CATHELICIDINS IN HUMANS AND ANIMALS

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Abstract: Cathelicidins are Important immunological peptides – HDPs (Host Defense Peptides) with high biological activity in mammals, including human and vertebrate animals. These evolutionary ancient molecules in these organisms are natural elements of antimicrobial, antiviral, antifungal and antiparasitic immunity against which germs and parasites have not developed immunity, which makes them alternatives to antibiotics. Cathelicidins in human and vertebrates affect the germs and parasites directly and indirectly by activating the immune system.

1. What are immune peptides.
2. Cathelicidins.
   2.1. Cathelicidins in humans.
   2.2. Cathelicidins in animals.
3. Summary

KATELICYDYNY U LUDZI I ZWIERZĄT

Streszczenie: Ważnymi peptydami odpornościowymi – HDP (Host Defence Peptides) o dużej aktywności biologicznej u ssaków, w tym człowieka i zwierząt kręgowych, są katelicydyny. Te stale ewolucyjnie cząsteczki efektorowe w tych organizmach, stanowią naturalne elementy odporności przeciwbakteryjnej, przeciwwirusowej, przeciwpowodzeniowej, wobec których zarazki i pasożyty nie wykształciły oporności, co powoduje, że stają się one substancjami alternatywnymi dla antybiotyków. Katelicydyny u ludzi i zwierząt kręgowych, oddziałują na zarazki i pasożyty bezpośrednio oraz poprzez aktywowanie układu odpornościowego.

1. Co to są peptydy odpornościowe.
2. Katelicydyny
   2.1. Katelicydyny u ludzi.
   2.2. Katelicydyny u zwierząt.
3. Podsumowanie

Key words: human, cathelicidins, animals
Słowa kluczowe: człowiek, katelicydyny, zwierzęta

1. What are immune peptides

Peptides of immunity – HDPs (Host Defense Peptides), form a complex of old, evolutionarily preserved effector molecules synthesized by the organisms of mammals (humans, animals – including marsupials and monotremes), birds, reptiles, amphibians, fish, insects and plants. Even microorganisms have not developed a defence mechanism against these substances along their evolutionary path, hence HDPs are often referred to as natural antibiotics [36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118]. Generally, HDPs began to elicit interest in 1980, when A and B cecropins were discovered [64, 94], although the research conducted in 1963 had already provided information on lysosomal cationic proteins with antimicrobial action [117]. In 1985, human α-defensins were described [84], and in 1987, magainins were found in frogs [116]. Currently, about 2 900 natural HDPs are known, which are characterized by a very diverse structure (7). An example of HDPs may be cathelicidins, containing from 12 to 80 amino acid residues and molecular weights ranging from 2 to 80 kDa. Moreover, due to the presence of arginine and lysine residues, HDPs have a positive charge, hence they are also referred to as cationic...
peptides [7, 18, 28, 36, 42, 56, 60, 64, 82, 96, 103, 108, 115]. When analysing the structure of HDPs and the presence of disulphide bridges as well as the number of amino acid residues, we can distinguish: 1) linear peptides, having an α-helical structure with no disulphide bonds, e.g. cathelicidin LL-37 in humans; 2) peptides with a β-sheet or hairpin structure, where there are three or more disulphide bridges, e.g. some α and β defensins in mammals; 3) peptides with a loop structure with one disulphide bridge, e.g. some cathelicidins in ruminants; 4) amino acid-rich peptides such as tryptophan – e.g. indolicidin in cattle, or rich in proline and arginine, e.g., cathelicidin PR-39 in pigs [56, 69, 118, 119]. The division of HDPs regarding the biological activity is also known. The division distinguishes: 1) peptides which impact bacterial structures, e.g. serprocidines; 2) peptides which bind elements, e.g. calprotectin; 3) peptides disrupting the bacterial membrane, e.g. cathelicidin [69]. Based on the size of the molecule and tertiary structure, we distinguish the so-called “Classic” HDPs peptides, which include cathelicidins and defensins [7]. Natural immune peptides (HDPs), have an amphipathic structure which allows them to interact with the membrane of pathogens in particular, which has a negative electric charge (–150 mV) while the presence of phospholipids in their membrane allows for their intense penetration, which causes change in their permeability and creation of pores in it [36, 42, 55, 56, 60, 64, 68, 82, 108, 118]. Research from recent years has shown that many HDPs appear abundantly in humans and animals, including farm animals. The skin and epithelial cells of the gastrointestinal tract and respiratory system are special locations (biotopes) of their occurrence [9, 11, 34, 36, 38, 45, 48, 58, 56, 63, 68, 69, 80, 87, 89, 118]. In these biotopes, mostly in the gastrointestinal tract, “classic” HDPs peptides in humans and vertebrate animals determine the correct homeostasis of these ecosystems, including their microbiome. Such state causes these peptides to affect the local immunity of these organisms (humans and vertebrate animals), it refers in particular to the intestines, where along with the defensins synthesized by Panetha, they form a strong anti-germ barrier [11, 12, 17, 28, 30, 38, 48, 49, 63, 68, 69, 75, 118].

2. Cathelicidins

Cathelicidins constitute the group of evolutionarily oldest proteins acting as precursor molecules, which release peptides after proteolysis. These peptides affect pathogens and parasites directly and indirectly by immunomodulating the immune system of mammals, also showing anti-cancer activity [2, 3, 15, 18, 28, 60, 64, 70, 89, 101, 107, 110, 118]. Their impact on bacteria and fungi is associated with disrupting of the cell membranes of these microorganisms [69, 108, 110], and in the case of viruses, they affect their casings and replication [2, 21, 50, 69, 115]. The first cathelicidins in mammals were isolated from bovine neutrophilia as a small cyclic dodecapeptide, whose name was formed from bacterium necare i.e. “bacteria killer” and was called bactenecin [48, 108, 118]. An analogous substance in pigs was called protegrin [48, 108, 110, 118]. In humans, the first described cathelicidin was the peptide hCAP (human Cathelicidin Antibacterial Peptide) or hCAP18 (human Cationic Antimicrobial Protein), which is now called cathelicidin LL-37 [28, 110]. Cathelicidins are produced as inactive pre-pro-peptides, consisting of 128–143 amino acid residues. They have a highly conserved N-terminal domain – which is a signal peptide, a cathelin domain with a molecular weight of 11 kDa and a C-terminal variable region, which is a “mature” peptide, which determines protranscriptional regulation of their synthesis and protects them against uncontrolled activity [28, 96, 108, 110]. The N-terminal part of the signal sequence alone has 29–30 amino acid residues, whose task is to release a biologically active peptide [28, 108, 110]. In contrast, the cathelin domain composed of 94–144 amino acid residues is responsible for protection against proteolysis [48], which was first described in porcine leukocytes [48, 78]. It was recorded that the cathelin domain is connected to a mature peptide C-terminal section consisting of 12–100 amino acid residues, which jointly constitute a pro-peptide. As a result of the activity of endogenous proteases such as protease 3, azurophil, or gastrixin, a fully mature peptide is released [96]. It has been shown that the sequences of the cathelin domain in various mammalian species, including humans, are very similar to each other, which may suggest that these peptides could have evolved as a result of duplication and modification of the common gene [28].

Cathelicidins have been found and described in humans and monkeys, as well as in domestic and farm animals – i.e. cattle, sheep, goats, pigs, horses, dogs, cats; laboratory animals – rabbits, rats, mice, guinea pigs; wild animals – i.e. deer, oxen of the Bovidae family, asses, pandas, marsupials and monotremes, as well as birds, fish, reptiles, amphibians and insects [6, 10, 19, 25, 46, 48, 52, 53, 56, 64, 69, 75, 86, 88, 96, 97, 99, 100, 102, 108, 111, 114, 116, 118, 119]. Only one cathelicidin has been described in humans, while animals are assumed to have more. According to many authors [10, 24, 48, 52, 56, 62, 75, 86, 88, 96, 106, 108, 112, 113], there exist 11 cathelicidins in pigs, 7–10 in sheep, 4–8 in cattle, 2–6 in fish, 4–5 in chickens, in goats 2–4, in monkeys, 3 in horses and rabbits, 2 in the platypus, with cats, dogs, mice, rats, guinea pigs, pandas and deer having 1 each. Two cathelicidins (HFIAP-1 and HFIAP-3) have also been shown to be present in primitive ani-
mals such as hagfish, in which the distribution of four cysteine residues is preserved in the cathelin domain, similarly as in mammals, birds and fish, although the cathelin domain in hagfish exhibits very low similarity to the cathelin domain in other animals [48, 99, 108, 111]. The best known cathelicidin in mammals is the cathelinidin in humans, which is different from those in immunity peptides in fish, amphibians and insects [96].

2.1. Cathelicidins in humans

These peptides in humans are represented by the cathelicidin LL-37, which is characterized by a linear structure with α-helix structure [2, 118]. It may exist in the form of a monomer, dimer or tetramer [74, 76], creating cationic, amphipathic structures composed of three parts [74, 76]. These are: the N-terminal and C-terminal part of the α-helix and the C-terminal region, where the α-helix at the N-terminus, participates in the oligomerization of the peptide and provides the molecule with resistance to proteases, since the C-terminal section is important for the formation of tetramers [101, 110]. Initially, cathelicidin LL-37 was called hCAP18, which referred to a peptide with size up to 18 kDa, which contained two disulphide bonds between the cysteine residue C85-C96 and C107-C124, produced by extracellular proteolysis of the C-terminal human CAP (Cationic Antimicrobial Protein) [110]. When the peptide was found to consist of 37 amino acids starting with two leucines, the name was changed from hCAP18 to LL-37. Currently, hCAP18 refers only to the prepeptide, whereas LL-37 alone denotes a mature peptide having pleiotropic properties upon release from the C-terminus of hCAP18. Human cathelicidin – the LL-37 peptide, is encoded by the CAMP gene (Cathelicidin Antimicrobial Peptide), which is found in the locus 21 of chromosome 3 (3p21.3) [110]. The LL-37 peptide is synthesized in the human body in response to bacterial, viral and fungal infections or is a result of neutrophil elastase, which does not activate its peptides accumulated in granular granulocytes, and breaks them down into active components secreted from these cells [97]. Human LL-37 peptide appears at a very early stage of development, because it has already been detected in new-borns in the skin and trachea [61, 81]. In adults, it undergoes expression, among others, in the gastrointestinal epithelium, including the epithelium of the oral cavity and intestines [28] and airways [11, 27, 28, 30, 32, 23, 34], as well as in keratinocytes [33, 66, 118]. It is also synthesized in neutrophils, monocytes-macrophages, NK cells, mast cells, dendritic cells and T and B lymphocytes, as well as conjunctival epithelial cells, urogenital and biliary tracts and in the liver, cervix, vagina, epidermidis, testicles and is also found in blood plasma, saliva, sweat, semen and secretion in the trachea [4, 6, 8, 16, 22, 26, 28, 33, 48, 65, 66, 4, 92, 107, 118]. The LL-37 peptide in neutrophils, in response to bacteria or their products, is produced constitutively, while in monocytes-macrophages, NK cells, mast cells, T and B lymphocytes, enterocytes and keratinocytes, it arises only through the action of proinflammatory cytokines (TNF, IL-1α, IL-6, IL-17A, IFN-γ), growth factors (IGF-1) and due to the active form of vitamin D [2, 733, 92, 101, 118]. Studies have demonstrated that as a result of proteolytic activity of serine proteases, which represent the tissue kallikrein family, derivatives of the LL-37 peptide are formed, which indicates its heterogeneity [112]. It was found that as a result of SCTE (Stratum Corneum Tryptic Enzyme), three peptides are formed – that is KS30, KS22 and LL29, while under the influence of SCCE (Stratum Corneum Chymotryptic Enzyme) action, two peptides are formed – RK31 and KR20. Therefore, it is assumed that the LL-37 peptide is only 20% of the cathelicidins in humans, while the rest are its derivatives, which exhibit both antimicrobial and immune system-modifying properties, and affect epithelial cells and keratinocytes [18, 20, 33, 35, 54, 64, 96, 108, 112].

The antibacterial activity of the LL-37 peptide is associated with its high concentration and the presence of divalent ions [18, 64]. In women in the reproductive tract (vagina), among its derivatives, the ALL-38 peptide has been described, which is a very important element in the defence of this section [21, 96, 108]. The LL-37 peptide, in addition to the mentioned anti-carcinogenic effect and modulation of the immune system, is characterized by pro-inflammatory and anti-inflammatory activity, proangiogenic and anti-apoptotic as well as anti-carcinogenic activity [2, 15, 18, 28, 33, 41, 59, 64, 70, 89, 101, 107, 118]. It exhibits a strong direct effect against bacteria and viruses possessing a cell envelope as well as fungi, [50, 69, 104, 108, 110]. Gram-positive bacteria are particularly sensitive to this peptide, like i.a. Staphylococcus spp., Enterococcus spp., Streptococcus spp., Bacillus spp., Lactobacillus acidophilus, Listeria monocytogenes, Propinibacterium acnes, as well as Gram-negative bacteria, i.a. Acinetobacter baumannii, Escherichia coli, Salmonella Typhimurium, Pseudomonas aeruginosa, Stenotrophomonas maltophilia, Proteus vulgaris, Klebsiella pneumoniae and Neisseria gonorrhoeae [1, 11, 14, 26, 28, 51, 60, 69, 90, 98, 101]. The impact of this peptide on the germs – mainly bacteria, is associated with its effect on their cell membrane, which leads to its fragmentation and the formation of pores therein. The LL-37 peptide can also induce the death of a bacterial cell by inhibiting the synthesis of its bacterial components, including the cell wall. It also has a neutralizing effect on bacterial LPS, which is important during infection with Gram-negative bacteria [60]. In vitro LL-37 exhibits an inhibitory effect on fibroblasts isolated from clinically healthy
gingiva in mammals which have been treated with LPS derived from E. coli [60], exerting an inhibitory influence on LPS. It is assumed that it can be used i.a. in the oral control of pathogens such as Porphyromonas gingivalis and Aggregatibacter actinomycetemcomitans [44]. The inhibitory effect of this peptide on the formation of bacterial biofilm Pseudomonas aeruginosa, Francisella novicida or Staphylococcus epidermidis was also recorded, as well as its direct destructive effects on the biofilm of these bacteria [5, 24, 379, 58]. It also has a destructive effect against mycobacteria, and in particular Mycobacterium (M.) smegmatis, M. bovis and M. tuberculosis, which is probably due to its exogenous action after penetrating into infected macrophages through endocytosis, which leads to the inactivation of mycobacteria [79, 91]. Another way of LL-37 activity against mycobacteria is the endogenous pathway through its synthesis in macrophages, as a result of the stimulation of these cells with vitamin D [79, 91]. Its antimicrobial action through the activation of immune cells takes place through TLR receptors [18, 44], except that it works via TLR5 in keratinocytes, via TLR2 and TLR3 monocytes, and in B-lymphocytes, dendritic cells and neutrophils through TLR9 [3, 43, 71]. It has now been demonstrated, on the example of cathelicidin – CATH2 (chicken), that this peptide supplying signal through TLRs 2 and 4, points to a new mechanism of “tuning” the immune response, resulting in the reduction of inflammation, which allows the immune system to distinguish between live and dead Gram-negative bacteria (E. coli), which can be very important, e.g. in sepsis [59]. It has been demonstrated that the LL-37 peptide can also activate other receptors than TLRs, because in neutrophils and lymphocytes it also stimulates the G Protein-Coupled Receptor (GPCR) e.g. FPRL-1 (Formyl Peptide Receptor-like 1), receptor of tyrosine kinases e.g. EGFR (Epidermal Growth Factor Receptor), as well as the receptor channel P_XX_R, which leads to a strong stimulation of innate immunity elements and activation of the pro-inflammatory signal cascade [3, 110]. It has been shown that the LL-37 peptide, acting on peripheral blood T and B lymphocytes, enhances the synthesis of, among others IL-6, IL-10 and chemokines CCL2 (CC-chemokine Ligand 2) and CCL7 (CC-chemokine Ligand 7) and increase the secretion of IL-1β, which is a potent inflammation activator [33, 44, 108, 110]. In contrast, induction with LL-37 peptide of FPRL-1 receptors in endothelial cells leads to an increase in their number, and in neutrophils increases the activation of FPRL-1 markers _X_Y. This results in the suppression of apoptosis of these cells and, as a result, prolongs their lifespan, resulting in a relative increase in the duration of neutrophil during infection [12, 67, 108, 110]. This peptide, by activating intracellular factors, induces autophagy of phospholipase A2 and enhances natural immunity [83]. In the case of airway epithelial cells, it activates not only the EGFR receptor, but also affects many molecular elements associated with the membrane. An example is the activation of metalloproteinase and the MAPK/ERK pathway (Mitogen-Activated Protein Kinases / extracellular Signal-regulated Kinases) [110]. It has been shown that an increase in the concentration of sodium chloride in the airway epithelial cells, causes a four to fivefold decrease in the activity of the LL-37 peptide, resulting in a reduction in the activity of various factors in these cells, which leads to the defect of the transmembrane expression regulator CFTR (Cystic Fibrosis Transmembrane Conductance Regulator) [74].

In the case of viral infection with the background of double-stranded viral RNA, the LL-37 peptide, increases the pro-inflammatory signalling in epithelial cells through TLR3 [20, 50]. However, when humans are infected with the HPV virus (Human Papillomavirus), this peptide seems to increase its activity in the epidermis, both in the development of normal and infectious warts, which proves that it is an important element of immunity during this infection [72]. This peptide is also active against HIV1 [104]. In the case of fungal infections with Candida albicans and Trichophyton (T) mentagrophytes and T. rubrum, increased expression of LL-37 has been recorded, which leads to inhibition of epidermal cell proliferation [28, 57, 110]. In non-infectious diseases, for example in the case of psoriasis, contact dermatitis and Lupus Erythematosus, the LL-37 peptide, as in the case of fungal infection, strongly activates keratinocytes [16]. It has been proven that the increased expression of this peptide in the case of psoriasis correlates with a low rate of secondary bacterial infections [16]. Although in people with atopic dermatitis, who are particularly susceptible to this type of bacterial and even viral infections, there is no secondary infection [22, 72]. In addition, the LL-37 peptide, acting as an inflammatory regulator, enhances wound healing and renewal of the superficial layer of the skin [28, 33], as it contributes to increased IL-8 and IL-6 synthesis in these cells cooperating in keratinocytes with IL-17 and IL-22, which leads to an increase in local immunity in the skin [20, 33]. The physiological concentration of LL-37 peptide in human plasma is 27.2 ng/ml, in saliva 30.5 ng/ml, in sweat 447 ng/ml, in sputum 3.0–5.0 ng/ml, in bronchial fluid – vesicles 4.8 ng/ml, while in the case of diseases such as tuberculosis and cystic fibrosis, it increases even 30–50 times [118].

2.2. Cathelicidins in animals

These peptides in monkeys, farm animals, carnivores, laboratory animals, wild animals and birds, fish, reptiles, amphibians and insects, occur in the cells of

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CATHELICIDINS IN HUMANS AND ANIMALS

lymphatic organs—bone marrow (mammals), bursa of Fabricius, (birds), in the cells of the immune system—neutrophils, although they also occur in the intestines, liver, showing large structural differences in relation to cathelicidins in humans, although in the field of biological activity, they are very similar to those occurring in humans [6, 10, 11, 19, 25, 46, 48, 52, 53, 56, 64, 69, 75, 86, 7, 88, 96, 97, 99, 100, 102, 108, 111, 114, 116, 118, 119].

In rhesus monkeys, cathelicidins rhLL-37 and rhCAP18 [10] or rhCAP18—CAP18 [48] have been described, which occur in particular in gastrointestinal and respiratory epithelial cells, and have similar α-helix structure in humans and are similar in biological activity to human cathelicidin LL-37, exhibiting anti-germ activity, including LPS of Gram-negative bacteria [10, 48]. These animals (rhesus monkeys) also have a cathelicidin RL-37 having an α-helix structure, whereas in macaques and orangutans, an analogous structure of the ppp RL-37 has been recorded, which has also been described in gibbons, in which it was designated as a peptide hmd SL-37 [62, 86].

However, in farm animals (cattle, sheep and goats), these peptides most often also have an α-helix structure, although in pigs these substances not only have an α-helical structure, e.g. cathelicidin PAMP (Porcine Antimicrobial Peptide), but also protegrins having a β-sheet structure. In sheep, cyclic cathelicidins, e.g. bactenecin-Bac and cathelicidins rich in proline and arginine residues have been recorded analogously to Bac in cattle, sheep and goats and prophenins (PG1 and 2) in pigs, as well as tryptophan-rich peptides, e.g. indolicidin in cattle or PR protegrins in pigs were have been recorded. [48, 52, 56, 96, 108, 114]. Genes encoding cathelicidins in cattle, sheep, goats and pigs, have the same organization and are 2 kbp in size. They are characterized by a high percentage of identical nucleotides, which indicates their origin from the same gene, and which in part confirms their location in the chromosome (in cattle, sheep and pigs, they are located close to each other) [114].

In cattle, the best known cathelicidins occurring in neutrophils is bactenecin 1 (Bac-1-cathelicidin 1), 5 (Bac5-cathelicidin 2) and 7 (Bac7-cathelicidin 3) — peptides rich in proline and arginine and indolicidin (cathelicidin 4) rich in tryptophan [48, 96]. These peptides have a strong antibacterial effect acting on the cell membrane and on their intracellular organelles, mainly against Gram-negative bacteria: E. coli, S. Typhimurium, Klebsiella pneumoniae and P. aeruginosa, as well as in Gram-positive bacteria, although for Enterobacter cloace, Leptospira (L) interrogans and L. biflexa, exhibit bacteriostatic activity [48, 96]. Furthermore, indolicidin, mentioned in cattle and occurring in neutrophilic granulomas, is characterized not only by antibacterial but also anti-fungal activity, e.g. against C. albicans, Cryptococcus neoformans and anti-protozoan activity against Leismania donovani and Giardia lamblia. In addition, it activates chemokine secretion, neutrophil autophagy, which is very important, in particular in the mammary gland in cattle during the drying period, where the neutrophil autophagy process is very intense [13, 85, 96]. In cattle a cathelicidin in a form of BMAP peptide have been described (bovine myeloid antimicrobial peptides) 27 (cathelicidin 6), 28 (cathelicidin 5) and 34 (cathelicidin 7) [48, 52, 56, 108] that affect mesosomes in bacteria and mitochondria in fungi and affect the secretion of TNF-α in mammary epithelial cells, which is valuable for mastitis in these animals, although they also have anti-carcinogenic effects [48, 56, 95, 108].

In sheep, the important cathelicidins are: a cyclic dodecapeptide under the names Oa Bac 5, 6, 7, 5 and 11, (bactenecin 5, 6, 7, 5 and 11) and cathelicidin 1 (bactecin 1), 2 (bactenecin 5) and 3 (bactenecin 7), and also the SMAP peptide (sheep myeloid antimicrobial peptide) (SC5-cathelin related peptide) and MAP (myeloid antimicrobial peptides) 29 and 34, rich in proline and arginine [48, 52]. All these peptides in these animals are characterized by antibacterial (Gram-negative and positive) and antifungal activity (C. albicans) [48, 52]. These compounds in sheep are synthesized by neutrophils and mammary epithelial cells, exhibiting inhibitory activity against Staphylococcus aureus, Streptococcus uberis and Mycoplasma agalactie — germs which are a very common cause of infection of this gland [23]. In addition, cathelicidin in sheep activates PMN cells in the scope of their antimicrobial activity and NET network formation. This peptide is a specific marker indicating udder inflammation [23].

In goats, cathelicidins Bac 7, 5, 3, 4 and cathelicidin 2 (Bac5) are known — peptides rich in proline and arginine, which are 50% similar in structure to Bac5 in cattle [48, 52, 108]. These peptides in goats, even in low and high concentration of sodium chloride, exhibit antibacterial activity against Gram-negative bacteria, e.g. E. coli, P. aeruginosa and some Gram-positive ones, e.g. Bacillus subtilis, S. aureus, while in low concentration they only eradicate C. albicans [48, 52].

In contrast, in pigs, cathelicidins are represented by Pell (Porcine antimicrobial peptide), 23.36 and 37 (α-helical structure), PR-39, prophenin 1 and 2 (PF 1 and 2) (rich in proline and arginine) and protegrin 1–5 (PG 1–5), which exhibit a β-sheet structure and have SS bridges. They are synthesized in neutrophils, bone marrow, and also occur in the bronchioles and tongue cells, small intestines, trachea and urogenital cells, demonstrating an activating effect on the elements and phenomena of the immune system, in particular the neutrophil phagocytosis [48, 52, 56, 75, 106, 108].
These peptides in pigs also show activity against Gram-negative bacteria such as *E. coli*, although for example: Prophenins 1 and 2 (PF 1 and 2) additionally combat Gram-positive bacteria, e.g. *L. monocytogenes*, and protegrins 1–5 (PG1–5) together with prophenins 1 and 2 (PF1 and 2), are particularly destructive towards *Chlamydia trachomatis*, *C. albicans*, *N. gonorrhoeae* and some viruses, as well as nematodes and flat worms [40, 48, 52, 56, 55, 105, 106]. In addition, protegrin 1 (PG1) in pigs impacts *M. tuberculosis* and bacteria which cause wound infections [77]. It has been reported that purified LPS of Gram-negative bacteria, increases the expression of PR-39 cathelicidin in bone marrow cells of these animals [109], and which peptide, affects wound healing and has an inhibitory effect on apoptosis [40, 77].

In horses, among the cathelicidins peptides called eCATH 1, 2 and 3 are known, which are synthesized in the bone marrow, are characterized by an α-helical structure and are rich in lysine. In terms of the impact on germs, they are characterized by potent destructive effect on Gram-negative and Gram-positive bacteria and fungi, such as: *Cryptococcus neoformans* and *Rodotorula rubrum* [25, 48, 56, 88].

However, in carnivorous animals – dogs, cathelicidin K9CATH has been described, whereas in cats FeCates – peptides which have an α-helical structure and occur in the bone marrow, are characterized by an α-helical structure and occur in the bone marrow and neutrophils, and are characterized – mainly in dogs – by strong antibacterial properties, e.g. *N. gonorrhoeae* and *Ureaplasma* sp. This explains the low susceptibility of these animals to sexually transmitted diseases [48, 56, 62, 112].

In laboratory animals, cathelicidin was found in rabbits, rats, mice and guinea pigs [48, 56]. Cathelicidins in rabbits are represented by the CAP 18 peptide and P15A and P15B proteins present in their neutrophils and kidneys; in rats by the rCRAMP peptide, whose origin in available literature is not mentioned; in mice the Cramp peptide is indicated, which occurs in the testicles of males, spleen, liver and gastrointestinal tract; in guinea pigs cathelicidins are represented by CAP11 peptide, found in neutrophils and bone marrow [48, 56]. These peptides in these laboratory animals exhibit antibacterial activity, including inhibitory effect on LPS of Gram-negative bacteria [48, 56].

In wild animals, cathelicidins have been described in deer in the form of bactenecin, which occurs in neutrophils and kidneys, characterized by antimicrobial activity against Gram-negative and Gram-positive bacteria [97]. Cathelicidin has also been described in these animals in the form of the P-9 peptide, which is rich in proline and arginine and has a bactericidal effect on many germs [29]. These compounds have also been recorded in buffaloes of the Bovidae family (*Bubalus bubalis*) in the form of a fragment of myeloid cathelicidin and a fragment of cathelicidin 4, found in the bone marrow and genital tract, whose activity has been described as anti-germ [17, 97]. Cathelicidins called EACATH 1 have been described in donkeys, characterized by α-helical structure [37] and in platypus in the form of PA1 and PA2 peptide [29], as well as in pandas in the form of the AM peptide [113]. The cathelicidins in these animals have not been well characterized yet in respect of their structure and biological activity.

The cathelicidins were also recorded in birds, in particular in chickens in which they are represented by cathelicidin 1 (CATH 1), 2 (CATH 2), 3 (CATH 3), cathelicidin B-1 (CATH B1) and peptide CMAP 27 (Chicken Myeloid Antimicrobial Peptide-27). These peptides have been found, among others, in their bursa of Fabricius, in the bone marrow, gastrointestinal tract, liver, respiratory system, kidneys, spleen, brain and muscles [48, 53, 56, 100, 107, 111]. They exhibit strong activity against Gram-negative and Gram-positive bacteria, including those resistant to antibiotics. It is assumed, however, that in chickens it is primarily the CMAP 27 peptide, which determines their natural immunity. According to Linde et al. [56] in chickens as well as turkeys, these peptides are observed in the bone marrow in the form of protegrin. It has also been reported [101, 111] that the cathelin region of cathelicidin in birds displays low homology in comparison to this region in mammalian vertebrates.

Cathelicidin has also been described in fish (Atlantic salmon, rainbow trout, Atlantic cod) in the form of peptide 29 (HFIAP-3) and 37 (HFIAP 1.2) and cathespin H and cathelicidin 2, which are found in the cells of the digestive tract, liver, kidneys, the skin and which are similar to some mammalian cathelicidins, because they have proline and cysteine in their structure and exhibit, in particular, antibacterial activity [19, 48, 52]. In addition, it is assumed [108] that in salmons there occurs a cathelicidin called rICATH 1 – rich in glycine, while in the Atlantic cod there occurs the Cod Cath cathelicidin – rich in glycine and serine.

Cathelicidins have also been recorded in snakes in the form of the OHCAT peptide – king cobra, NACATH peptide – cobra and BF-CATH peptide and BF cathelicidin in the banded krait [102, 108].

Literature data [48, 64, 93, 96, 108] also indicate the existence of cathelicidins in amphibians and insects, but mainly in amphibians; details on the structure of these peptides and their biological activity is lacking. On the other hand, in 1980 it was demonstrated in insects that apart from the isolation of cecropins from the pupae of the *Hyalophora cypria* moth, many peptides had been registered in various representatives of this cluster [64]. And thus in *Drosophila melanogaster*, 8 families of AMPs have been found, and in *Galleria mellonella* caterpillars 12 peptides which are synthesized in the fat body, haemocytes and epithelial cells have been...
3. Summary

Cathelicidins are natural elements of antimicrobial resistance, to which the microorganisms inhabiting mammals, including humans and animals, among others farm, laboratory and wild ones, as well as birds and fish, have not developed immunity in the course of evolution. These peptides participate mainly in bacterial and viral infections, although they are also active in fungal and protozoan infections, acting directly and indirectly, as they exert their influence on signalling pathways and immune cell activity, including i.a. the expression of cytokines, chemokines and growth factors, which causes them to become very important components of the natural resistance of mammals, including humans, in whom they are best known and are assumed to be a counterpart for other mammalian vertebrates in respect of their bactericidal activity.

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References


CATHELICIDINS IN HUMANS AND ANIMALS


