockroach type* (>70 peptides, consensus sequence FGLa), comprising e.g. Dippu-AST 1 (LYDFGLa), Dippu-AST 2 (AYSIVSEYKR¹⁰LPVYNFGLa), Dippu-AST 5; (b) the *cricket type* (consensus sequence WX₆Wa), with Grybi-AST 1 (H-Gly-Trp-Gln-Asp-Leu-Asn-Gly-Gly-Trp-NH₂) and Grybi-AST 5 (H-Ala-Trp-Asp-Gln-Leu-Arg-Pro-Gly-Trp-NH₂); and (c) the *Manduca type* (consensus sequence PISCF). Members of the latter family are highly homologous (<EXRZRQCYFN¹⁰PISCF with X = V,I and Z = F,Y) between the species *Manduca sexta*, *Drosophila melanogaster*, and *Anopheles gambiae*. AST inhibit the synthesis of the juvenile hormone in the *corpora allata*, which regulates insect metamorphosis. However, it has been proposed that this effect appeared secondarily, and that the ancestral function was the modulation of myotropic activity. Further effects of the different AST include endocrine and interneuronal functions, neuromodulatory effects, and direct action on biosynthetic pathways; mostly being species- or order-specific. Picomolar concentrations of the *Drosophila melanogaster* Drome-AST 3 (H-Ser-Arg-Pro-Tyr-Ser-Phe-Gly-Leu-NH₂) from the head of *Drosophila* activate a fruit-fly G protein-coupled receptor that shows striking sequence similarities to mammalian galanin and somatostatin/opioid receptors [A. P. Woodhead et al., *Proc. Natl. Acad. Sci. USA* 1989, 86, 5997; W. G. Bendena et al., *Ann. N. Y. Acad. Sci.* 1989,

897, 311; J. G. Yoon, B. Stay, *J. Comp. Neurol.* **1995**, 363, 475; N. Birgul et al., *EMBO J.* **1999**, 18, 5892].

Alloc (Aloc), → allyloxy-carbonyl group.

Allom, Alom, → allyl-type protecting groups.

Allopeptide, a word derived from the noun "peptide" that means in immunology a peptide from different individual (Greek *allos*, other) of the same species [J. H. Jones, Editorial, *J. Peptide Sci.* **2006**, 12, 79].

Allyl ester, → allyl-type protecting groups.

Allyloxy-carbonyl group (Alloc, Aloc), an urethane-type protecting group for the amino function during peptide synthesis. The Alloc group is completely orthogonal to Boc and Fmoc, and is especially suited for the synthesis of labile derivatives. The group can be smoothly removed by treatment with a suitable nucleophile, e.g., amines, amine-borane complexes, organosilanes, in the presence of a palladium catalyst (palladium(0)-catalyzed allyl transfer) [H. Kunz, C. Unverzagt, *Angew. Chem. Int. Ed.* **1984**, 23, 436; A. Loffet, H. X. Zhang, *Int. J. Pept. Protein Res.* **1993**, 42, 346; F. Guibe, *Tetrahedron* **1998**, 54, 2967].

Allyl-type protecting groups, protecting groups used in peptides synthesis bearing the allyl moiety. This type of protecting group has the advantage of being completely orthogonal to most other protecting groups, and provides an excellent tool for temporary reversible protection in glycopeptide synthesis. Beside the → allyloxy-carbonyl group, *allylester* (OAll) of amino acids are very easy to obtain, are stable under glycosylation conditions, and can be cleaved by Rh^I catalysis. An even milder method for the selective cleavage of allyl esters utilizes palladium(0)-catalyzed allyl transfer to morpholine. Allyl-type linker moieties are also suited for the solid-

phase synthesis of complex glycopeptides. The *allyloxy-carbonylaminomethyl* (Allocam) group was described as a thiol-protecting group in 1999, while the *N*^π-allyl moiety was suggested as an imidazole-protecting group by the same authors one year later. Last, but not least, the *N*^π-*allyloxymethyl* (Allom) group has also been described as an imidazole-protecting group [A. Loffet, H. X. Zhang, *Int. J. Pept. Protein Res.* **1993**, 42, 346; A. M. Kimbonguila et al., *Tetrahedron* **1997**, 53, 12525; A. M. Kimbonguila et al., *Tetrahedron* **1999**, 55, 6931; S. J. Harding, J. H. Jones, *J. Peptide Sci.* **1999**, 5, 368; H. Herzner et al., *Chem. Rev.* **2000**, 100, 4495].

Alterobactin, a 19-membered macrocyclic → depsipeptide containing two types of unusual building block, two *L*-threo-β-hydroxyaspartic acids and one (3*S*,4*S*)-4,8-diamino-3-hydroxyoctanic acid attached to a catechol carboxylate at the *N*^ω-site. It was isolated from an open-ocean bacterium *Alteromonas luteoviolacea* collected off Chub Cay, Bahamas. Alterobactin is a depsipeptide → siderophore exhibiting extraordinary affinity for ferric ion. The total synthesis has been described [R. T. Reid et al., *Nature* **1993**, 366, 455; J. Deng et al., *Synthesis* **1998**, 627].

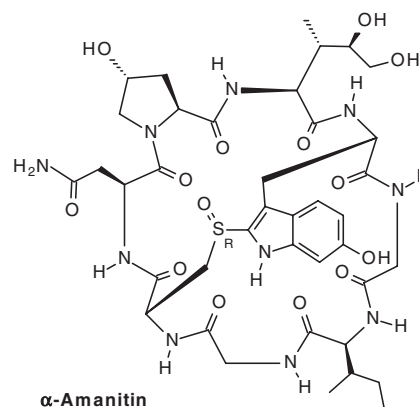
Alytensin, <EGRLGTQWAV¹⁰GHLMa, a 14-peptide amide belonging to the → bombesin family. Alytensin was isolated from the skin of the European amphibian *Alytes obstetricans* in 1971. It is structurally very similar to → bombesin, and displays similar biological activities when applied to mammals [A. Anastasi et al., *Experientia* **1971**, 27, 166; V. Erspamer, P. Melchiorri, *Trends Biochem. Sci.* **1980**, 1, 391].

Alzheimer's disease (AD), the most prominent severe dementia in the elderly population, first described by Alzheimer in 1907. AD is a widespread, neurodegenerative,

dementia-inducing disorder characterized mainly by amyloid deposits surrounding dying neurons (senile plaques), neurofibrillar degeneration with tangles, and cerebrovascular angiopathies. AD is clinically characterized by a progressive loss of cognitive abilities, progressive memory and intellectual deficits. In 1998, it was estimated that 25 million people worldwide suffered from AD. Amyloid- β and tau protein are responsible for the formation of the plaques and tangles of AD. The mechanism of neurodegeneration caused by \rightarrow amyloid- β in AD is controversial. The primary pathogenic event of AD is the progressive cerebral accumulation of amyloid- β ($A\beta$), a proteolytic product of the β -amyloid precursor protein (APP). Tau protein is the major component of paired helical filaments that form a compact filamentous network described as "neurofibrillary tangles." From culture experiments there was derived the existence of a relationship between fibrillary amyloid and the cascade of molecular signals that trigger tau hyperphosphorylations. The cyclin-dependent kinase Cdk5 and glycogen synthase kinase GSK3 β are the two main protein kinases involved in the anomalous tau phosphorylations. Inhibitors of both kinases and antisense oligonucleotides exert protection against neuronal death. On the other hand, it has been reported that oxidative stress constitutes a main factor in the modification of normal signaling pathways in neuronal cells. In brain tissue from AD patients, some major species of soluble $A\beta$ have been identified: the full-length form $A\beta(1-42)$, and at residues Glu³ and Glu¹¹, respectively, truncated $A\beta$ peptides, such as $A\beta(3-40/42)$ and $A\beta(11-40/42)$. The shortened forms bear at the *N*-terminus a pyroglutamic acid residue which might be result from the corresponding Glu residues

catalyzed by the glutamyl cyclase activity of \rightarrow glutaminyl cyclase. It has been reported that, *in vitro*, these smaller peptides are more neurotoxic and aggregate more rapidly than the full-length isoforms. A rational design of inhibitors against glutaminyl cyclase-associated disorders has been started [R. B. Maccioni et al., *Arch. Med. Res.* **2001**, *35*, 367; T. Hashimoto et al., *EMBO J.* **2002**, *21*, 1524; C. Morgan et al., *Prog. Neurobiol.* **2004**, *74*, 323; S. Schilling et al., *FEBS Lett.* **2004**, *563*, 191; K.-F. Huang et al., *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 13117; S. Schilling et al., *Biochemistry* **2005**, *44*, 13415; M. Goedert, M. G. Spillantini, *Science* **2006**, *314*, 777].

Amanitins, a group of toxic components of *Amanita phalloides* (\rightarrow amatoxins).



Amatoxins, heterodetic bicyclic 8-peptides from *Amanita* species, but also detected in *Galerina* and *Lepiota* species, which are responsible for the fatal intoxications by the mentioned toadstools. The toxic peptides are readily absorbed by the intestine, and in humans the lethal dose of amatoxin is ~ 0.1 mg kg^{-1} body weight, or even lower. The gut cells of humans seem to be the first cells affected, and the intestinal phase begins about 9 h after

administration of the toxins. There is no effective therapy of *amanita* poisoning, as the amatoxins inhibit strongly and specifically the eukaryotic RNA-polymerases II (B) in the nuclei. To date, nine members of the amatoxins have been isolated, among which α -*amanitin* is the best studied. The individuals are derived from the parent structure, and differ mainly by the number of hydroxyl groups and by an amide versus carboxy function. Amatoxins contain exclusively L-amino acids and glycine, together with uncommon moieties such as the bridging 6'-hydroxytryptathionine-(R)-sulfoxides between residues 4 and 8. The fundamental studies on structure elucidation and biochemical effects were carried out by Theodor Wieland and coworkers [Th. Wieland, *Peptides of Poisonous Amanita Mushrooms*, Springer Series in Molecular Biology, Springer-Verlag, New York, Berlin, 1986].

American Peptide Society (APS), a non-profit scientific and educational organization founded in 1990, providing a forum for advancing and promoting knowledge of the chemistry and biology of peptides. The near-1000 members of the Society come from North America and from more than 30 other countries worldwide. The establishment of the American Peptide Society was a result of the rapid worldwide growth that has occurred in peptide-related research, and of the increasing interaction of peptide scientists with virtually all fields of science. Members of the APS are involved in research in academia, industry, and government, covering all aspects of peptide chemistry, biology, and pharmaceutical sciences. Research topics include the synthesis of biologically important targets, the isolation and characterization of new products, structure-activity relationship studies, molecular diversity, *de-novo*

design, drug delivery, and the discovery of new pharmaceutical agents. The APS is a member of the Federation of American Societies for Experimental Biology (FASEB). The affiliation with FASEB increases the visibility of APS in the biomedical research community, and allows the participation in any FASEB public affairs initiatives. The APS sponsors *Biopolymers: Peptide Science*, published by Wiley-Interscience, as the official journal of the Society. A full year subscription to this journal is automatically included with membership in the APS. One very important activity of the APS is the organization of a biennial international symposium in North America. The 20th *American Peptide Society Symposium* was held in Montreal, Quebec, Canada, in June 2007. The APS Council administers *The R. Bruce Merrifield Award*, which recognizes the lifetime scientific work of a peptide chemist, *The Vincent du Vigneaud Award* for outstanding achievements in peptide research, which is presented at the Gordon Research Conferences every two years, besides further honors such as the *Makinen Lectureship*, the *Achievement Award for Scientific and Administrative Excellence*, the *Young Investigator's Mini-Symposium*, and the *Young Investigator's Poster Competition*.

Amidation, the formation of amides. Amino acid and peptide amides are synthesized by reaction of the appropriate esters or activated carboxylic acid derivatives with ammonia. Amidation of bioactive peptides is performed using the bifunctional enzyme peptidylglycine α -amidating monooxygenase (PAM) by N-oxidative cleavage of a glycine-extended precursor [S. T. Prigge et al., *Science* 1997, 278, 1300].

Amide-protecting groups, protecting groups for C-terminal amides of amino

acids and peptides, for backbone amide groups (\rightarrow backbone amide protecting groups), as well as for the side-chain ω -carboxamide groups of Gln and Asn. Although these rather unreactive functionalities usually do not require further protection, side reactions sometimes occur at the side-chain carboxamides of Asn and Gln during peptide synthesis. Under the strongly dehydrating conditions of carbodiimide couplings, unwanted nitrile formation may prevail. Strongly activating reagents (BOP, PyBOP, HBTU) also may favor this dehydration. Asn in the peptide chain has been observed to cyclize, with release of ammonia, to give aspartimides that in turn are hydrolyzed to a mixture of α -aspartyl and β -aspartyl peptides. Most side-chain reactions can be suppressed by reversible blocking of these functionalities with, e.g., substituted *N*-benzyl derivatives, *N*-methoxybenzyl residues, or the *N*-diphenylmethyl moiety, all of which can be cleaved by liquid HF. *N*-Triphenylmethyl (Trt) and *N*-trimethoxybenzyl (Tmb) are very appropriate carboxamide-protecting groups for solid-phase synthesis, in combination with Fmoc as the temporary protecting group. The carbonyl and amino groups of a peptide bond potentially act as hydrogen bond acceptors and donors, favoring aggregation and leading to the formation of secondary structures and aggregation. This may prevent further reactions of the amino terminus and lead to truncated sequences. The phenomenon is sequence-dependent (\rightarrow difficult sequences). In such cases, e.g. \rightarrow backbone amide protecting groups with Hnb or Hmb residues is required [P. Sieber, B. Riniker, *Tetrahedron Lett.* **1991**, 32, 739; B. Riniker et al., *Tetrahedron* **1993**, 49, 9307].

Amine capture strategy, a variant of prior capture-mediated ligation by means of

quinolinium thioester salts. Quinolinium thioester salts has been designed as a so-called new electrophilic platform capable of acting as an amine capture device [S. Leleu et al., *J. Am. Chem. Soc.* **2005**, 127, 15668].

Amino acid analysis, determination of amino acid composition of a peptide by complete hydrolysis followed by the quantitative analysis of the liberated amino acids. For hydrolysis, numerous chemical and enzymatic protocols are known. Based on the pioneering studies of \rightarrow Stein and \rightarrow Moore, amino acid analysis has been automated. Nowadays, instruments are in use for quantitative amino acid analysis which are based on partition chromatography, such as HPLC and gas-liquid chromatography [S. Blackburn, *Amino Acid Determination*, M. Dekker, New York, **1978**; W. S. Hancock, *Handbook of HPLC for the Separation of Amino Acids, Peptides, and Proteins*, CRC Press, Boca Raton, **1984**].

Amino acid anhydrides, \rightarrow anhydrides.

Amino acid chloride, \rightarrow acyl halides.

Amino acids, the monomeric units of peptides and proteins. From analysis of the vast number of proteins, it follows that 20 proteinogenic or "standard amino acids" are the building blocks of all proteins. These amino acids are specified by the genetic code. With \rightarrow selenocysteine and \rightarrow pyrrolysine two additional members have been identified. Besides the imino acid proline, all other building blocks are known as α -amino acids, $H_2N-CHR-COOH$, but the zwitterion form, $H_3N^+-CHR-COO^-$, occurs at physiological pH values. The amino acids can therefore act as either acids or bases. Depending on the side-chain residue R, amino acids can be classified into those with: (a) non-polar side chains [Gly/G; Ala/A; Val/V; Leu/L; Ile/I; Met/M; Pro/P; Phe/F; Trp/W];

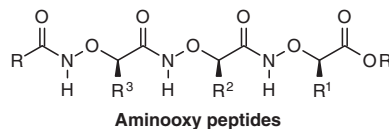
(b) uncharged polar side chains [Ser/S; Thr/T; Asn/N; Gln/Q; Tyr/Y; Cys/C; Sec/U]; and (c) charged polar side chains [Lys/K; Arg/R; His/H; Asp/D; Glu/E; Pyl/O]. In brackets are given the three-letter abbreviations and one-letter symbols of the 22 proteinogenic amino acids. With the exception of glycine, all proteinogenic amino acids are optically active – that is, they have an asymmetric center or chiral center localized at the C_α atom. Threonine and isoleucine each have two asymmetric centers, and therefore four possible stereoisomers (L-, D-, L-*allo*-, and D-*allo*-). The 22 common amino acids are not the only amino acids that occur in biological systems. The number of non-proteinogenic is approaching 300; these occur mostly in plants [H. B. Vickery, *Adv. Protein Chem.* **1972**, *26*, 81; L. Fowden et al., *Adv. Enzymol.* **1979**, *50*, 117; J. S. Davies (Ed.), *Amino acids and Peptides*, Chapman & Hall, London, **1985**; G. C. Barrat (Ed.), *Chemistry and Biochemistry of Amino Acids*, Chapman & Hall, London, **1985**].

Aminoacyl-tRNA, an amino acid intermediate in ribosomal peptide synthesis. The first step in the aminoacylation process of tRNA is activation of the amino acid, catalyzed by the aminoacyl-tRNA synthetase (aatRS). An amino acid reacts with ATP under the elimination of pyrophosphate to yield a mixed anhydride, the aminoacyl adenylate, which normally remains tightly bound to the aa-tRS. In the second step, the highly activated aminoacyl moiety is transferred to the appropriate tRNA, thereby forming the aminoacyl-tRNA and liberating ADP.

α -Aminoisobutyric acid (Aib), $C^{\alpha\alpha}$ -dimethylglycine, a strongly helicogenic, non-coded, C^α -tetrasubstituted amino acid. This occurs naturally, and is a building block in \rightarrow alamethicin and other \rightarrow peptaibols. Aib is often incorporated into peptides to in-

vestigate the conformational requirements of receptors. Furthermore, it plays an important role as building block for the stabilization of 3_{10} -helices [I. L. Karle, *Biopolymers* **1996**, *40*, 157; F. Formaggio et al., in: *Houben-Weyl: Methods of Organic Synthesis*, M. Goodman et al. (Eds.), Volume E22c, Thieme, Stuttgart, Germany, **2003**, p. 292].

Aminoxy peptides, correlates of β -peptides composed of α -aminoxy acids as analogues of β -amino acids with replacement of C^β by an oxygen atom. The lone pair repulsion of the nitrogen and oxygen atoms renders the backbone of aminoxy peptides more rigid than that of β -peptides [X. Li, *Chem. Commun.* **2006**, 3367].



Amino protection, the reversible blocking of the amino function (\rightarrow temporary protecting groups) during peptide synthesis. The necessity for sequence-specific incorporation of amino acids into a peptide requires protection of the N^α amino function, together with most functional groups present in the side chains. While the latter usually remain attached throughout the synthesis (\rightarrow semipermanent protecting groups), the N^α function requires temporary protection by groups that are cleaved after each coupling step in order to allow for further elongation of the peptide. Temporary and semipermanent protecting groups must be cleaved independently (\rightarrow orthogonal protecting groups) and the nature of the N^α protection determines the tactics of the peptide synthesis and the selection of the side chain-protecting groups. The most widely employed temporary protecting groups are the

→ benzyloxycarbonyl group (Z), → *tert*-butoxycarbonyl (Boc), and → 9-fluorenylmethoxycarbonyl (Fmoc) groups. Side-chain amino groups (e.g., Lys N^ω) must be protected with semipermanent protecting groups. In the Fmoc approach, Boc protection for Lys N^ω is most appropriate. If completely orthogonal protection of the N^ω -amino group is necessary, the → Tfa, → Dde, → Alloc, or Npys groups are available. Tfa and Npys are well compatible with Boc chemistry, as cleavage occurs in the first case with piperidine and in the latter case with triphenylphosphine. Dde and the related ivDde are orthogonal to Boc and Fmoc, as they are removed with dilute hydrazine solutions.

AMP, acronym for a) → antimicrobial peptides, or b) adenosine monophosphate.

Amphiregulin (AR), a bifunctional cell growth modulator belonging to the → epidermal growth factor (EGF) family. Human amphiregulin contains 84 aa, while a truncated form consists of 78 aa. The amino-terminal region is extremely hydrophilic, and contains a huge number of lysine, arginine, and asparagine, whereas amphiregulin-(46-84) exhibits striking sequence homology to the members of the EGF family. AR binds to the EGF receptor, but exhibits a weaker affinity compared to EGF. In murine keratinocyte growth, AR fully supplants the requirement for EGF or transforming growth factor- α . However, in other cell systems it is a much weaker growth stimulator. Recently, it has been reported that T helper 2 cells, but not other T-cell subsets, express AR. EGF receptor ligands induce epithelial cell proliferation, and a lack of AR delayed expulsion of the nematode *Trichuris muris*. The new link between T helper 2 cells and epithelial proliferation provides new aspects for planning therapeutic interventions for helminth in-

fections and other diseases that involve both cell proliferation and allergy, such as asthma [M. Shoyab et al., *Science* **1989**, *243*, 1074; D. M. Zaiss et al., *Science* **2006**, *314*, 1746].

Amphomycins, a group of lipopeptide antibiotics that are highly active against multi-resistant bacteria. *Amphomycin*, the first member of this group was discovered during the early 1950s. In 1968, there followed the isolation of *tsushimycin*, and later more members of this group of lipopeptides – such as friulimicin B and laspartomycin – are described. Amphomycins are characterized by a peptide framework consisting of a 10-membered cyclopeptide and an exocyclic amino acid acylated at the amino group by a fatty acid residue. Members of this group differ principally in the type of fatty-acid substituent. The lipopeptide antibiotic → daptomycin (Cubicin[®]), which was approved in the USA for the treatment of skin infections in 2003, may also belong to this group due to the 10-membered cyclopeptide core and the fatty acid constituent. However, the amino acid sequence is markedly different. Amphomycins have been found to be active against Gram-positive bacteria, but the exact mechanism of action remains an ongoing debate. *Tsushimycin* has been crystallized and its X-ray structure determined at 1.0 Å resolution. The backbone of the cyclopeptide core adopts a saddle-like conformation that is stabilized by a Ca^{2+} ion bound within the peptide ring, while an additional Ca^{2+} links the molecule to dimers enclosing an empty space resembling a binding cleft [B. Heinemann et al., *Antibiot. Chemother.* **1953**, *3*, 1239; J. Shoji et al., *J. Antibiot.* **1968**, *21*, 439; G. Bunkoczi et al., *Acta Crystallogr.* **2005**, *D61*, 1160].

AM-PS, aminomethyl polystyrene.

Amylin, KCNTATCATQ¹⁰RLANFLVHSS²⁰NNFGAILSST³⁰NVGSNTY^a (human amylin; disulfide bond: C²-C⁷), *islet amyloid polypeptide (IAPP)*, *diabetes-associated peptide (DAP)*, a 37-peptide amide which belongs to the \rightarrow calcitonin/calcitonin gene-related peptide family. Amylin is generated from a gene located on chromosome 12p12.3 sharing 46% sequence homology with the two \rightarrow calcitonin gene-related peptides and 20% with human \rightarrow calcitonin. Amylin was first isolated from an insulinoma and from pancreatic amyloid deposits of patients with non-insulin-dependent (type II) diabetes mellitus (NIDDM). It may be involved in the pathogenesis of type II diabetes by deposition as amyloid within the pancreas, which leads to β -cell destruction. It shows calcitonin-like activity on bone metabolism and a CGRP-like activity (\rightarrow calcitonin gene-related peptide) action on the vasculature. From studies on knockout mice, it follows that amylin should be important for the regulation of glucose-induced insulin secretion and the rate of blood glucose elimination. Human amylin and other mammalian amylin are synthesized as relatively small precursor proteins. Mature amylin is liberated from the 89-polypeptide precursor by proteolytic processing, in a similar way to that of proinsulin and other islet prohormones. Amylin is co-synthesized with insulin, stored in the β -cell secretory granules (in analogy to insulin), and secreted with insulin from the islet β -cells. Normally, the rate of synthesis is only about 1% of that of insulin, but this can increase after prolonged stimulation *in vivo* with increased concentrations of glucose. This behavior seems to be a link to the contribution of amylin in the pathogenesis of type II diabetes. Amylin has a vasodilatory effect like other members of the calci-

tonin/calcitonin gene-related family. It also acts as an agonist at the calcitonin receptor, but efficient signaling of amylin requires the formation of a receptor complex of the calcitonin receptor with \rightarrow receptor activity-modifying proteins (RAMP). Despite being less potent than insulin, amylin shows growth factor-like effects and inhibits insulin-stimulated incorporation of glucose into muscle glycogen. An action in the brain to reduce body weight has been reported, resulting in a hypothesis that amylin acts as a signal to the brain contributing to the maintenance of long-term energy balance [R. Muffet et al., *Eur. J. Endocrinol.* **1995**, *133*, 17; S. J. Wimalawansa, *Crit. Rev. Neurobiol.* **1997**, *11*, 167; P.A. Rushing et al., *Endocrinology* **2000**, *141*, 850].

Amyloid- β (A β), β -amyloid, *amyloid- β* peptide, a physiological peptide occurring in the brain, and enzymatically released from the amyloid precursor protein (APP). APP is an ubiquitously expressed membrane-bound protein with elusive function. The accumulation of A β in the brain is a triggering primary event to the pathological cascade for \rightarrow Alzheimer's disease (AD). The accumulation of A β appears to be caused by an increase in the anabolic activity, as demonstrated in familial AD, or by a decrease in catabolic activity. The predominant forms of A β consist of the 40- and 42-peptides, termed A β -(1-42), DAEFRHDSGY¹⁰EVHHQKLVFF²⁰AEDVGSNKGA³⁰IIGLMVGGVV⁴²IA, and A β -(1-40), respectively. In normal, non-AD, individuals the principal A β forms are A β -(1-40) and A β -(1-42), of which the former constitutes about 90%. The N-terminal partial sequence 1-28 stems from the extracellular domain of APP and is predominantly hydrophilic, whereas the C-terminal part 29-39/43 stems from the

transmembrane domain and is characterized by hydrophobic amino acids. $A\beta$ -(1-42) is thought to have a more critical function than $A\beta$ -(1-40) in amyloid formation and pathogenesis of AD, whereas $A\beta$ -(1-40) is the major component secreted from cultured cells, and occurs in cerebrospinal fluid. Most of the knowledge about APP processing derives from studies with cultured cells. The α -, β - and γ -secretases are involved in APP processing. α -Secretase action provides a large soluble ectodomain, termed sAPP α . The remaining C-terminal part of the protein is subject of γ -secretase cleavage that does not produce full-length $A\beta$ peptides, but leads to a truncated form known as p3 fragment comprising the residues 17-40/2 of $A\beta$. In an alternative pathway, β -secretase cleaves the bond between 671 and 672 of APP, thereby releasing the soluble ectodomain, sAPP β , whereas the $A\beta$ sequence remains bound to the membrane with the C-terminal domain of the protein. Finally, cleavage by γ -secretase within the membrane-spanning region of APP provides several C-terminal variants of the $A\beta$ peptide bearing 39 to 43 residues. Mutations in APP can cause either increased overall secretion of $A\beta$ or secretion of "long" (42- to 43-residue) forms of $A\beta$ -(1-42) relative to the shorter $A\beta$ -(1-40) form. Despite the increasing production of research data, AD remains an enigma. AD is characterized by a variety of pathological features, such as extracellular senile plaques, synaptic loss, intracellular neurofibrillary, and brain atrophy. The senile plaques are mainly composed of $A\beta$ with 40–43 aa, whereas the neurofibrillary tangles consist of twisted filaments of hyperphosphorylated tau protein. Especially, the heterogeneity of this neuropathology and the lack of screening of AD patients on an early stage and a better delineation of pathological

subtypes of AD inhibit significantly the progress in understanding of AD. In order to develop new methods to prevent and treat AD, it must be possible to diagnose the preclinical stage of AD using biological markers, before the brain damage becomes irreversible. Suitable markers may include high plasma concentrations of $A\beta$ -(1-42) and findings of hippocampal atrophy on magnetic resonance imaging (MRI) of the brain. Solid-state NMR has been developed as a useful probe of amyloid structure. Currently, there are no known cures for AD, although some drugs have been approved for its treatment, such as donepezil (Pfizer), galantamine (Sanochemia), and rivastigmine (Novartis). According to the "amyloid cascade hypothesis," the reduction of $A\beta$ in the brain is discussed as being a therapeutic intervention in AD. Disaggregation of the senile plaques found in the brain is another strategy. For example, the 5-peptide, Leu-Pro-Phe-Phe-Asp, has attracted attention as a β -sheet-breaking peptide. Further future targets may be the inhibition of the activity of β -secretase, besides alternative treatment strategies [J. Kang et al., *Nature* **1987**, 325, 733; J. Wiltfang et al., *Gerontology* **2001**, 47, 65; A. B. Clippingdale et al., *J. Peptide Sci.* **2001**, 7, 227; K. Fassbender et al., *Naturwissenschaften* **2001**, 88, 261; N. Iwata et al., *Pharm. Ther.* **2005**, 108, 129; A. K. Tickler et al., *Prot. Pept. Lett.* **2005**, 12, 513; Y. Sohma, Y. Kiso, *ChemBioChem.* **2006**, 7, 1549; R. Tycko, *Prot. Pept. Lett.* **2006**, 13, 229].

Amyloid-forming proteins, mainly in native state α -helical proteins undergoing α -helix to β -strand conversion before or during fibril formation. Partially unfolded or misfolded β -sheet fragments are discussed as precursors of amyloids. Protein aggregation combined with other events leads to the deposition of insoluble protein

forms, causing an increasing number of neurodegenerative diseases such as → Alzheimer's disease, Parkinson's, and Creutzfeld-Jakob disease. The molecular structures of amyloid fibrils are of considerable interest for an understanding of the interactions that drive amyloid formation. The conformational transition shifting the equilibrium from the functional to the pathological protein isoform can occur sporadically. However, the conformational change can also be triggered by mutations as well as by changes of the environmental conditions (oxidative stress, ionic strength, free radicals, pH, metal ions, protein concentration) or physiological or pathological chaperones (→ molecular chaperones). Furthermore, misfolded protein fragments acting as a structural template can be involved in the initiation of the conformational conversion that causes the disease. Recent investigations with solid-state NMR of fibrils have indicated that the β -sheets in amyloid fibrils have structures that tend to maximize contacts among hydrophobic residues. Amyloid fibrils formed by peptides and proteins lacking hydrophobic segments may be stabilized by different sets of interactions. Protein fragments that are rich in Gln or Asn are of special interest because of their involvement in Huntington's disease, spinocerebellar ataxia, and particularly in amyloid-forming yeast → prion proteins [D. J. Selkoe, *Nature* **2003**, 426, 900; C. Soto, *Nat. Rev. Neurosci.* **2003**, 4, 49; R. Tycko, *Prot. Pept. Lett.* **2006**, 13, 229; J. P. Sipe (Ed.), *Amyloid Proteins*, Wiley-VCH, **2005**].

Amythiamicins, naturally occurring → thiopeptide antibiotics isolated from a strain of *Amycolatopsis* sp. M1481-42F4. The amythiamicins A–D belong to the very few thiopeptides that do not contain a dehydroalanine moiety. They inhibit both the

growth of Gram-positive bacteria, including the methicillin-resistant *Staphylococcus aureus* (MRSA), and the action of elongation factor Tu (EF-Tu), a GTP-dependent translation factor. Amythiamicin A is the most potent inhibitor (IC_{50} 0.01 μ M) against *Plasmodium falciparum*, the parasite that causes the majority of malarial infections in humans. It has been reported that amythiamicin binds to the EF-Tu of the parasite, thereby blocking protein synthesis. The total synthesis of amythiamicin D was reported in 2005 [K. Shimanaka et al., *Antibiotics* **1994**, 47, 1153; R. A. Hughes et al., *J. Am. Chem. Soc.* **2005**, 127, 15644].

Anabaenopeptins, a main class of cyanobacterial peptides. These cyclic peptides are characterized by a peptide bond between the ϵ -amino group of Lys² with the α -carboxyl function of the amino acid in position 6. An amino acid unit is attached to the ring by an ureido bond formed between the α -amino group of Lys² and the α -amino function of the appropriate building block [K.-I. Harada et al., *Tetrahedron Lett.* **1995**, 36, 1511; M. Welker, H. von Döhren, *FEMS Rev.* **2006**, 30, 530].

Anchoring group, *linker*, a group bound to the polymeric support for the attachment of the first amino acid in polymer-supported peptide synthesis. The chloromethyl group was the first anchoring moiety in the polystyrene/divinylbenzene resin for solid-phase peptide synthesis developed by Bruce Merrifield [R. B. Merrifield, *J. Am. Chem. Soc.* **1963**, 85, 2149].

Ancovenin, a member of the subclass B → lantibiotics first isolated from the culture broth of a *Streptomyces* sp. (No. A647P-2) acting as an inhibitor of → angiotensin-converting enzyme. In the biosynthesis of ancovenin, the 19-prepeptide (CVQSCS FGPL¹⁰TWSCDGNTK) is first modified

and processed by enzyme systems that are involved in the transformation of the acyclic precursors. It contains unusual amino acids such as (2*S*,3*S*,6*R*)-3-methylanthionine, *meso*-lanthionine, and dehydroalanine [T. Wakamiya et al., *Tetrahedron Lett.* **1985**, 26, 665; R. Kellner et al., *Eur. J. Biochem.* **1988**, 177, 53].

Androctonin, RSVCRQIKIC¹⁰RRRGGCY YKC²⁰TNRPY (disulfide bonds: C⁴-C²⁰/C¹⁰-C¹⁶), a hydrophilic antimicrobial peptide (→ antimicrobial peptides) isolated from the blood of the scorpion *Androctonus australis*. Androctonin inhibits the growth of both Gram-positive and Gram-negative bacteria, and displays a large spectrum of activity against filamentous fungi. In contrast to amphipathic α -helical antimicrobial peptides that bind and permeate negatively charged vesicles, androctonin binds only to negatively charged lipid vesicles; this might explain the selective lytic activity towards bacteria but not to red blood cells [L. Ehret-Sabatier et al., *J. Biol. Chem.* **1996**, 271, 29537; C. Hetru et al., *Biochem. J.* **2000**, 345, 653; L. P. Silva, *Lett. Drug Design Discov.* **2004**, 1, 230].

ANF, atrial natriuretic factor.

Anfinsen, Christian, (1916–1995), American biochemist and winner of the Nobel Prize in Chemistry 1972 (shared with → Moore and → Stein) for his work on ribonuclease (RNase), especially concerning the connection between the amino acid sequence and the biologically active conformation. Anfinsen demonstrated that RNase could be refolded after denaturation without loss of enzymatic activity. In 1943, Anfinsen received his Ph.D from Harvard University, and then held various research and teaching positions. In 1950, he joined the staff of the National Institute of Health (Bethesda, MD), and headed the laboratory

of chemical biology in the National Institute of Arthritis, Metabolism, and Digestive Diseases from 1963 to 1982. Anfinsen was a professor of biology at Johns Hopkins University from 1982 until his death.

Angiotensin-converting enzyme (ACE), *peptidyl dipeptidase A*, a zinc metallopeptidase with great importance in the regulation of blood pressure as well as fluid and salt balance in mammals. ACE is a dipeptidyl-carboxypeptidase that catalyzes the conversion of the inactive 10-peptide angiotensin I into the potent vasoconstrictor, the 8-peptide angiotensin II (→ angiotensins). In addition, ACE inactivates → bradykinin, a vasodilatory peptide; hence, ACE raises blood pressure. The function of ACE in blood pressure control and water and salt metabolism has been elucidated mainly by the use of highly specific → ACE inhibitors. Approaches for regulation of blood pressure based on the ACE homologue → angiotensin-converting enzyme 2 are in progress [N. M. Hooper, *Int. J. Biochem.* **1991**, 23, 641; A. Turner, N. M. Hooper, *Trends Pharmacol. Sci.* **2002**, 23, 177; J. F. Riordan, *Genome Biol.* **2003**, 4, 225; D. Coates, *Int. J. Biochem. Cell Biol.* **2003**, 35, 769; K. M. Esalad et al., *Hypertension* **2005**, 46, 953; L. S. Zisman, *Eur. Heart J.* **2005**, 26, 322].

Angiotensin-converting enzyme 2 (ACE 2), a novel human zinc metalloprotease originally discovered in the testis, heart and kidney, but later found in a wide variety of tissues and seeming to be localized in much the same places as → angiotensin-converting enzyme (ACE). ACE 2 is a glycoprotein of 120 kDa, contains a single HEXXH zinc-binding domain, and shows considerable homology to human ACE (40% identity and 61% similarity). However, it differs greatly in substrate specificity and its activity is not inhibited by classical → ACE inhibitors, but by EDTA. It has

been reported that ACE 2 belongs to several enzymes that catalyze the degradation of angiotensin I (AT I, → angiotensins) to angiotensin 1-9 [AT I(1-9)] and angiotensin II to angiotensin 1-7 [AT I(1-7)], respectively. ACE 2 functions as a carboxypeptidase. It has been suggested that ACE 2 and the proteolysis product AT I(1-7) play an important role in the renin-angiotensin system, setting the balance of pressor/depressor tone, and have both cardioprotective and renoprotective potential. ACE 2 functions as a novel target for gene therapy for hypertensive disorders [S. R. Tipnis et al., *J. Biol. Chem.* **2000**, *275*, 33238; M. Donoghue et al., *Circ. Res.* **2000**, *87*, 1; M. A. Crackower et al., *Nature* **2002**, *417*, 822; J. L. Guy et al., *Biochemistry* **2003**, *42*, 13185; M. J. Katovich et al., *Exp. Physiol.* **2005**, *90*, 299; L. S. Zisman, *Eur. Heart J.* **2005**, *26*, 322; C. M. Ferrario, *Hypertension* **2006**, *47*, 515; K. M. Elased et al., *Hypertension* **2006**, *47*, 1010].

Angiotensinogen, → angiotensins.

Angiotensins (AT), *angiotonins*, *hypertensins*, tissue peptide hormones occurring both in the periphery and in the brain, with influence on blood pressure. The source of the AT is *angiotensinogen*, a plasma protein ($M_r \sim 60$ kDa) of the α_2 -globulin fraction which is initially cleaved by the kidney aspartyl protease → renin, yielding the inactive 10-peptide *angiotensin I*, AT I, H-Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu¹⁰-OH. *Angiotensin II*, AT II, H-Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-OH, is formed by proteolytic cleavage of AT I catalyzed by → angiotensin-converting enzyme (ACE). Angiotensin was initially described as a peripheral hormone that mediates the effects of the classical renin-angiotensin system (RAS). Circulating AT II induces vasoconstriction, aldosterone release, sodium and water retention, increases fluid intake, and plays a key role

in the regulation of blood pressure and fluid homeostasis. Two AT II receptors, AT₁ and AT₂, with similar binding affinity for AT II, are known that belong to the superfamily of seven membrane-spanning G protein-coupled receptors. The AT II effects, including vasoconstriction, increased aldosterone secretion and sympathetic tone and cardiac and vascular hypertrophy, are predominantly mediated via the AT₁ receptor. However, the functions of the AT₂ receptor have not been clearly characterized. AT II is formed in many tissues, including most peripheral organs and the brain. It has been reported that local AT II systems are regulated independently from the classical RAS. The effects of both circulating and locally formed AT II seems to be more complex and widespread than initially envisioned. Although, in the brain all components of RAS (e.g., angiotensinogen, renin, ACE and AT II) are present, it has been suggested that the brain may possess alternative enzymatic mechanisms for the formation of AT II distinct from those occurring in the classical RAS. One-fifth of the adult population suffers from chronic hypertension. The application of AT II inhibition either by → ACE inhibitors or by AT₁ receptor blockade with specific non-peptidic antagonists for treatment of hypertension, ischemic heart disease, and heart failure, was started during the early 1970s and remains important to the present day. AT II is inactivated in the blood by angiotensinase. On the basis of structure–activity relationship studies it could be established that, according to modifications of AT II in positions 8 (type I) and 4 (type II), two classes of antagonists can be synthesized. Type I antagonists show protracted effects on smooth muscle tissue, whereas type II antagonists are competitive antagonists at AT II receptors. Furthermore, cyclic analogues of AT II

characterized by their conformational constraint show high activity and selectivity. There are no significant differences in the central effects of AT II and its linear analogues, but cyclic analogues produce sedation or neuroleptic-like activity. *Angiotensin III*, AT III, H-Arg-Val-Tyr-Ile-His-Pro-Phe-OH, is formed by cleavage of the N-terminal Asp of AT II under the catalysis of aminopeptidase A. *Angiotensin IV*, AT IV, H-Val-Tyr-Ile-His-Pro-Phe-OH, results from the cleavage of AT III with aminopeptidase N. AT III acts as a central regulator of → vasopressin release and blood pressure. It has been reported that → angiotensin-converting enzyme 2, acting as a carboxypeptidase, catalyzes the formation of both AT I(1-9) and AT II(1-7). The latter is involved in the activation of peripheral vasodilator mechanisms, and shows antitrophic effects mediated by the inhibition of protein synthesis. Furthermore, AT II(1-7) amplifies the vasodilator actions of → bradykinin, and it has been suggested that it reduces the release of norepinephrine acting via a bradykinin/nitric oxide-mediated mechanism [I. H. Page, *Hypertension Mechanisms*, Grune & Stratton, New York, 1987, 1102; K. Sasaki et al., *Nature* 1991, 351, 230; J. M. Saavedra, *Endocr. Rev.* 1992, 13, 329; R. L. Davisson et al., *Circ. Res.* 1998, 83, 1047; Z. Lenkei et al., *Front. Neuroendocrinol.* 1997, 18, 383; A. Reaux et al., *Trends Endocrinol. Metab.* 2001, 12, 157; H. Gavras, H. R. Brunner, *Hypertension* 2001, 37 (part 2), 342; J. M. Saavedra, *Cell. Mol. Neurobiol.* 2005, 25, 485; C. M. Ferrario, *Hypertension* 2006, 47, 515].

Angiotonin, → angiotensins.

Anhydrides, species that readily react with a huge number of nucleophiles. Basic considerations towards the application of anhydrides in peptide synthesis date back

to the early investigations of Theodor → Curtius in 1881. In the course of hippuric acid synthesis from benzoyl chloride and silver glycinate, Curtius had carried out the first peptide bond formation of all. About 70 years later, Theodor Wieland made the → mixed anhydride method available for peptide synthesis. Besides this method, → symmetrical anhydrides and → N-carboxy anhydrides are used in peptide coupling.

Anorectin, → somatoliberin.

Anorexigenic peptide, <Glu-His-Gly-OH, a central appetite-inhibiting peptide isolated from the urine of women suffering from anorexia nervosa.

ANP, atrial natriuretic peptide.

Ans, anthracene-9-sulfonyl.

Anserine, β-alanyl-L-1-methylhistidine, a naturally occurring analogue of → carnosine exhibiting numerous biological activities, e.g., pH buffering, complexation of zinc, cobalt and ferrous ions, scavenging of free radical species [E. C. Bate-Smith, *J. Phys.* 1938, 92, 336; E. J. Baran, *Biochemistry (Moscow)* 2000, 65, 789; A. Guiotto et al., *Curr. Medicinal Chem.* 2005, 12, 2293].

Antagonist, an analogue of a biological active peptide that acts as competitive inhibitor. It occupies the appropriate receptor and displaces the → agonist from the receptor, but does not transmit the biological signal.

Antamanide (AA), “anti-amanita peptide”, cyclo(-Val-Pro-Pro-Ala-Phe-Phe-Pro-Phe-Phe¹⁰-), a non-toxic cyclic 10-peptide from *Amanita phalloides*. Antamanide was isolated from the lipophilic part of extracts of *A. phalloides* by chromatographic procedures, structurally characterized, and synthesized by Th. Wieland and co-workers in 1968. Administration at

0.5 mg kg⁻¹ causes full protection of mice from death by phalloidin (→ phallotoxins) after injection about 1 h before or, at the latest, simultaneously with 5 mg kg⁻¹ of the toxin. Antamanide is a competitive inhibitor of the transport system for phallotoxins and amatoxins in the parenchyma cells of the liver [Th. Wieland, *Peptides of Poisonous Amanita Mushrooms*, Springer Series in Molecular Biology, Springer Verlag, Berlin, New York, 1986; K. Münster et al., *Biochem. Biophys. Acta* 1986, 860, 91].

Antho-Kamide, L-3-phenyllactyl-Phe-Lys-Ala-NH₂, a neuropeptide isolated from the simple sea anemone *Anthopleura elegantissima* [K. Morihara, H. Tsuzuki, *Arch. Biochem. Biophys.* 1971, 146, 291].

Anthopleurin A, GVSCLCSDSG¹⁰PSVRGNTLSG²⁰TLWLYPSGCP³⁰SGWHNCKAHG⁴⁰PTIGWCKQ, a 49-peptide containing three disulfide bridges isolated from the sea anemone species *Anthopleura*. Anthopleurin-A causes, in nanomolar concentration, a positive ionotropic effect. This peptide is a member of the → β-defensin-fold family [M. W. Pennington et al., *Int. J. Pept. Protein Res.* 1994, 43, 463; P. K. Pallaghy et al., *Biochemistry* 1995, 34, 3782; A. M. Torres et al., *Toxicon* 2004, 44, 581].

Antho-Rlamide I, L-3-phenyllactyl-Tyr-Arg-Ile-NH₂, a neuropeptide isolated from the sea anemone species *Anthopleura elegantissima* [C. J. P. Grimmelikhuijzen et al., *Proc. Natl. Acad. Sci. USA* 1990, 87, 5410].

Antibodies, proteins (→ immunoglobulins) produced by B lymphocytes or B cells responsible for humoral immunity. An enormously diverse collection of related proteins mediates humoral immunity that is most effective against bacterial infections and the extracellular phases of viral infec-

tions [J. Kuby, *Immunology* 2nd edn., Freeman, 1994].

Antibody-catalyzed synthesis, → abzyme-catalyzed synthesis.

Anticancer peptides, peptides displaying antitumor activity on the basis of different modes of action. They may be derived from sites of protein interaction, phosphorylation, or cleavage and, e.g., interfere with apoptotic pathways. Peptide-based approaches are reported to target, e.g., MDM2, p53, NF-κB, ErbB2, MAPK, Smac/DIABLO, IAP BIR domains, and Bcl-2 interaction domains. Proteasome inhibitors, → integrin binding → RGD peptides (cilengitide), cationic amphipathic peptides, → somatostatin analogues such as octreotide, → gastrin-releasing peptide antagonists, → gonadotropin-releasing hormone agonists, → histone deacetylase (HDAC) inhibitors, → atrial natriuretic peptides, DNA-binding peptides (→ actinomycins), antimetabolic peptides (→ cryptophycins, → dolastatins, phomopsin A), and Ras farnesyl transferase inhibitors form therapeutically important classes. Marine peptides such as → didemnins, → kahalalides, → hemiasterlin, → dolastatins, cemadotin, soblidotin, and aplidine have also been clinically tested. In addition, peptide conjugates with antimetabolic agents or radioactive isotopes for tumor-selective delivery must be mentioned [Y. L. Janin, *Amino Acids* 2003, 25, 1].

Antifreeze proteins (AFPs), and *antifreeze glycoproteins (AFGPs)*, synthesized from teleost fish that encounter extreme cold seawater conditions for protection against freezing. All fish AFPs lower the solution freezing point through a non-colligative mechanism. Antifreeze proteins bind to particular surfaces of ice crystals, thereby modifying the crystal structure

followed by inhibition of further ice growth. Thermal hysteresis is used as a measure of antifreeze activity. AFPs are divided into four distinct classes: types I to IV. The different classes of AFPs are synthesized by various taxonomic groups. For example, type I AFPs are characterized by a high alanine content (>60 mol.%) and an amphipathic α -helical secondary structure. They occur in sculpins, right-eye flounders, and snailfish. Usually, the type I AFPs are synthesized in the liver for transfer into blood, providing extracellular freeze protection. Furthermore, a novel subclass of type I AFPs, designated skin-type AFPs, have been found in the skin of winter flounder, shorthorn, and longhorn; these AFPs are encoded by a separate subset of genes from liver-expressed proteins [K. V. Ewart et al., *Cell. Mol. Life Sci.* **1999**, 55, 271; G. L. Fletcher et al., *Annu. Rev. Physiol.* **2001**, 63, 359; R. P. Evans, G. L. Fletcher, *J. Mol. Evol.* **2005**, 61, 417].

Antigens, foreign macromolecules, predominantly proteins, carbohydrates and nucleic acids, that trigger the immune response, usually performed by production of defense proteins, known as \rightarrow antibodies [J. Kuby, *Immunology* (2nd edn.), Freeman, **1994**].

Antihemophilic factor, Factor VIII, a protein ($M_r \sim 265$ kDa) acting as component of the blood clotting cascade in humans. Activated Factor VIII_a acts as an accessory factor during the activation of Factor X (\rightarrow Stuart factor) by activated Christmas factor IX_a. Factor VIII forms a complex with the Willebrandt factor during circulation in blood [T. Halkier, *Mechanisms in Blood Coagulation, Fibrinolysis and the Complement System*, Cambridge University Press, **1991**].

Antimicrobial peptides (AMP), *host defense peptides*, **HDP**, small (<50 aa), cationic (mostly due to the presence of two to nine positively charged Arg and Lys residues), amphiphilic peptides containing up to 50% hydrophobic amino acids with microbicidal activity against both bacteria and fungi. AMP play an important role in protection from invading microorganisms. They have been isolated from all the phyla investigated, such as plants, invertebrates, vertebrates, and humans, including microbes themselves. In amphibians, AMP are usually secreted by the dermal glands located in the outer layer of the skin. In mammals, including humans, AMP are located in the granules of neutrophils and in epithelial cells throughout the body. AMP are an essential part of the innate immunity that has evolved in most living organisms over 2.6 billion years to combat microbial challenge. It has been suggested that AMP are effective adjuvants, synergistic with other immune effectors, polarizing the adaptive response, and support wound healing. The antimicrobial peptides show potent antimicrobial activity against Gram-positive and Gram-negative bacteria, fungi, parasites, and some enveloped viruses. Cationic AMP interact with the negatively charged bacterial phospholipids and permeate the membrane via the formation of transmembrane pores. Furthermore, it has been verified that AMP can also use the passive transport system to enter bacteria, from where they are capable of disrupting multiple cellular processes within the bacteria. However, the vast majority of the cationic peptides appear to act by permeabilization of the bacterial cell membrane. Despite the fact that AMP are considered as endogenous antibiotics, several additional features have recently become clear. Some AMP are chemotactic for leukocytes, or are involved in the

regulation of cell proliferation, angiogenesis, wound healing, epithelialization, or adaptive immunity. AMP are being considered as potential alternatives to current antibacterial agents, especially with the emerging problem of drug-resistant pathogenic bacteria. Therefore, they are promising candidates for drug development. Up until 2006, approximately 900 AMP have been isolated; details may be found in a periodically updated data base on the Internet, for example, at <http://www.bbcm.units.it/~tossi/pag1.htm>. AMP can be divided into classes based on the mechanism of their biosynthesis: non-ribosomally synthesized and ribosomally synthesized peptides. According to their secondary structure, eukaryotic AMP usually can be grouped into four main classes: (i) linear peptides with an α -helix structure, which do not contain Cys residues; the \rightarrow cecropins (insects, pigs), \rightarrow magainins (frogs), LL-37, a human cathelicidin-derived antimicrobial peptide, and CAP18 (rabbits) are members of the first group. (ii) β -Sheets stabilized by disulfide bridges; representatives of the second group are the \rightarrow defensins, divided into α -defensins (humans, rats, guinea pigs, rabbits), β -defensins (humans, cattle, mice), θ -defensins and insect defensins, as well as \rightarrow protegrins (pigs), \rightarrow tachyplesins (crabs), and insect defensins. (iii) Extended structure with a predominance of certain amino acid residues, especially Pro, Arg, Trp; examples of the group are \rightarrow drosocin (insects), \rightarrow batenecin-5 (cattle, sheep, goats), \rightarrow indolicidin (cattle), and \rightarrow PR-39 (pigs). (iv) Loop structures with an intramolecular disulfide bridge, represented by \rightarrow brevinins (frogs), esculentin (frogs), and \rightarrow batenecin (cattle). AMP that may belong to either all or none of these four groups include the family of host-defense-related ribonucleases, angiogenin 4, and

the cryptidin-related sequence (CRS) peptides. The \rightarrow cathelicidins, originally identified in myeloid cells, comprise a protein family with members in all of the four groups [T. Ganz, R. Lehrer, *Curr. Opin. Immunol.* **1998**, *10*, 41; H. G. Boman, *Scand. J. Immunol.* **1998**, *48*, 15; A. Tossi et al., *Biopolymers* **2000**, *55*, 4; A.M. Cole, T. Ganz, *BioTechnology* **2000**, *29*, 822; M. Zasloff, *Nature* **2002**, *415*, 389; H. Ulvatne, *Am. J. Dermatol.* **2003**, *4*, 591; R. E. Hancock, D. R. Devine, *Mammalian Host Defence Peptides*, Cambridge University Press, Cambridge, UK, **2004**; C. Beisswenger, R. Bals, *Curr. Prot. Pept. Sci.* **2005**, *6*, 255; J. B. McPhee, R. E. W. Hancock, *J. Peptide Sci.* **2005**, *11*, 677; K. A. Brogden, *Nat. Rev. Microbiol.* **2005**, *3*, 238; K. L. Brown, R. E. W. Hancock, *Curr. Opin. Immunol.* **2006**, *18*, 24].

α_2 -Antiplasmin, \rightarrow α_2 -macroglobulin.

Antisense peptide, *complementary peptide*, a peptide sequence hypothetically deduced from the nucleotide sequence that is complementary to the nucleotide sequence coding for a naturally occurring peptide (*sense sequence*). It could be demonstrated that antisense peptide exerts biological responses through the interaction with the receptors for the sense peptides. Potential applications of antisense peptide lie in the area of biomedical research. For example, antisense peptide (or antibodies against it) may promote the purification of both endogenous ligands as well as receptors. Furthermore, the development of highly selective antisense peptides against tumor cell markers may aid in the diagnosis and therapeutic modalities of the appropriate state of the disease. The *in vivo* administration of antisense peptides may help in better modulation of biological responses caused by their endogenous sense counterparts. The concept of antisense peptides was suggested by Mekler in 1969, and three years later

independently proposed and tested by Jones using a synthetic peptide that was antisense to the C-terminal tetrapeptide of gastrin [L. B. Mekler, *Biophys. USSR (Engl. Trans.)* **1969**, *14*, 613; D. S. Jones, *J. Chem. Soc. Perkin Trans. I* **1972**, 1407; K. L. Bost, J. E. Blalock, *Methods Enzymol.* **1989**, *168*, 16; Y. Shai et al., *Biochemistry* **1989**, *28*, 8804; R. S. Root-Bernstein, D. D. Holsworth, *J. Theoret. Biol.* **1998**, *190*, 107].

Antistatin (ATS), an anticoagulant protein ($M_r \sim 15$ kDa) isolated from the salivary glands of the Mexican leech *Haementeria officinalis*. ATS has been reported to be a potent inhibitor of Factor X_a (\rightarrow Stuart factor). The C-terminal region ATS-(109-119) has been suggested to be an important determinant of inhibitory potency. Structure-activity relationship studies of fragment analogues have been described [S. S. Mao et al., *Thromb. Haemost.* **1993**, *69*, 1046; D. L. Danalev et al., *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4217].

Antithrombin III (AT3), a protein (432 aa, $M_r \sim 58$ kDa) acting as inhibitor of thrombin and all active proteases of the blood clotting system (\rightarrow serpins) except Factor VII_a by binding to them in 1:1 complex in similar manner as BPTI binds to trypsin. The presence of heparin enhances the inhibitory activity of antithrombin by several hundredfold. In antithrombin, Arg³⁹³ is the reactive center residue that provides a specific cleavage site for thrombin [T. Halkier, *Mechanisms in Blood Coagulation, Fibrinolysis and the Complement System*, Cambridge University Press, **1991**].

α_1 -Antitrypsin, a glycoprotein (394 aa, $M_r \sim 51$ kDa) acting as an effective inhibitor of \rightarrow trypsin, but its prime physiological function is as an inhibitor of the elastase released by leukocytes. It is the archetype of the serpin family. In α_1 -antitrypsin, Met³⁵⁸

functions as a reactive center residue, providing a cleavage site of choice for leukocyte elastase. Interestingly, in a pathological variant of α_1 -antitrypsin found in a child with a bleeding disorder, Met³⁵⁸ was substituted by an arginine, thus converting this protein from an inhibitor of elastase to a highly effective inhibitor of thrombin [H. Loebermann et al., *J. Mol. Biol.* **1984**, *177*, 531; W. Bode et al., *Protein Sci.* **1992**, *1*, 426; P. R. Elliott et al., *Nature Struct. Biol.* **1996**, *3*, 676].

Anxiety peptide, \rightarrow diazepam-binding inhibitor peptide.

Aoc, 1-azabicyclo[3.3.0]octane-2-carboxylic acid.

AOC, (S)-2-amino-8-oxo-(S)-9,10-epoxi-decanoic acid.

AOP, 7-azabenzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate.

Apa, 6-aminopenicillanic acid.

Apamin, CNCKAPETAL¹⁰CARRCQQHa (disulfide bonds: C¹-C¹¹/C³-C¹⁵), a 18-peptide amide of the bee venom (1-3% of the venom) causing neurotoxic effects. The two arginine residues are of essential importance for the biological activity. Similar to the \rightarrow mast cell-degranulating peptide, apamin blocks selectively Ca²⁺-dependent K⁺ channels in neurons; this results in serious disturbances of CNS function [R. C. Hider, *Endeavour, New Series* **1988**, *12*, 60; E. Moczydlowski et al., *J. Membr. Biol.* **1988**, 105].

Apelin, human apelin: LVQPRGSRNG¹⁰PGPWQGGRRK²⁰FRRQRPRLSH³⁰KGPMPF, a 36-peptide acting as the endogenous ligand of the orphan G protein-coupled receptor APJ (putative receptor protein related to the \rightarrow angiotensin II receptor AT₁). APJ consists of 377 aa and

seven transmembrane domains, the gene of which is localized on the long arm of chromosome 11. Angiotensin II does not bind APJ. Apelin and APJ mRNA are widely expressed in several human and rat tissues, and exhibit functional effects in both the CNS and periphery. A 77-aa preproprotein can be cleaved into a 55 aa fragment and then into shorter forms. Apelin-36 is the physiologically active form, although shorter C-terminal sequences also increase extracellular acidification rates and inhibit cAMP production in Chinese hamster ovary cells. Synthetic human [*p*Glu²⁴]-apelin-(24-36), corresponding to the C-terminal 13 residues with pGlu at the N-terminus, shows a much higher acidification rate than that of parental apelin. The primary structure of apelin was determined by cDNA cloning. The bovine peptide differs in only two residues from the human apelin. Apelin and its receptor have been discovered in heart, large or small conduit vessels, and endothelial cells. Apelin has been reported to be involved in the regulation of cardiovascular functions, fluid homeostasis, vessel formation and cell proliferation. Furthermore, it has been shown that apelin inhibits insulin secretion in mice. Recently, it has been reported that apelin is a newly identified adipokine up-regulated by insulin and obesity. However, despite some very interesting effects, and the demonstration that apelin circulates in plasma, the functions of apelin *in vivo* remains unknown [K. Tatemoto et al., *Biochem. Biophys. Res. Commun.* **1998**, *251*, 471; B. Masri et al., *Cell. Signal.* **2005**, *17*, 415; M. Sorhede Winzell et al., *Regul. Pept.* **2005**, *131*, 12; E. A. Ashley et al., *Cardiovasc. Res.* **2005**, *65*, 73].

Apidaecins, proline-rich short peptides from insects. These are highly bactericidal against Gram-negative organisms via

a mechanism that includes stereoselective elements but differs completely from any pore-forming activity. *Apidaecin Ia*, GNNR PVYIPQ¹⁰PRPPHPRIa, has been isolated from honeybee (*Apis mellifera*) [P. Casteels, P. Tempst, *Biochem. Biophys. Res. Commun.* **1994**, *199*, 339; M. Castle et al., *J. Biol. Chem.* **1999**, *46*, 32555].

Apm, 2-aminopimelinic acid.

Apolipoprotein, → lipoproteins.

Apopeptide, a word derived from the noun peptide that means the free peptide component of a bioactive peptide missing a cofactor complex, the cofactor having been removed (Greek *apo-*, away from) [J. H. Jones, Editorial, *J. Peptide Sci.* **2006**, *12*, 79].

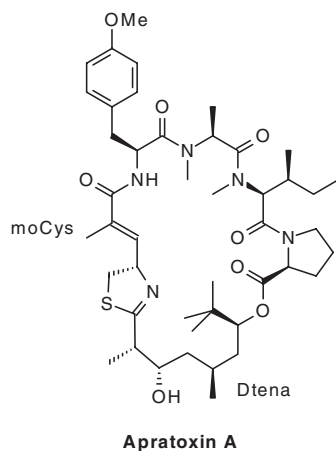
Apoptotic protease-activating factor 1 (Apaf-1), a protein controlling → caspase activation during apoptosis. Apaf-1 consists of an N-terminal caspase recruitment domain (CARD), a central nucleotide-binding oligomerization domain (NOD), and multiple WD40 repeats at the C-terminal half. The WD40 repeats have been reported to be responsible for cytochrome c binding and fulfill a regulatory role on Apaf-1 function. Apaf-1 occurs in cells in an inactive conformation and requires ATP/dATP for activation. It binds to cytochrome c and, in the presence of ATP/dATP, forms a apoptosome that leads to the recruitment and activation of the initiator caspase, caspase-9. The hydrolysis of ATP/dATP causes conformational changes which are essential for the formation of the apoptosome and the activation of caspase-9. The fine mechanism of Apaf-1 function remains to be investigated. The 2.2 Å crystal structure of ADP-bound, WD40-deleted Apaf-1, were described in 2005 [P. Li et al., *Cell* **1997**, *91*, 479; S. J. Riedl, Y. Shi, *Nature Rev. Mol. Cell*

Apratoxin A

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Biol. **2004**, *5*, 897; S. J. Riedl et al., *Nature* **2005**, *434*, 926].

Apratoxin A, a 25-membered cyclodepsipeptide (\rightarrow depsipeptides) isolated from the marine cyanobacterium *Lyngbya majuscula*, and exhibiting potent cytotoxic activity. Apratoxin A consists of a proline, three methylated amino acids (*N*-methylisoleucine, *N*-methylalanine, *O*-methyltyrosine), an α,β -unsaturated modified cysteine residue (moCys) and a dihydroxylated fatty acid moiety, 3,7-dihydroxy-2,5,8,8-tetramethylnonanoic acid (Dtena) [H. Luesch et al., *J. Am. Chem. Soc.* **2001**, *123*, 5418; H. Luesch et al., *J. Bioorg. Med. Chem.* **2002**, *10*, 1973; J. Chen, C. J. Forsyth, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 12067; T. Doi et al., *Org. Lett.* **2006**, *8*, 531; D. Ma et al., *Chem. Eur. J.* **2006**, *12*, 7615].



Aprotinin, *bovine pancreatic trypsin inhibitor* (Kunitz), BPTI, a bovine protein consisting of 58 aa residues and three disulfide bridges ($M_r \sim 6512$ kDa). Aprotinin belongs to the serpins, and acts as inhibitor for serine proteases, but not for \rightarrow thrombin and Factor X_a . In the past, aprotinin was used for the treatment of acute pancreatitis, but today this is no longer valid.

By inhibiting fibrinolysis and preserving platelet function, aprotinin has been shown to reduce blood loss and transfusion requirements in cardiac surgery, lung, and liver transplantations, and surgery for hip replacement. Additional indications are hyperfibrinolytic hemostatic disorders and complications of thrombolytic therapies. In Europe, aprotinin has been in clinical use for about 40 years, but in the United States it has been approved for intravenous applications only since 1993 [M. Kunitz, J. H. Northrop, *J. Gen. Physiol.* **1936**, *19*, 991; H. Fritz, G. Wunderer, *Arzneim. Forsch./Drug Res.* **1983**, *33*, 479; W. Gebhard et al., in: *Proteinase Inhibitors*, A. Barret, G. Salvesen (Eds.), p. 375, Elsevier, Amsterdam, **1986**; W. Beierlein et al., *Ann. Thorac. Surg.* **2005**, *79*, 741].

AQP, aquaporin.

Aquaporins (AQP), members of the major intrinsic protein (MIP) superfamily of integral membrane proteins, which are found throughout Nature. AQP facilitate water transport in various eukaryotes and prokaryotes. The archetypal aquaporin, *AQP1* ($M_r \sim 28$ kDa), also known as CHIP, channel-forming integral membrane protein of 28 kDa, forms a partly glycosylated water-selective channel that is widely expressed in the plasma membranes of various water-permeable epithelial and endothelial cells. The three-dimensional structure (7 Å resolution) of the deglycosylated human erythrocyte *AQP1* shows that the structure has an in-plane, intramolecular 2-fold axis of symmetry located in the hydrophobic core of the bilayer. The monomer is composed of six membrane-spanning, tilted α -helices forming a right-handed bundle surrounding a central density. From these results, a model is suggested that identifies the aqueous pore in the *AQP1* molecule and

indicates the organization of the tetrameric complex in the membrane. Five members of the mammalian aquaporins are described. AQP1 acts as an osmotically driven, water-selective pore, while AQP2 mediates vasopressin-dependent renal collecting duct water permeability. AQP3, located in the basolateral membrane of the collecting duct, forms an exit pathway for reabsorbed water. AQP4 is abundant in brain and seems to participate in the reabsorption of cerebrospinal fluid and osmoregulation, whereas AQP5 mediates fluid secretion in salivary and lacrimal glands [J. S. Jung et al., *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 13052; J. H. Park, M. H. Saier, *J. Membr. Biol.* **1996**, *153*, 171; T. Walz et al., *Nature* **1997**, *38*, 624; A. Cheng et al., *Nature* **1997**, *38*, 627].

Ar, aryl.

Arenastatin A, *cryptophycin-24*, a 16-membered cyclodepsipeptide (\rightarrow dep-sipeptides) isolated from the Okinawan marine sponge *Dysidea arenaria* with structural similarity to \rightarrow cryptophycins and identical with cryptophycin-24. Arenastatin A inhibits microtubule assembly *in vitro*. It binds to tubulin at the rhizoxin/maytansine binding site. The total synthesis was described in 2000 [M. Kobayashi et al., *Chem. Pharm. Bull.* **1994**, *42*, 2196; M. J. Eggen et al., *Org. Chem.* **2000**, *65*, 7792].

Arene sulfonyl-type protecting groups, Ar-SO₂-NH-R, sulfonamide-based protecting groups used preferentially for reversible blocking of the guanidino side-chain of arginine, and also for the amino function. In the past, mainly the *toluene-4-sulfonyl* (*tosyl*, *Tos*) group has been used, though this suffers from the disadvantage that it is only cleavable with liquid HF or Na/NH₃. *o*- and *p*-nitro substituents in the phenyl moiety led to residues (oNbs,

pNbs, dNbs, Bts) cleavable by treatment with thiophenol or alkanethiols, and hence are orthogonal to *tert*.-butyl and 9-fluorenylmethyl-type protecting groups. For the guanidino protection, the arene sulfonyl moiety has been modified with respect to acid lability by the introduction of electron-donating substituents on the aryl residue. 4-Methoxybenzenesulfonyl (Mbs), 2,4,6-trimethylbenzenesulfonyl (Mts), 4-methoxy-2,3,6-trimethylbenzenesulfonyl (Mtr), 2,2,5,7,8-pentamethylchroman-6-sulfonyl (Pmc) and 2,2,4,6,7-pentamethyl-dihydrobenzofuran-5-sulfonyl (Pbf) have become very popular in SPPS. Acid lability increases in the series Tos < Mbs < Mts < Mtr < Pmc < Pbf, with Pbf displaying the best deprotection kinetics. The 9-anthracenesulfonyl (Ans) is cleavable by mild reducing agents.

Arenesulfonamide linker, \rightarrow safety-catch linker.

Arg, arginine.

Arginine (Arg, R), α -amino- δ -guanidino-valeric acid, C₆H₁₄N₄O₂, M_r 174.2 Da, the most basic of the proteinogenic amino acids.

Argitoxin-636, a polyamine amide spider toxin. This is a glutamate receptor antagonist with potential as a neuroprotective agent. The toxin paralyzes insects by blocking the neuromuscular transmission mediated via glutamate receptors. The total synthesis by a practical reductive alkylation strategy was described [I. S. Blagbrough, E. Moya, *Tetrahedron Lett.* **1995**, *36*, 9393].

Arrestins, a family of intracellular proteins playing an important role in quenching signal transduction initiated by G protein-coupled receptors (GPCRs). Members of this family are *visual arrestin*, β -*arrestin 1*, and β -*arrestin 2*. All of

these arrestins desensitize GPCRs, while β -arrestin 1 and β -arrestin 2 additionally target desensitized receptors to clathrin-coated pits for endocytosis. Visual arrestin, first named retinal S antigen, is a 48-kDa protein. The 2.8 Å crystal structure shows a bipartite molecule with an unusual polar core. Furthermore, arrestin is described as being a dimer of two asymmetric molecules. In the photoreceptor cell, the activation of rhodopsin by a photon initiates signal transduction and signal termination. Arrestin binds selectively to the light-activated rhodopsin in its phosphorylated form, thereby shutting down the phototransduction cascade by blocking transducing activation [T. Shinohara et al., *Proc. Natl. Acad. Sci. USA* **1987**, *84*, 6975; J. A. Hirsch et al., *Cell* **1999**, *97*, 257; R. H. Oakley et al., *J. Biol. Chem.* **2000**, *275*, 17201; V. V. Gurevich, J. L. Benovic, *Methods Enzymol.* **2000**, *315*, 422; M. Han et al., *Structure* **2001**, *9*, 869].

Aschheim-Zondek reaction, \rightarrow chorionic gonadotropin.

Asn, asparagine.

Asp, aspartic acid.

Asparagine (Asn, N), β -semiamide of aspartic acid, $\text{H}_2\text{N-CO-CH}_2\text{-CH(NH}_2\text{)-COOH}$, $\text{C}_4\text{H}_8\text{N}_2\text{O}_3$, M_r 132.12, a non-polar protenogenic amino acid.

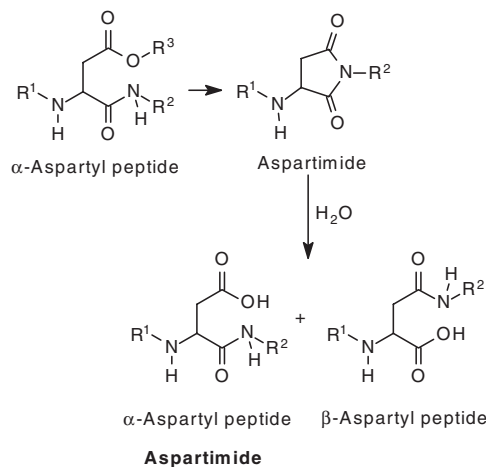
Aspartame (APM), H-Asp-Phe-OMe, a non-nutritive high-intensity sweetener. APM is about 200 times sweeter than sucrose. It was first approved by the FDA in 1981 as a table-top sweetener and an additive, for example, in dry-based beverages, dry cereals, chewing gum, gelatins, puddings, instant coffee, and tea. APM was discovered accidentally during the recrystallization of an intermediate of the synthesis of the C-terminal tetrapeptide of \rightarrow gastrin at Searle & Co. For commercial synthesis, various

methods have been developed including thermolysin-catalyzed synthesis [Y. Isowa et al., *Tetrahedron Lett.* **1979**, *28*, 2611; K. Oyama et al., *J. Org. Chem.* **1981**, *46*, 5242].

Aspartic acid (Asp, D), α -aminosuccinic acid, $\text{HOOC-CH}_2\text{-CH(NH}_2\text{)-COOH}$, $\text{C}_4\text{H}_7\text{NO}_4$, M_r 133.10, an acidic proteinogenic amino acid.

Aspartic peptidases, *aspartic proteases*, *aspartic proteinases*, \rightarrow peptidases catalyzing the hydrolysis of peptide bonds without the use of nucleophilic attack by a functional group of the enzyme. The nucleophile attacking the scissile peptide bond is, in this case, an activated water molecule, and no covalent intermediate will be formed between the enzyme and a fragment of the substrate. The name of this group of peptidases is based on the catalytic apparatus which consists of two aspartic acid side chains (Asp³² and Asp²¹⁵ of the porcine pepsin numbering system) activating directly the water molecule. These two side-chain carboxyl groups are close enough to share a hydrogen bond between two of their oxygens, holding the water in place. However, not all members of aspartic peptidases include two Asp residues in the catalytic dyad. An endopeptidase from nodavirus has an Asp and an Asn as catalytic residues, whilst in a related tetra virus endopeptidase the Asp residue is replaced by Glu. It is interesting to note that all the enzymes so far described are endopeptidases. Members of aspartic peptidases are, for example, pepsin, cathepsin, and \rightarrow renin [V. Kostka (Ed.), *Aspartic Proteinases and their Inhibitors*, de Gruyter, Berlin, **1985**].

Aspartimide, cyclization product of asparagine in a peptide chain involving the β -carboxamide group with release of ammonia. The aspartimide derivative may subsequently undergo hydrolysis to give a mixture of α -aspartyl and β -aspartyl



peptides. The side reaction can be suppressed by reversible blocking of the side-chain carboxamide group. An aspartimide derivative can also be formed from an Asp side-chain ester by nucleophilic attack of the nitrogen atom of the amino acid located C-terminally with respect to the Asp residue in the peptide chain. Aspartimide formation appears to be sequence-dependent, and leads to β -aspartyl moieties and deamidation of L-asparagine. It occurs in peptides and proteins at alkaline, neutral and acidic pH, both *in vitro* and *in vivo* [S. Capasso, P. Di Cerbo, *J. Peptide Res.* **2000**, 56, 382; R. Dölling et al., *J. Chem. Soc. Chem. Commun.* **1994**, 853; P. Stathopoulos et al., *J. Peptide Sci.* **2005**, 11, 658].

β -Aspartylpeptides, aspartic acid-containing peptides in which the β -carboxyl group is a constituent of the peptide bond. The unwanted formation of β -aspartylpeptides occurs by nucleophilic ring opening of \rightarrow aspartimide [M. Bodanszky et al., *Int. J. Pept. Protein Res.* **1978**, 12, 57].

Asperlicin, isolated from *Aspergillus alliaceus* acting as a competitive antagonist

both of CCK-33 (\rightarrow cholecystokinin) in rat pancreatic tissue, and it inhibits CCK-8 induced guinea pig gallbladder contractions [R. S. L. Chang et al., *Science* **1985**, 230, 177].

Asu, α -aminosuberic acid.

At, azabenzotriazolyl.

AT, angiotensin.

Ataxin-7, the *SCA7* gene product consisting of 897 aa with an expandable polyglutamine tract close to the N-terminus. Spinocerebellar ataxia type 7 (SCA7) is a member of a family of neurodegenerative diseases characterized by a CAG DNA triplet repeat expansion leading to polyglutamine expansion in the gene product. The mutant ataxin-7 protein may contain polyglutamine repeats from 38 to 300 residues in length. Further members of this polyglutamine expansion disease family are, e.g., Huntington's disease and spinobulbar muscle atrophy. Although the precise biological function of ataxin-7 is unknown beside other described actions, it appears to be a transcription factor and a component of the STAGA transcription coactivator complex. Furthermore, ataxin-7 has

the capability to export from the nucleus via a conserved exportin-dependent signal [J. Taylor et al., *J. Biol. Chem.* **2006**, *281*, 2730].

Atosiban, *Tractocile*[®] (Europe), Mpa-D-Tyr(Et)-Ile-Thr-Asn-Cys-Pro-Orn-Gly-NH₂ (disulfide bond: Mpa¹-Cys⁶), an → oxytocin (OT) antagonist that is produced by large-scale, solution-phase synthesis with an future annual production scale in the range of 50–100 kg. It is used to treat preterm labor and delivery. However, the combined → vasopressin V_{1a} and OT receptor antagonist atosiban is not an ideal OT antagonist, as it is highly non-selective for OT receptors versus VP V_{1a} receptors. For example, in human receptor binding assays, atosiban exhibits 15-fold greater affinity for the V_{1a} receptor than for the OT uterine receptor [P. Melin et al., *J. Endocrinol.* **1986**, *111*, 125; C. Johansson et al., *Peptides* **1994**, *H. L. S. Maia* (Ed.), Escom, Leiden, **1995**, 34; P. Melin, *Baillieres Clin. Obstet. Gynaecol.* **1993**, *7*, 577; M. Manning et al., *J. Peptide Sci.* **2005**, *11*, 593].

ATP, adenosine triphosphate.

Atrial natriuretic peptide (ANP), *atrial natriuretic factor*, *ANF*, *atriopeptide*, *atriopeptin*, *cardionatrin I*, SLRRSSCFGG¹⁰RMDRIGAQSG²⁰LGCNSFRY (disulfide bridge: C⁷–C²³), a 28-peptide hormone isolated from the atrium of the mammalian heart. It belongs to the family of → natriuretic peptides. ANP is a potent hypotensive and natriuretic agent. It is synthesized as prepro-ANP (human: 151 aa), and stored as 126-polypeptide pro-ANP (also termed: atriopetigen, cardionatrin IV) in specific granules of atrial cardiocytes. The latter is secreted from the atria and then processed proteolytically by corin, a type II transmembrane serine protease, to the hu-

man circulating 28-peptide ANP, and the N-terminal pro-AFP-(1-98). The latter contains three peptide hormones: *long-acting natriuretic peptide*, LANP, AFP-(1-30); *vessel dilator*, AFP-(31-67); and *kaliuretic peptide*, AFP-(79-98). The main known biological properties of these peptide hormones are blood pressure regulation and the maintenance of plasma volume in animals and humans. In the atria, the quantity of ANP is orders of magnitude higher than in extracardiac tissues such as CNS and kidney. Receptors (→ natriuretic peptides) have been found in blood vessels, kidney, and adrenal cortex. In the adrenal cortex, ANP mediates the decrease of aldosterone release, while in the kidney it increases glomerular filtration rate, renal blood flow, urine volume and sodium excretion [T. G. Flynn et al., *Biochem. Biophys. Res. Commun.* **1983**, *117*, 859; K. Kangawa et al., *Biochem. Biophys. Res. Commun.* **1984**, *118*, 131; K. Kangawa et al., *Nature* **1985**, *313*, 397; A. J. deBold, *Science* **1985**, *230*, 767; G. McDowell et al., *Eur. J. Clin. Invest.* **1995**, *25*, 291; M. Forero McGrath et al., *Trends Endocrinol. Metab.* **2005**, *16*, 469; D. L. Vesely, *Clin. Exp. Pharmacol. Physiol.* **2006**, *33*, 169].

Atriopeptide, → atrial natriuretic peptide.

Atriopeptin, → atrial natriuretic peptide.

Aurelin, AACSDRAHGH¹⁰ICESFKSFCK²⁰DSGRNGVKLR³⁰ANCKKTCGLC⁴⁰, an antimicrobial 40-peptide (M_r 4297 Da) isolated from the mesoglea of the scyphoid jellyfish *Aurelia aurita*. The six cysteines form three disulfide bonds. Aurelin is synthesized as a 84 aa prepro-aurelin containing a 22 aa signal peptide and a propeptide segment of the same size. Aurelin exhibits activity against Gram-positive and Gram-negative bacteria. It shows structural features of → defensins and channel-blocking

toxins [T. V. Ovchinnikova et al., *Biochem. Biophys. Res. Commun.* **2006**, *348*, 514].

Aureobasidins, a family of cyclodepsipeptides (\rightarrow depsipeptides) produced by *Aureobasidium pullulans* consisting of more than 20 members. *Aureobasidin A*, consists of eight lipophilic amino acid residues and one hydroxy acid in its 27-membered macrocycle. Aureobasidins A, B, C, S_{2b}, S₃, and S₄ have been shown to be potent, with MICs of 0.05 to 3.12 $\mu\text{g mL}^{-1}$ for *Candida* species and *C. neoformans* isolates. Aureobasidins are characterized by several desirable properties, including lethality for growing *C. albicans* with a low level of acute toxicity, and improved survival and sterilization of kidneys in a murine model. Aureobasidin A was one of the few peptides that had appreciable oral bioavailability [K. Takesako et al., *J. Antibiot.* **1991**, *44*, 919; K. Takesako et al., *J. Antibiot.* **1993**, *46*, 1414; T. Kurome et al., *J. Antibiot.* **1998**, *51*, 353].

Australian Peptide Association (APA), a non-profit scientific organization founded in 1992 providing a forum for advancing and promoting peptide research throughout Australia by way of support for annual local one-day meetings, as well as a biennial symposium. The first Australian Peptide Symposium was held in 1994, and has been held biennially since then. The 2007 symposium was held jointly with the 2nd Asia-Pacific and 4th International Peptide Symposia. The Association's website is <http://www.peptideoz.org>. Membership of the association is free to any interested people from anywhere in the world, upon registration at this site.

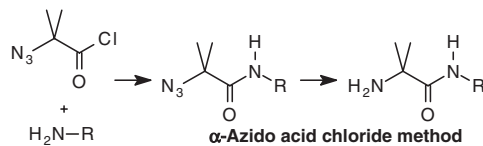
Avidin, a glycoprotein in the egg white of many birds and amphibians. Chicken avidin ($M_r \sim 66$ kDa) consists of four identical subunits (without carbohydrate: $M_r \sim 14$ kDa; 128 aa). Avidin binds four molecules of the vitamin biotin with high affinity (dis-

sociation constant, $K_d \sim 10^{-15}$ M). Each monomer is an eight-stranded antiparallel β -barrel, remarkably similar to that of the genetically distinct bacterial analogue \rightarrow streptavidin. The resulting complex is stable against proteolysis, and prevents its intestinal adsorption. Avidin inhibits the growth of microorganisms in egg whites. Together with biotin, avidin is used for the immobilization of ligands in immunoassays and in affinity chromatography [N. M. Green, *Methods Enzymol.* **1990**, *184*, 51; O. Livnah et al., *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 5076].

AVP, arginine vasopressin.

Azadepsipeptides, a new class of pseudo-peptides. Analogously to \rightarrow azapeptides, the α -carbon atom in \rightarrow depsipeptides is replaced isoelectronically by a trivalent nitrogen. Synthesis and structure evaluation have been demonstrated using a bis-aza analogue of the antiparasitic cyclooctadepsipeptide PF 1022A as a model [H. Dyker et al., *J. Org. Chem.* **2001**, *66*, 3760].

Azapeptides, $-\text{NH}-\text{CHR}^1-\text{CO}-\text{NH}-\text{NR}^2-\text{CO}-\text{NH}-\text{CHR}^3-\text{CO}-$, a class of backbone-modified peptides in which the α -CH of one or more amino acid residues in the peptide chain is isoelectronically replaced by a trivalent nitrogen atom. This alteration results in a loss of asymmetry associated with the α -CH, and yields a structure that can be considered intermediate in configuration between D- and L-amino acids. This α -carbon replacement is connected with the capability to provide resistance to enzymatic cleavage, and the capacity to act as selective inhibitor of serine and cysteine proteases [J. Gante, *Synthesis* **1989**, 405; J. Magrath et al., *J. Med. Chem.* **1992**, *35*, 4279; R. Xing et al., *J. Med. Chem.* **1998**, *41*, 1344; E. Wiczczak et al., *J. Med. Chem.* **2002**, *45*, 4202].



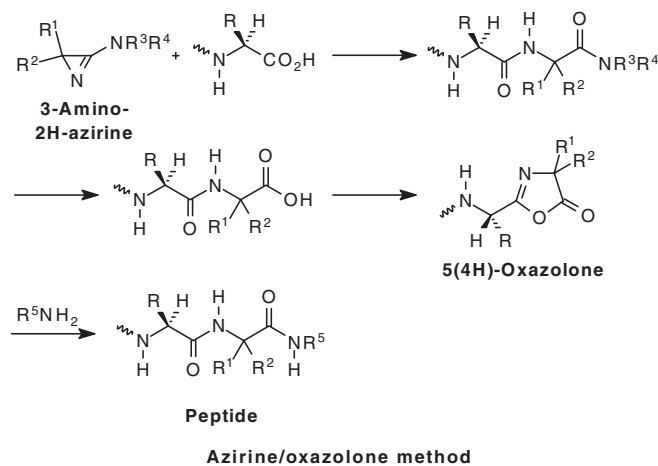
Azatides, $-\text{NH}-\text{NR}^1-\text{CO}-\text{NH}-\text{NR}^2-\text{CO}-\text{NH}-\text{NR}^3\text{CO}-$, biopolymer mimetics consisting of α -aza-amino acids (hydrazine carboxylates). In contrast to an \rightarrow azapeptide, an azatide is a so-called pure azapeptide. The earliest attempts to synthesize pure azatides using hydrazine units was described by Gante and coworkers in 1965, but stepwise chain lengthening of monomeric α -aza-amino acids in a repetitive manner, both as solution and liquid-phase approach, was performed in 1996 [J. Gante, *Chem. Ber.* **1965**, 98, 3340; J. Gante et al., *Proc. 13th American Peptide Symposium 1994*, 299; H. Han, K. D. Janda, *J. Am. Chem. Soc.* **1996**, 118, 2539].

Aze, azetidine-2-carboxylic acid.

Azide coupling, \rightarrow acyl azide method.

α -Azido acid chloride method, an approach especially useful for the incorporation of α,α -disubstituted amino acids into peptides. It employs α -azido acid chlorides as masked equivalents of activated N^α -protected amino acids; the azido group can easily be reduced to a free amine, even under SPPS conditions [M. Jost et al., *Angew. Chem. Int. Ed.* **2002**, 41, 4267].

Azirine/oxazolone method, a synthetic method for the introduction of sterically highly hindered α,α -disubstituted α -amino acids into peptides. The synthesis of, e.g., Aib-rich peptides requires either highly reactive coupling reagents (e.g., amino acid halides) or special derivatives (such as 3-amino-2H-azirines or α -azido carboxylic acid chlorides). The azirine/oxazolone method utilizes an amino component that



is formally activated by the ring strain. Upon reaction with a carboxy component, dipeptide amides are obtained that undergo acid-catalyzed cyclization with 5(4H)-oxazolone formation, followed by reaction with, for example, an amino acid ester to give, e.g., tripeptides with α,α -disubstituted amino acids in the middle position [H. Heimgartner, *Angew. Chem. Int. Ed.* **1991**, *30*, 238].

