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REVIEW

Antimicrobial Peptides in the Brain

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Abstract Antimicrobial peptides (AMPs) are an evolutionarily conserved component of the innate immune system of many species. The brain is an immunologically privileged organ but can produce a robust immune response against pathogens and cell debris, promoting rapid and efficient clearance. AMPs may be critically involved in the innate immune system of the brain. Though the mechanisms of AMPs' action in the brain still need further elucidation, many studies have shown that AMPs are multifunctional molecules in the brain. In addition to antimicrobial action, they take part in congenital and adaptive immune reactions (immunoregulation), function as signaling molecules in tissue repair, inflammation and other important processes through different mechanisms, and they might, in addition, become diagnostic markers of brain disease.

Keywords Antimicrobial peptides · Brain · Antimicrobial activity · Immunomodulatory activity · Signaling molecules

Abbreviations

AMPs	Antimicrobial peptides
BBB	Blood–brain barrier
CNS	Central nervous system
PRRs	Pattern-recognition receptors
PAMPs	Pathogen-associated molecular patterns
NODs	Nucleotide-binding oligomerization domain proteins
TLR	Toll-like receptor
HBD	Human β defensin
HNP	Human α-defensin
HD-5	Human α-defensin 5
LPS	Lipopolysaccharide
IL	Interleukin
TNF	Tumor necrosis factor
CRAMP	Cathelicidin-related antimicrobial peptide
LL-37	Human cathelicidin
hCAP18	Human cathelicidin antimicrobial protein
rCRAMP	Rat CRAMP
NAMPs	Neuro-antimicrobial peptides
PMNs	Polymorphonuclear leukocytes
PEA	Proenkephalin A
NK1	Neurokinin-1
NPY	Neuropeptide Y
BRPs	Bombesin-related peptides family
DCD	Dermcidin
AD	Alzheimer's disease
PD	Parkinson's disease
PKC	Protein kinase C

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Introduction

Infectious agents threaten every organism. Therefore, natural defense systems are vital to organisms surviving in heterogeneous conditions and environments. Antimicrobial peptides (AMPs), which are either induced at the time of infection or released from stores in secretory cells, are an important group of molecules involved in the first line of

defense (Bulet et al. 2004). AMPs are found in most classes of living organisms and contribute significantly to the innate host defense by rapidly inhibiting microbial proliferation. The brain is protected against invading pathogens by the blood-brain barrier (BBB) and meninges, and also by its own innate defense system. AMPs are a part of the innate immune system, and may also have important functions in the brain. AMPs, such as defensins, cathelicidins, or dermcidin (DCD), have all been shown to be expressed in the human brain (Zasloff 2002). However, the occurrence of AMPs in the central nervous system (CNS) has received only limited attention. Better understanding of these molecules will shed further light on the mechanisms responsible for brain diseases.

The Immune Defense of the Brain

Innate immunity is a first line of defense of the human organism, which is constantly exposed to a large variety of pathogenic microorganisms and their products. Complement proteins, lectins, chemokines, cytokines, and AMPs are now considered a fundamental component of the innate immune system (Radek and Gallo 2007).

Although shielded by the BBB, the brain mounts robust and effective immune responses in a unique way (Galea et al. 2007; Nguyen et al. 2002) (Fig. 1). The BBB regulates the passage of molecules and cells into the brain and is largely impermeable to large and hydrophilic molecules as well as most bacteria and viruses. So, the brain is well protected from invading pathogens compared to other tissues, and infection of the brain is a relatively rare clinical phenomenon (Kim 2003). Innate immunity of the brain is a constitutive component of the CNS and acts as a first line of defense in a coordinated network against infection (Nguyen et al. 2002). CNS-resident cells, such as microglia, astrocytes and even neurons, are major contributors to the cellular innate immune system of the brain, sensing pathogens and launching an innate immune response (Falsig et al. 2008). Further, leukocytes, such as neutrophils,

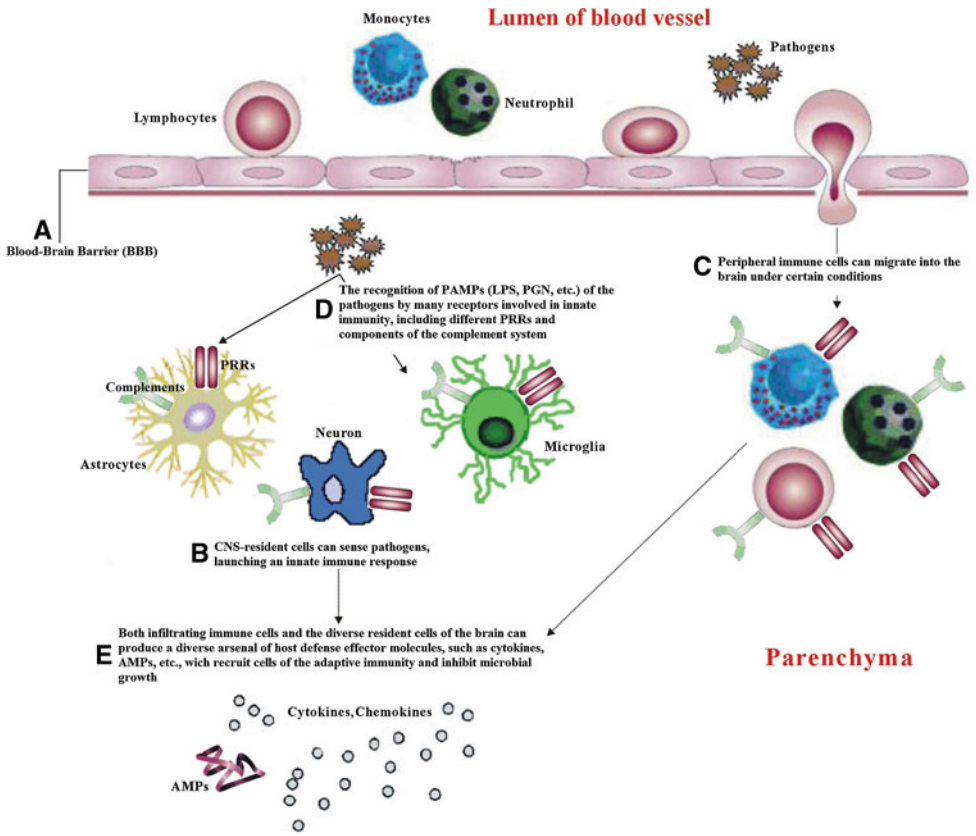

Fig. 1 The immune defense of the brain. **a** The brain is well protected from invading pathogens by the blood–brain barrier; **b** CNS-resident cells, microglia, astrocytes and neurons, are major contributors to the cellular innate immune system of the brain, sensing pathogens and launching an innate immune response; **c** peripheral immune cells can migrate into the brain under certain conditions; **d** many receptors associated with the detection of pathogens and the initiation of an immune response at the periphery are also expressed by brain cells, which display an array of receptors involved in innate immunity, including PRRs and components of the complement system; **e** both infiltrating immune cells and resident cells of the brain can produce a diverse arsenal of host defense effector molecules, such as cytokines, chemokines and AMPs, which recruit cells of the adaptive immune system and inhibit microbial growth and invasion

macrophages, T and B and natural killer cells, are major contributors to inflammation of the brain. Peripheral immune cells can migrate into the brain and affect the course of CNS diseases and are major contributors to neuropathological processes (Aravalli et al. 2007; Becher et al. 2006; Simard et al. 2006). There are several distinct routes of leukocyte entry into the CNS, which are fundamental to normal physiology, immunopathology and host defense (Ransohoff et al. 2003). Microglia communicate reciprocally with astrocytes, endothelial cells and CNS-infiltrating immune cells (Hanisch 2002). It has also been suggested that neurons participate in the immune defense of the CNS by signaling to microglia (Polazzi and Contestabile 2002).

Many receptors associated with the detection of pathogens and the initiation of an immune response at the periphery are also expressed by brain cells, which display an array of receptors involved in innate immunity, including Toll-like receptors (TLRs), nucleotide-binding oligomerization domain proteins (NOD), double-stranded RNA-dependent protein kinase, scavenger receptors, mannose receptor and components of the complement system (Farina et al. 2007).

Notably, the recognition of infectious non-self is mediated in part by a limited number of germline-encoded pattern-recognition receptors (PRRs), such as TLRs or NODs. PRRs are a group of evolutionarily conserved receptor families capable of detecting the presence of infection by recognizing specific microorganism-derived biomolecules, the so-called pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharide (LPS) or peptidoglycan. The release of PAMPs during an infection provides a "danger signal" and triggers the defensive innate immune response (Akira and Takeda 2004; Barton and Medzhitov 2003). The recognition of components specific to the pathogen by PRRs is a characteristic of the innate immune system. The expression of PRRs is found in various immune and non-immune cell types of the CNS. Microglial cells express an extensive repertoire of PRRs and act as sentinels, surveying the CNS for possible damage or infection. Astrocytes are the most abundant cell type in the brain, and they are capable of launching a strong supportive innate immune response. Recent findings showed that both astrocytes and, surprisingly, even neurons express PRRs. Activation of these receptors leads to a functional response, indicating that cells in the brain are capable of initiating a primary innate immune response against CNS-invading pathogens.

Both infiltrating immune cells and resident cells of the brain, such as neurons, astrocytes, and microglia, can produce a diverse arsenal of host defense effector molecules, such as cytokines, chemokines and small molecules, which recruit cells of the adaptive immunity and inhibit microbial growth and invasion (Braff and Gallo 2006; Brandenburg et al. 2008). Prominent among these molecules are the AMPs, which are capable of killing a wide range of bacterial, fungal, and viral pathogens (Hancock and Sahl 2006; Hirsch et al. 2008).

For many years, attention was focused on adaptive immunity as the main antimicrobial defense system. The discovery of AMPs changed this point of view. The production of a large variety of natural nontoxic AMPs from both plants and animals is attracting increasing attention, and it has become apparent that AMPs are an essential component of the innate immune system of multicellular organisms (Ganz 2003). More recently, studies have detected AMPs in the brain (Bergman et al. 2005). This indicates that AMPs may also be involved in the innate immune system of the brain. However, the occurrence of AMPs in the brain has received only limited attention.

What are AMPs?

AMPs are a major component of the innate immune response towards pathogen infections. Multicellular organisms are permanently exposed to potentially pathogenic microorganisms. Innate immunity forms the first line of defense against infection by these microorganisms. AMPs are evolutionarily ancient weapons and are known as evolutionarily conserved essential components of congenital immunity, which is the principal natural defense system for the majority of living organisms. They are found among all classes of life ranging from prokaryotes to humans (Beisswenger and Bals 2005; Lai and Gallo 2009; Radek and Gallo 2007; Zaiou 2007; Zhang and Falla 2009). AMPs were first isolated in the 1980s (Boman 1995). Up to now, a very large number of AMPs have been isolated from nature and thousands of synthetic variants produced. AMPs from plants and animals now number in the hundreds (Radek and Gallo 2007; Steiner et al. 2009). For a regularly updated list of AMPs, see the website: http://aps.unmc.edu/AP/main.php (Radek and Gallo 2007).

AMPs are a diverse group of small (6–100 amino acids) molecules and include defensins, cathelicidins, DCD, hepcidin, neuropeptides, peptide hormones and many other proven and putative peptides. AMPs are very heterogeneous in length, sequence and structure. The diversity of AMPs discovered is so great that it is difficult to categorize them except broadly on the basis of their secondary structure (Hoskin and Ramamoorthy 2008). Among most classes of AMPs, a common structure can be observed, with domains of hydrophobic and cationic amino acids spatially arranged into an amphipathic design, which facilitates interaction with bacterial membranes (Brogden 2005; Brogden et al. 2003; van 't Hof et al. 2001). All the

studies suggest that AMPs are employed as part of a synergistic arsenal of molecules that defends against exogenous microbes.

AMPs are produced by many tissues and cell types, with phagocytic and epithelial cells as the predominant source. In humans and other mammals, peptide concentrations from these cells increase significantly following infection or injury (Brogden et al. 2005).

There is now increasing evidence that AMPs are multifunctional molecules of fundamental importance in host defense (Radek and Gallo 2007). AMPs have a broad range of biological properties: an increasing number of studies have shown that AMPs, which are toxic to bacteria but not to normal mammalian cells, have a broad but not identical spectrum of antimicrobial activity against Gram-positive and Gram-negative bacteria, yeasts, fungi, enveloped viruses and even tumor cells (Allaker 2008; Chan et al. 2006). The growing problem of resistance to conventional antibiotics is a global public health problem and the need for new antibiotics has stimulated interest in the development of AMPs as human therapeutics (Bals 2000). Several AMPs have already entered pre-clinical and clinical trials to promote wound healing and for the treatment of cystic fibrosis, catheter site infections, acne, and patients undergoing stem cell transplantation (Koczulla and Bals 2003; Lee and Herzog 2009; Mader and Hoskin 2006). Many AMPs kill microbes by membrane-targeting, pore-forming mechanisms difficult to escape (Hancock and Sahl 2006; Rotem and Mor 2009; Sang and Blecha 2008).

Although originally characterized as natural antimicrobial agents, it is now appreciated that these peptides also can modify host inflammatory responses. This includes effects on innate immune cells, including neutrophils and epithelial cells, and in those cells that bridge the innate and adaptive immune systems, including monocytes, macrophages and other antigen-presenting cells. These peptides modify cellular functions such as chemotaxis, apoptosis, gene transcription and cytokine production. In addition, they have roles in the stimulation of wound healing, angiogenesis, homeostasis, and proliferation. They have anticancer properties and preserve a balance between proteases and protease inhibitors (Brogden et al. 2005; De Smet and Contreras 2005; Hancock and Diamond 2000; Zasloff 2002).

AMPs in the Brain

Many studies have detected mRNAs of AMPs in the brain (Becher et al. 2006; Bergman et al. 2005; Maxwell et al. 2003; Ostergaard et al. 2009; Simard et al. 2006). Peptides identified early were defensins and cathelicidin (Zasloff 2002). Defensins and cathelicidin are two major families and can serve as excellent examples of the potential function of AMPs in brain defense. Surprisingly, several neuropeptides in the brain are very similar to AMPs in their amino acid composition, amphipathic design, cationic charge and size. Their antimicrobial activities suggest they may also be directly involved in innate defense of the brain. Here we will discuss several AMPs of the brain (Table 1), which include the cathelicidins (hCAP-18/LL-37), the defensins, neuropeptides, hepcidin and DCD.

Defensins

Defensins are members of an evolutionarily old family of cysteine-rich peptides, widely distributed in nature and found in vertebrates and invertebrates. On the basis of size and pattern of disulfide bonding, mammalian defensins are classified into three classes: α-, β- and θ-defensins, with the majority of research focused on the first two classes (Menendez and Brett Finlay 2007). Up to now, five different human α-defensin genes and six different human α-defensin molecules have been described (HNP-1, HNP-2, HNP-3, HNP-4, HD-5 and HD-6) (Mallow et al. 1996; Schneider et al. 2005; Skalicky et al. 1994; Yamasaki and Gallo 2008). Over the past years, six human β-defensins (HBD) have been identified (HBD-1, HBD-2, HBD-3, HBD-4, HBD-5 and HBD-6) (Duits et al. 2002; Fang et al. 2003; Liu et al. 2002; Pazgiera et al. 2006; Weinberg et al. 1998).

Defensins are found in neutrophils, epithelial cells, certain macrophage populations and Paneth cells of the small intestine (Schluesener and Meyermann 1995; Yang et al. 2002). Recent studies have demonstrated defensin mRNA in the CNS of many species (Bergman et al. 2006; Chen et al. 2006; Giuliani et al. 2007; Maxwell et al. 2003; Ostergaard et al. 2009). Transcripts of the bovine defensin tracheal antimicrobial peptide and lingual antimicrobial peptide have been detected in brain by in situ hybridization. The mRNA was present in the meninges, throughout the cortex and in Purkinje cells of the cerebellum (Stolzenberg et al. 1997). HBD-1 mRNA has been found in human, mouse, rat, cow and pig brain (Hao et al. 2001; Hiratsuka et al. 2001; Huttner et al. 1997; Stolzenberg et al. 1997; Zhang et al. 1998). HBD1 mRNA is produced by astrocytes, microglia and meningeal fibroblasts, but not neurons, whereas HBD2 mRNA production is inducible and is detected in astrocytes only after incubation with LPS, interleukin (IL)-1β or tumor necrosis factor (TNF) (Bergman et al. 2005). However, HBD-1 or HBD-2 was not detected in neurons (Hao et al. 2001). The transcript of HBD-1 is also present in the choroid plexus (Nakayama et al. 1999; Stolzenberg et al. 1997), which produces cerebrospinal fluid.

Table 1 Antimicrobial peptides in the brain

Peptides	Localization of expression in CNS	Identified function in CNS	References
Defensins	Meninges, cortex, cerebellum, choroid plexus	Antimicrobial, immunomodulatory, signaling molecules	[Chen et al. 2006; Giuliani et al. 2007; Hao et al. 2001; Hiratsuka et al. 2001; Huttner et al. 1997; Maxwell et al. 2003; Nakayama et al. 1999; Ostergaard et al. 2009; Zhang et al. 1998]
Cathelicidins (CRAMP/LL-37)	Blood–brain barrier, meninges, hippocampus, striatum, olfactory bulb, cerebellum, spinal cord	Antimicrobial, immunomodulatory, signaling molecule	[Bals et al. 1998; Bergman et al. 2005; Bergman et al. 2006]
NAMPs			
Proenkephalin A	Hippocampus, thalamus, brainstem, spinal cord	Antimicrobial, immunomodulatory, signaling molecule	[Behar et al. 1994; Metz-Boutigue et al. 2003; Salzet and Tasiemski 2001]
Neurokinin-1	Throughout the CNS	Antimicrobial, immunomodulatory, signaling molecule	[Hansen et al. 2006; Lundy et al. 2008; Scholzen et al. 1998]
Neuropeptide Y	Throughout the CNS	Antimicrobial, immunomodulatory, signaling molecule	[Benarroch 2009; Hansen et al. 2006; Lee and Herzog 2009; Wu et al. 2003]
Bombesin	Hypothalamus, olfactory bulb, dentate gyrus, the solitary tract of the hindbrain	Antimicrobial, immunomodulatory, signaling molecule	[Brogden et al. 2005; El Karim et al. 2008; Li et al. 2006; Moody and Merali 2004]
Other AMPs			
Dermcidin	Pons, midbrain hypothalamus, paracentral gyrus	Antimicrobial, immunomodulatory, antitumor, signaling molecule	[Cunningham et al. 2002; Lai et al. 2005; Porter et al. 2003; Schittek et al. 2001; Wang et al. 2003]
Hepcidin	Olfactory bulb, cortex, hippocampus, amygdala, thalamus, mesencephalon, cerebellum, pons, spinal cord, striatum	Antimicrobial, immunomodulatory, signaling molecule, regulator of iron homeostasis	[Dringen et al. 2007; Hänninen et al. 2009; Jeyakumar et al. 2009; Nemeth et al. 2004; Wang et al. 2008; Zechel et al. 2006]

AMPs antimicrobial peptides, *CNS* central nervous system, *CRAMP* cathelicidin-related antimicrobial peptide, *NAMPs* neuro-antimicrobial peptides

Defensins act as a first line of defense against invading pathogens (Kapetanovic and Cavaillon 2007; Klotman and Chang 2006; Zhu 2008). Recent studies have shown that some defensins stimulate human keratinocytes to express IL-6 and IL-10 and chemokines, which act as a link between innate and adaptive immune responses (Niyonsaba et al. 2007). Some defensins are specific, potent chemoattractants for monocytes and dendritic cells, and may function as a regulator in inflammation (Bowdish et al. 2006).

Cathelicidins

Cathelicidins are the second largest family of AMPs in mammals (Chromek et al. 2006; Iimura et al. 2005; Schauber and Gallo 2009; Zanetti 2005). Cathelicidins are characterized by an evolutionarily conserved amino-terminal cathepsin L N-terminal domain, called the cathelin domain. The cathelin-like prodomain is named for its similarity to the cystatin family of cysteine protease inhibitors and shows approximately 60% sequence identity between species (Lehrer and Ganz 2002). Humans and rats have one cathelicidin gene each in their genomes. These are the mouse CRAMP (cathelicidin related anti-microbial peptide) and the human cathelicidin LL-37 (Agerberth et al. 1995; Cowland et al. 1995; Schauber and Gallo 2008). Mouse CRAMP and human LL-37 peptides share only 67% homology. Human cathelicidin is often referred to by one of its peptide forms (LL-37) or the nomenclature assigned to its precursor protein (hCAP18 or CRAMP) (Pestonjamasp et al. 2001). This peptide is derived by extracellular proteolysis from the C-terminal end of the human CAP18 protein (hCAP18). LL-37/hCAP18 is a small peptide of 37 amino acids starting with two leucine residues. LL-37/hCAP-18 is found at high concentrations in its unprocessed form in the granules of neutrophils and is processed upon degranulation and release. It is also produced by epithelial cells and is found in a number of tissues and body fluids (Hase et al. 2003; Murakami et al. 2002a, b, 2005; Nijnik and Hancock 2009). The upregulation of human cathelicidin hCAP-18/LL-37 expression upon the

reception of inflammatory stimuli has been reported previously (Van Wetering et al. 2005).

Cathelicidin mRNA has been detected in the brain by dot–blot hybridization (Bals et al. 1998). Cellular localization and possible functions of LL-37 at this location remain to be determined. Recently, rCRAMP mRNA was detected in the rat CNS with a distinct regional distribution (Bergman et al. 2005), notably in the olfactory bulb, cerebellum, medulla oblongata and spinal cord. Moreover, the transcript of rCRAMP has been detected in primary cultures from hippocampus, striatum, cerebellum and spinal cord, as shown by RT-PCR and Southern blot. In addition, the rCRAMP peptide exhibits in vitro activity against the neuropathogenic bacterium *Neisseria meningitidis* and the induction of CRAMP in rat endothelial cells of the BBB and in cells of the meninges after meningococcal infection has been described (Bergman et al. 2006). Another study showed that a homologue of the human LL-37 is expressed in rat astrocytes and microglia after incubation with different bacterial components (Brandenburg et al. 2008). Taken together, these data suggest that cathelicidin rCRAMP may play a role in the innate immunity of the CNS.

Neuro-antimicrobial peptides

Many neuropeptides share similar characteristics with AMPs in their amino acid composition, amphipathic design, cationic charge, and size, which facilitate their deposition into the aqueous space between the target membrane and within the nerve terminal and respective receptor. This shared property of amphipathicity led to discovery of the antimicrobial activities of many neuropeptides. The term "NAMPs" (neuro-antimicrobial peptides) can be coined as an AMP derived from neuropeptides, molecules that mediate communication between the nervous and immune system. Although in its infancy, recent developments in the neuroimmunology field support the notion that both the brain and peripheral nervous system directly influence the activity of the innate and adaptive immune system. The inclusion of neuropeptides in the armamentarium of AMPs extends the known mechanisms by which the nervous system contributes to innate immune defense. Several peptides with neural or neuroendocrine signaling functions have been shown to have potent antimicrobial activity (Brogden et al. 2005). Furthermore, they are widely distributed not only in endocrine, neuroendocrine and nerve cells but also in immune cells. Chromofungin and enkelytin are released from polymorphonuclear leukocytes (PMNs), suggesting that they might act locally at sites of infection as defensive molecules. Their liberation from cells indicates that these peptides probably play a role in the processes of inflammatory and immune responses. The following section describes several neuropeptides that act as AMPs in addition to their originally identified function.

Proenkephalin A

Proenkephalin A (PEA) is expressed at specific sites in the brain and certain cells of the adrenal medulla and the immune system. It is the precursor of the enkephalin opioid peptides and is proteolytically processed to yield Met-enkephalin, Leu-enkephalin, enkelytin and other PEA-derived peptides, such as peptide B (Metz-Boutigue et al. 2003; Salzet and Tasiemski 2001). Enkelytin is a major PEA-derived peptide and is active against gram-positive bacteria including *Staphylococcus aureus* in the micromolar range. Antimicrobial PEA-derived peptides have been identified in numerous bovine and rabbit infectious fluids and in secretions of stimulated polynuclear neutrophils, and it has been shown that, after administration of LPS, PEA mRNA increases rapidly in rat monocytes and macrophages in lymph nodes and in chromaffin cells of the adrenal medulla (Behar et al. 1994; El Karim et al. 2008; Hansen et al. 2006). These findings indicate that PEA-derived peptides are involved in the process of host defense and establish communication between the neuroendocrine and the immune system (Brogden et al. 2005).

Neurokinin-1

Neurokinin-1 (NK1; also known as substance P) is widely distributed throughout the peripheral and CNS. Like other AMPs, NK1 has a cationic amphipathic secondary structure and probably shares a common mechanism of antimicrobial activity. NK1 is present in a subpopulation of unmyelinated, sensory nociceptive neurons (C-type fibers) that transmit pain messages from mucosa subjected to chemical irritants, heat, cold or other noxious stimuli (Lundy and Linden 2004). Stimulated NK1-immunoreactive nerves release NK1, which can rapidly induce a variety of local defensive responses, inhibiting the growth of local microorganisms (El Karim et al. 2008; Hansen et al. 2006). In patients affected by periodontitis, the concentration of NK1 is substantially increased in gingival crevicular fluid of disease-affected teeth compared with healthy sites (Lundy and Linden 2004). In the skin, NK1 induces rounding of endothelial cells, capillary leakage and vasodilatation, chemotaxis of neutrophils and macrophages,

proliferation of keratinocytes and fibroblasts, mast cell degranulation, and the expression of various adhesion proteins by local endothelial, epithelial and inflammatory cells (El Karim et al. 2008; Scholzen et al. 1998).

Neuropeptide Y

Neuropeptide Y (NPY) contains 36 amino acids and is the most ubiquitously expressed peptide in the mammalian central and peripheral nervous system (Lee and Herzog 2009). In the brain, NPY has a number of functions in mammalian physiology. It is a sympathetic co-transmitter released preferentially during intense or prolonged stress and has been implicated in diverse processes such as feeding, behavior and metabolism (Wu et al. 2003). Apart from its role as a hormone and neurotransmitter, NPY may also play a role in innate immunity. It has been shown that NPY is a potent antifungal peptide against *Candida albicans* in vitro (Vouldoukis et al. 1996). NPY mRNA has been found in non-neuronal cells, such as sustentacular and olfactory ensheathing cells (Benarroch 2009; Wu et al. 2003), and thus may create a local antimicrobial barrier discouraging microbial invasion along the axonal tract and suppressing a need for the assistance of tissue destructive inflammatory cells in the clearance of microbes.

Bombesin

Bombesins constitute a large family of neuropeptides mediating a variety of biological activities in the gastrointestinal (GI) tract and CNS of mammals, including contraction of smooth muscle, secretion of other GI hormones, processing of memory, enhancement of cell proliferation, and regulation of central homeostatic mechanisms (appetite and feeding behavior, thermoregulation) (Baranowska 2009; Li et al. 2006; Moody and Merali 2004). Proline-rich bombesin (PR-bombesin) (originally isolated from Chinese red belly toad, *Bombina maxima*) is a 16-amino acid peptide member of the bombesin-related peptides (BRPs) family. BRPs are produced by neurons of the central and peripheral nervous system, and many other neuroendocrine cell types (Moody and Merali 2004). PR-bombesin, like substance P and NPY, might also have direct effects on invading microbes (Li et al. 2006). These antimicrobial activities add a further dimension to the immunomodulatory roles of neuropeptides in inflammatory and immune responses. This discovery suggests that the nervous system might use these peptides as anti-infective agents by delivering them rapidly and precisely to innervated sites (Brogden et al. 2005; El Karim et al. 2008).

Other AMPs of the Brain

In addition to cathelicidins, defensins and neuropeptides, many other new AMPs, such as DCD or hepcidin, have been found in the brain. DCD is a gene encoding an anionic AMP and shares no homology with any other known AMPs (Schittek et al. 2001; Senyürek et al. 2009). DCD is most highly expressed in sweat glands of the skin (Schittek et al. 2001), as well as in breast tissue and in the CNS. A high level of expression was detected in the pons of the brain. In xenograft experiments in rat brains, Cunningham et al. reported that mouse cells stably overexpressing DCD were not immunosuppressed and exhibited substantial invasion and migration from the lesion/injection site into white matter tracts and along blood vessels of the forebrain and thalamus of the host (Cunningham et al. 2002). While the detailed molecular characteristics of DCD require further clarification, it has been demonstrated that DCD may function as an antibiotic peptide in the skin, diffusible survival evasion peptide in the brain or cancer cachectic factor in patients with pancreatic, breast, lung, and ovarian cancer, and malignant melanoma (Cunningham et al. 2002; Niyonsaba et al. 2009; Porter et al. 2003; Schittek et al. 2001; Wang et al. 2003).

Hepcidin, formerly named liver-expressed antimicrobial peptide, plays a major role in innate immunity and the maintenance of the body iron status. A typical pattern of six to eight conserved cysteines involved in disulphide bridges has been found in all vertebrate hepcidins (Ganz 2006; Oates 2007). Iron serves as an essential trace element for all body tissues, including the CNS. Iron deficiency as well as iron overload is known to cause damage to the mammalian brain, so the maintenance of iron homeostasis is crucial. It is important to note that hemochromatosis may represent a risk factor for Alzheimer's disease (AD), indicating that imbalances in iron homeostasis of the brain contribute to neurodegenerative processes (Jeyakumar et al. 2009; Zechel et al. 2006). Studies have shown a widespread distribution of hepcidin mRNA in different brain areas, including the olfactory bulb, amygdala, thalamus, hypothalamus, mesencephalon, cerebellum, pons, spinal cord, and in dorsal root ganglia of the peripheral nervous system (Hänninen et al. 2009; Zechel et al. 2006). The hepcidin protein is expressed by neurons and glia cells (Brandenburg et al. 2008; Dringen et al. 2007; Jeyakumar et al. 2009). Recent data have provided further evidence for the existence of hepcidin mRNA in the brain, including the cortex, substantia nigra, hippocampus and other regions, and LPS induced a significant increase in abundance of hepcidin mRNA and protein in the cortex and substantia nigra, but not in the hippocampus and striatum, indicating a regionally specific regulatory effect of LPS on hepcidin gene expression (Wang et al. 2008).

Role of AMPs in the Brain

As AMP research has proliferated, the known repertoire of biological roles of AMPs has expanded to include a number of other functions. In addition to their broad-spectrum antimicrobial, antifungal and antiviral activities, studies have now provided compelling evidence for their involvement in the complex network of immune responses and inflammatory diseases, thereby influencing diverse processes, including cytokine release, chemotaxis, signaling, mitogenesis, angiogenesis, wound repair, cell migration and adaptive immune induction (Allaker 2008; Kamysz et al. 2003; Koczulla et al. 2003; Shaykhiev et al. 2005; Zanetti 2004). All of this indicates that AMPs are multifunctional molecules of fundamental importance in host defense. Here we will review the roles of AMPs in the brain. These include: antimicrobial activity through different mechanisms, immunomodulatory activities linking innate to adaptive immune responses, and chemokine-like signaling activity (see Fig. 2), such as the interaction of β-defensins with certain chemokine receptors.

Antimicrobial Activity of AMPs in the Brain

AMPs have both direct and indirect antimicrobial activity contributing to brain defense against infection (Bergman et al. 2005; Brandenburg et al. 2008; Jeyakumar et al. 2009; Ostergaard et al. 2009). In the very few instances in which patients have been demonstrated to have defective host defense peptide expression, these individuals suffer from frequent infections. Inflammatory bowel diseases are characterized by localized deficiencies of antibacterial peptides and the defect in the expression and/or function of defensins could give rise to an increase in frequency and severity of colonic Crohn's disease (Fellermann et al. 2003; Ramasundara et al. 2009; Wehkamp et al. 2007).

CRAMP of the brain is active against the CNS pathogen *Neisseria meningitidis* and the peptide contributes to the known antibacterial activity of rat brain peptide/protein extracts. CRAMP is induced in endothelial cells of the BBB and in cells of the leptomeninges after meningococcal infection. CRAMP knockout mice were more susceptible to meningococcal infection at the blood brain barrier than

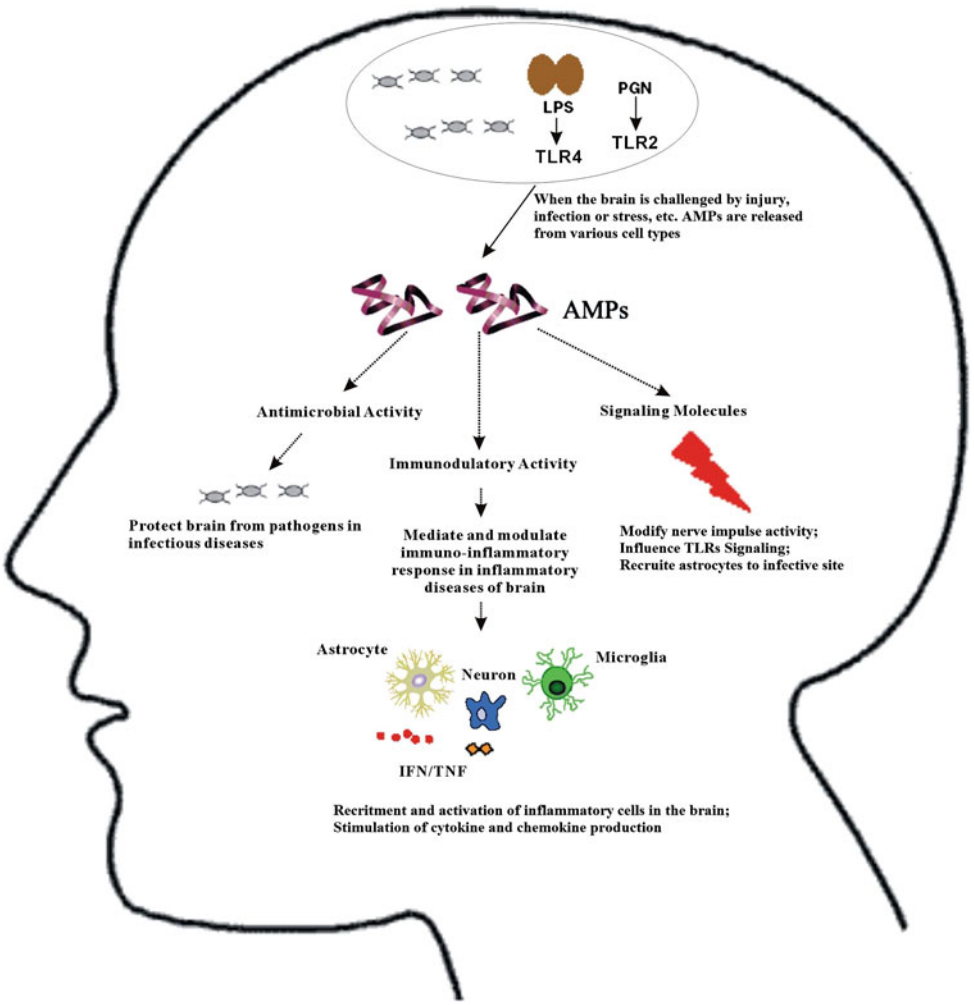

Fig. 2 Roles of antimicrobial peptides in the brain. AMPs are multifunctional molecules of fundamental importance in host defense. When the brain is challenged by injury, infection or stress, AMPs are released from various cell types and exert effects such as: antimicrobial activity, which can protect the brain from pathogens in infectious diseases; immunomodulatory activities, which can mediate and modulate immuno-inflammatory responses in inflammatory diseases of the brain; and chemokine-like signaling activity, which can modify nerve impulse activity and influence TLR signaling and recruitment of astrocytes to infective sites through different mechanisms, including cytokine release, chemotaxis, signaling, mitogenesis, angiogenesis, wound repair, cell migration or induction of adaptive immunity

wild-type mice. Moreover, results from in vivo experiments in mice demonstrated that CRAMP inhibits bacterial growth in blood, liver, and spleen early in meningococcal sepsis (Bergman et al. 2005; 2006). HBD-2 mRNA was detected in astrocyte cultures treated by LPS, suggesting that defensins may play a role in host defense against bacterial CNS pathogenesis (Hao et al. 2001). Moreover, the antimicrobial activity of synthetic hepcidin has been demonstrated and hepcidin might be involved in processes of iron homeostasis in the brain (Krause et al. 2000). Recently, several peptides with neural or neuroendocrine signaling functions have been shown to have potent antimicrobial activity (Brogden 2005). Direct antimicrobial activity of some neuropeptides, such as substance P and NPY, against a range of micro-organisms, has been demonstrated (Hansen et al. 2006; Lundy et al. 2008). Synthetic and recombinant DCD-1 peptide also exhibits antimicrobial activities against a wide range of microbial pathogens (Lai et al. 2005). These discoveries suggest that the brain might use these peptides as anti-infective agents (Li et al. 2006). The continuous use of chemical antibiotics has led to the appearance of multiresistant bacterial strains all over the world. Several human pathogens are now becoming resistant to a number of clinically significant antibiotics, causing a crisis in the treatment and management of infectious diseases and resulting in higher mortality. Therefore, it is imperative to search for alternatives to traditional antibiotics (Marshall and Arenas 2003; Cohen 2000). AMPs from various natural sources as well as novel synthetic antibacterial peptides represent a promising family of antibiotics that have stimulated research and clinical interest as new therapeutic options for infections caused by multidrug-resistant bacteria (Zaiou 2007).

Immunomodulatory Activity of AMPs in the Brain

AMPs have immunomodulatory activities, linking innate to adaptive immune responses. Inflammation is generally beneficial to the organism in limiting the survival and proliferation of invading pathogens, and promoting tissue survival, repair and recovery. The brain has distinctive features and is uniquely sensitive to inflammation. Inflammation in the brain is regularly seen in trauma, ischemia, infection, degeneration, and malignancy. Recent evidence suggests that inflammation and immune function in the brain may play a considerable role in the progression of many brain diseases, such as infections, e.g. meningitis, measles, cerebral malaria or multiple sclerosis (Brown and Hancock 2006; Selsted and Ouellete 2005; Yang et al. 2007; Schikorski et al. 2008; Scapini et al. 2000).

Defensins are small, cationic, cyclic peptides that are abundantly stored in granules of neutrophils and are modulators of immune function. They induce chemotactic activity in neutrophils and chemokinetic activity in macrophages. Neutrophils are a prominent immunologic infiltrate of ischemic lesions in vivo. There is striking evidence that the infiltration of activated PMNs into the injured parenchyma plays an important role in the pathology of cerebral ischemia. Neutrophils are an essential part of the innate immune system. Their cytoplasm contains granules and secretory vesicles that can release a wide range of microbicidal effector molecules, including AMPs, proteinases and others (Faurschou and Borregaard 2003). Neutrophils are not observed in the normal nervous system but are found in significant numbers at the site of injury in peripheral nerves (Zuo et al. 2003). Schluesener showed that defensins, constituting up to 5% of the total cellular protein of human neutrophils, are associated with neutrophil activation, such as morphological alterations and migration through the BBB (Schluesener and Meyermann 1995). Other studies have also shown that defensins stimulate mast cell degranulation, leading to locally increased vascular permeability, neutrophil accumulation and induction of epithelial synthesis of the potent neutrophil chemokine IL-8. Local inflammatory cascades can be further amplified by the stimulatory effects of neutrophil defensins on the production of macrophage proinflammatory cytokines, such as TNF and IL-1-β, and through the inhibition of IL-10 production (Chaly et al. 2000; Welling et al. 1998).

It is generally accepted that iron accumulates in specific brain areas which are preferentially targeted in neurodegenerative diseases such as AD and Parkinson's disease (PD) (Zecca et al. 2004) (Qian and Wang 1998). In PD, iron has been suggested to contribute to oxidative stress (Bush 2000), and, therefore, has been considered as an important factor in the pathogenesis of PD. Hepcidin is distributed widely throughout the brain and spinal cord, suggesting an essential role for hepcidin in iron metabolism of the CNS. LPS induced a significant increase in the hepcidin mRNA and protein in the cortex and substantia nigra, but not in hippocampus and striatum, indicating a regionally specific regulation.

Neuropeptides are widely distributed throughout the brain. In addition to their role in inflammation, for example in initiating and sustaining neurogenic inflammation (Hökfelt et al. 2003), neuropeptides have also been implicated in immune regulation (Bost 2004). A growing body of evidence now supports a role for neuropeptides in modulation of the immune response through direct AMP-like actions (Brogden et al. 2005). DCD, which was isolated from oxidatively stressed neural cell lines, promotes neural cell survival under oxidative conditions. Using serial analysis of gene expression, DCD was identified as a candidate oncogene of breast cancer (Porter et al. 2003).

There is a growing body of evidence suggesting that the immunomodulatory properties of these small, naturally occurring molecules might be harnessed for development as novel therapeutic agents. Further scrutiny of the biochemical and regulatory mechanisms of AMPs might lead to novel alternative approaches to the treatment of human brain disorders.

Signaling of AMPs in the Brain

The role of peptides as signaling molecules in the nervous system has been studied for more than 30 years. AMPs are involved in immune response modulation, not only through their antimicrobial activities, but also as signaling molecules (Salzet 2002). Notably, defensins are increasingly recognized as signaling molecules in adaptive immunity (De Leeuw and Lu 2007). Human defensins are potent inhibitors of protein kinase C (PKC), whereas they have little or no effect on the activity of myosin light chain kinase and protein kinase A (Charp et al. 1988). The specificity of kinase inhibition supports the notion that defensins are involved in particular signaling pathways (Kamysz et al. 2003).

The human homologue of rat CRAMP, LL-37, has the capacity to act as a chemokine, attracting immune cells via formyl peptide receptor like-1 (Niyonsaba et al. 2002; De Yang et al. 2000). Interestingly, this receptor is expressed by astrocytes. Thus, CRAMP could hypothetically function as a signaling molecule, recruiting astrocytes to a site of infection or injury. Furthermore, rabbit defensin has been reported to act as an agonist of slow sodium receptors on the membrane of rat spinal ganglion neurons, suggesting that this AMP can modify nerve impulse activity (Bergman et al. 2005). LL-37 was shown to influence TLR signaling in immune cells through interaction with the cellular membrane and epidermal growth factor receptor transactivation to increase intracellular Ca^{++} mobilization. Cathelicidin peptides increase cell migration and secretion of chemokines and other signaling molecules from activated cells (Schauber and Gallo 2008). Another AMP, the neutrophil granule derived peptide cap37 (cationic antimicrobial protein of 37 kDa), can also act as a signaling molecule, causing the upregulation of PKC activity (Pereira et al. 1996).

The functions of neuropeptides range from neurotransmitter to growth factor. They are present in glial cells, are hormones in the endocrine system, and messengers of the immune system. Much evidence indicates that neuropeptides are of particular importance when the nervous system is challenged (by stress, injury, or drug abuse) (Wu et al. 2003; Moody and Merali 2004). This evidence demonstrates that NAMPs have the potential to be involved in many stages of a proinflammatory response as signaling molecules and play a more general role in the strategy of immune protection.

Concluding remarks

Research in the field of AMPs has developed over the past years. AMPs with multifaceted activities represent exceptional candidates for the development of novel therapeutic agents to inhibit microbial pathogenesis and to modulate host immune responses, and they might become diagnostic markers. AMPs may offer a solution to the problem of drug resistance and hold promise for development of new therapeutic agents. Furthermore, elucidation of the basic molecular structure and regulation of AMPs will increase knowledge of their involvement in shaping the innate immune response of the brain, provide new insights into the intrinsic capacity of the brain to face pathogenic insults, and facilitate the identification of molecular targets for therapeutic interventions in a variety of immune-mediated pathogenic processes, such as neuroinflammatory and neurodegenerative diseases.

References

Agerberth B, Gunne H, Odeberg J et al (1995) FALL-39, a putative human peptide antibiotic, is cysteine-free and expressed in bone marrow and testis. Proc Natl Acad Sci USA 92:195–199

Akira S, Takeda K (2004) Toll-like receptor signaling. Nat Rev Immunol 4:499–511

Allaker RP (2008) Host defense peptides-a bridge between the innate and adaptive immune responses. Trans R Soc Trop Med Hyg 102:3–4

Aravalli RN, Peterson PK, Lokensgard JR (2007) Toll-like receptors in defense and damage of the central nervous system. J Neuroimmune Pharmacol 2:297–312

Bals R (2000) Epithelial antimicrobial peptides in host defense against infection. Respir Res 1:141–150

Bals R, Wang X, Zasloff M et al (1998) The peptide antibiotic LL-37/hCAP-18 is expressed in epithelia of the human lung where it has broad antimicrobial activity at the airway surface. Proc Natl Acad Sci USA 95:9541–9546

Baranowska B (2009) Bombesin modulates the control of energy homeostasis and pituitary hormone release. Neuro Endocrinol Lett 30:3–5

Barton GM, Medzhitov R (2003) Toll-like receptor signaling pathways. Science 300:1524–1525

Becher B, Bechmann I, Greter M (2006) Antigen presentation in autoimmunity and CNS inflammation: how T lymphocytes recognize the brain. J Mol Med 84:532–543

Behar O, Ovadia H, Polakiewicz RD et al (1994) Lipopolysaccharide induces proenkephalin gene expression in rat lymph nodes and adrenal glands. Endocrinology 134:475–481

Beisswenger C, Bals R (2005) Functions of antimicrobial peptides in host defense and immunity. Curr Protein Pept Sci 6:255–264

Benarroch EE (2009) Neuropeptide Y: its multiple effects in the CNS and potential clinical significance. Neurology 72:1016–1020

Bergman P, Termén S, Johansson L et al (2005) The antimicrobial peptide rCRAMP is present in the central nervous system of the rat. J Neurochem 93:1132–1140

Bergman P, Johansson L, Wan H et al (2006) Induction of the antimicrobial peptide CRAMP in the blood-brain barrier and meninges after meningococcal infection. Infect Immun 74:6982–6991

Boman HG (1995) Peptide antibiotics and their role in innate immunity. Annu Rev Immunol 13:61–92

Bost KL (2004) Tachykinin-mediated modulation of the immune response. Front Biosci 9:3331–3332

Bowdish DM, Davidson DJ, Hancock RE (2006) Immunomodulatory properties of defensins and cathelicidins. Curr Top Microbiol Immunol 306:27–66

Braff MH, Gallo RL (2006) Antimicrobial peptides: an essential component of the skin defensive barrier. Curr Top Microbiol Immunol 306:91–110

Brandenburg LO, Varoga D, Nicolaeva N et al (2008) Role of glial cells in the functional expression of LL-37/rat cathelin-related antimicrobial peptide in meningitis. J Neuropathol Exp Neurol 67:1041–1054

Brogden KA (2005) Antimicrobial peptides: pore formers or metabolic inhibitors in bacteria? Nat Rev Microbiol 3:238–250

Brogden KA, Ackermann M, McCray PB Jr et al (2003) Antimicrobial peptides in animals and their role in host defences. Int J Antimicrob Agents 22:465–478

Brogden KA, Guthmiller JM, Salzet M et al (2005) The nervous system and innate immunity: the neuropeptide connection. Nat Immunol 6:558–564

Brown KL, Hancock RE (2006) Cationic host defense (antimicrobial) peptides. Curr Opin Immunol 18:24–30

Bulet P, Stöcklin R, Menin L (2004) Anti-microbial peptides: from invertebrates to vertebrates. Immunol Rev 198:169–184

Bush AI (2000) Metals and neuroscience. Curr Opin Chem Biol 4:184–191

Chaly YV, Paleolog EM, Kolesnikova TS et al (2000) Neutrophil alpha-defensin human neutrophil peptide modulates cytokine production in human monocytes and adhesion molecule expression in endothelial cells. Eur Cytokine Netw 11:257–266

Chan DI, Prenner EJ, Vogel HJ (2006) Tryptophan- and arginine-rich antimicrobialpeptides: structures and mechanisms of action. Biochim Biophys Acta 1758:1184–1202

Charp PA, Rice WG, Raynor RL et al (1988) Inhibition of protein kinase C by defensins, antibiotic peptides from human neutrophils. Biochem Pharmacol 37:951–956

Chen H, Xu Z, Peng L et al (2006) Recent advances in the research and development of human defensins. Peptides 27:931–940

Chromek M, Slamová Z, Bergman P et al (2006) The antimicrobial peptide cathelicidin protects the urinary tract against invasive bacterial infection. Nat Med 12:636–641

Cohen ML (2000) Changing patterns of infectious disease. Nature 406:762–767

Cowland JB, Johnsen AH, Borregaard N (1995) hCAP-18, a cathelin/pro-bactenecin-like protein of human neutrophil specific granules. FEBS Lett 368:173–176

Cunningham TJ, Jing H, Akerblom I et al (2002) Identification of the human cDNA for new survival/evasion peptide (DSEP): studies in vitro and in vivo of overexpression by neural cells. Exp Neurol 177:32–39

De Leeuw E, Lu W (2007) Human defensins: turning defense into offense? Infect Disord Drug Targets 7:67–70

De Smet K, Contreras R (2005) Human antimicrobial peptides: defensins, cathelicidins and histatins. Biotechnol Lett 27:1337–1347

Dringen R, Bishop GM, Koeppe M et al (2007) The pivotal role of astrocytes in the metabolism of iron in the brain. Neurochem Res 32:1884–1890

Duits LA, Ravensbergen B, Rademaker M et al (2002) Expression of beta-defensin 1 and 2 mRNA by human monocytes, macrophages and dendritic cells. Immunology 106:517–525

El Karim IA, Linden GJ, Orr DF et al (2008) Antimicrobial activity of neuropeptides against a range of micro-organisms from skin, oral, respiratory and gastrointestinal tract sites. J Neuroimmunol 200:11–16

Falsig J, van Beek J, Hermann C et al (2008) Molecular basis for detection of invading pathogens in the brain. J Neurosci Res 86:1434–1447

Fang XM, Shu Q, Chen QX et al (2003) Differential expression of alpha- and beta-defensins in human peripheral blood. Eur J Clin Invest 33:82–87

Farina C, Aloisi F, Meinl E (2007) Astrocytes are active players in cerebral innate immunity. Trends Immunol 28:138–145

Faurschou M, Borregaard N (2003) Neutrophil granules and secretory vesicles in inflammation. Microbes Infect 5:1317–1327

Fellermann K, Wehkamp J, Herrlinger KR et al (2003) Crohn's disease: a defensin deficiency syndrome? Eur J Gastroenterol Hepatol 15:627–634

Galea I, Bechmann I, Perry VH (2007) What is immune privilege (not)? Trends Immunol 28:12–18

Ganz T (2003) Defensins: antimicrobial peptides of innate immunity. Nat Rev Immunol 3:710–720

Ganz T (2006) Hepcidin and its role in regulating systemic iron metabolism. Hematology Am Soc Hematol Educ Program 29–35:507

Giuliani A, Pirri G, Nicoletto SF (2007) Antimicrobial peptides: an overview of a promising class of therapeutics. Cent Eur J Biol 2:1–33

Hancock RE, Diamond G (2000) The role of cationic antimicrobial peptides in innate host defences. Trends Microbiol 8:402–410

Hancock RE, Sahl HG (2006) Antimicrobial and host-defense peptides as new anti-infective therapeutic strategies. Nat Biotechnol 24:1551–1557

Hanisch UK (2002) Microglia as a source and target of cytokines. Glia 40:140–155

Hänninen MM, Haapasalo J, Haapasalo H et al (2009) Expression of iron-related genes in human brain and brain tumors. BMC Neurosci 10:36

Hansen CJ, Burnell KK, Brogden KA (2006) Antimicrobial activity of substance P and neuropeptide Y against laboratory strains of bacteria and oral microorganisms. J Neuroimmunol 177:215–218

Hao HN, Zhao J, Lotoczky G et al (2001) Induction of human beta-defensin-2 expression in human astrocytes by lipopolysaccharide and cytokines. J Neurochem 77:1027–1035

Hase K, Murakami M, Iimura M et al (2003) Expression of LL-37 by human gastric epithelial cells as a potential host defense mechanism against Helicobacter pylori. Gastroenterology 125:1613–1625

Hiratsuka T, Nakazato M, Date Y et al (2001) Nucleotide sequence and expression of rat beta-defensin-1: its significance in diabetic rodent models. Nephron 88:65–70

Hirsch T, Jacobsen F, Steinau HU et al (2008) Host defense peptides and the new line of defence against multiresistant infections. Protein Pept Lett 15:238–243

Hökfelt T, Bartfai T, Bloom F (2003) Neuropeptides: opportunities for drug discovery. Lancet Neurol 8:463–472

Hoskin DW, Ramamoorthy A (2008) Studies on anticancer activities of antimicrobial peptides. Biochim Biophys Acta 1778:357–375

Huttner KM, Kozak CA, Bevins CL (1997) The mouse genome encodes a single homolog of the antimicrobial peptide human beta defensin1. FEBS Lett 413:45–49

Iimura M, Gallo RL, Hase K et al (2005) Cathelicidin mediates innate intestinal defense against colonization with epithelial adherent bacterial pathogens. J Immunol 174:4901–4907

Jeyakumar M, Williams I, Smith D et al (2009) Critical role of iron in the pathogenesis of the murine gangliosidoses. Neurobiol Dis 34:406–416

Kamysz W, Okrój M, Łukasiak J (2003) Novel properties of antimicrobial peptides. Acta Biochim Pol 50:461–469

Kapetanovic R, Cavaillon JM (2007) Early events in innate immunity in the recognition of microbial pathogens. Expert Opin Biol Ther 7:907–918

Kim KS (2003) Pathogenesis of bacterial meningitis: from bacteraemia to neuronal injury. Nat Rev Neurosci 4:376–385

Klotman ME, Chang TL (2006) Defensins ininnate antiviral immunity. Nat Rev Immunol 6:447–456

Koczulla AR, Bals R (2003) Antimicrobial peptides: current status and therapeutic potential. Drugs 63:389–406

Koczulla R, von Degenfeld G, Kupatt C et al (2003) An angiogenic role for the human peptide antibioticLL-37/hCAP-18. J Clin Invest 111:1665–1672

Krause A, Neitz S, Mägert HJ et al (2000) LEAP-1, a novel highly disulfidebonded human peptide, exhibits antimicrobial activity. FEBS Lett 480:147–150

Lai Y, Gallo RL (2009) AMPed up immunity: how antimicrobial peptides have multiple roles in immune defense. Trends Immunol 30:131–141

Lai YP, Peng YF, Zuo Y et al (2005) Functional and structural characterization of recombinant dermcidin1-L, a human antimicrobial peptide. Biochem Biophys Res Commun 328:243–250

Lee NJ, Herzog H (2009) NPY regulation of bone remodelling. Neuropeptides 43:457–463

Lehrer RI, Ganz T (2002) Cathelicidins: a family of endogenous antimicrobial peptides. Curr Opin Hematol 9:18–22

Li J, Xu X, Yu H et al (2006) Direct antimicrobial activities of PR-bombesin. Life Sci 78:1953–1956

Liu AY, Destoumieux D, Wong AV et al (2002) Human beta-defensin-2 production in keratinocytes is regulated by interleukin-1, bacteria, and the state of differentiation. J Invest Dermatol 118:275–281

Lundy FT, Linden GJ (2004) Neuropeptides and neurogenic mechanisms in oral and periodontal inflammation. Crit Rev Oral Biol Med 15:82–98

Lundy FT, Nelson J, Lockhart D et al (2008) Antimicrobial activity of truncated alpha-defensin (human neutrophil peptide (HNP)-1) analogues without disulphide bridges. Mol Immunol 45:190–193

Mader JS, Hoskin DW (2006) Cationic antimicrobial peptides as novel cytotoxic agents for cancer treatment. Expert Opin Investig Drugs 15:933–946

Mallow EB, Harris A, Salzman N et al (1996) Human enteric defensins. Gene structure and developmental expression. J Biol Chem 271:4038–4045

Marshall SH, Arenas G (2003) Antimicriobial peptides: a natural alternative to chemical antibiotics and a potential for applied biotechnology. Electron J Biotechnol 6:271–284

Maxwell AI, Morrison GM, Dorin JR (2003) Rapid sequence divergence in mammalian-defensins by adaptive evolution. Mol Immunol 40:413–421

Menendez A, Brett Finlay B (2007) Defensins in the immunology of bacterial infections. Curr Opin Immunol 19:385–391

Metz-Boutigue MH, Kieffer AE, Goumon Y et al (2003) Innate immunity: involvement of new neuropeptides. Trends Microbiol 11:585–592

Moody TW, Merali Z (2004) Bombesin-like peptides and associated receptors within the brain: distribution and behavioral implications. Peptides 25:511–520

Murakami M, Ohtake T, Dorschner RA et al (2002a) Cathelicidin antimicrobial peptides are expressed in salivary glands and saliva. J Dent Res 81:845–850

Murakami M, Ohtake T, Dorschner RA et al (2002b) Cathelicidin anti-microbial peptide expression in sweat, an innate defense system for the skin. J Invest Dermatol 119:1090–1095

Murakami M, Dorschner RA, Stern LJ et al (2005) Expression and secretion of cathelicidin antimicrobial peptides in murine mammary glands and human milk. Pediatr Res 57:10–15

Nakayama K, Okamura N, Arai H et al (1999) Expression of human beta-defensin-1 in the choroid plexus. Ann Neurol 45:685

Nemeth E, Rivera S, Gabayan V et al (2004) IL-6 mediates hypoferremia of inflammation by inducing the synthesis of the iron regulatory hormone hepcidin. J Clin Invest 113:1271–1276

Nguyen MD, Julien JP, Rivest S (2002) Innate immunity: the missing link in neuroprotection and neurodegeneration? Nat Rev Neurosci 3:216–227

Nijnik A, Hancock RE (2009) The roles of cathelicidin LL-37 in immune defences and novel clinical applications. Curr Opin Hematol 16:41–47

Niyonsaba F, Iwabuchi K, Someya A et al (2002) A cathelicidin family of human antibacterial peptide LL-37 induces mast cell chemotaxis. Immunology 106:20–26

Niyonsaba F, Ushio H, Nakano N et al (2007) Antimicrobial peptides human beta-defensins stimulate epidermal keratinocyte migration, proliferation and production of proinflammatory cytokines and chemokines. J Invest Dermatol 127:594–604

Niyonsaba F, Suzuki A, Ushio H et al (2009) The human antimicrobial peptide dermcidin activates normal human keratinocytes. Br J Dermatol 160:243–249

Oates PS (2007) The role of hepcidin and ferroportin in iron absorption. Histol Histopathol 22:791–804

Ostergaard C, Sandvang D, Frimodt-Møller N et al (2009) High cerebrospinal fluid (CSF) penetration and potent bactericidal activity in CSF of NZ2114, a novel plectasin variant, during experimental pneumococcal meningitis. Antimicrob Agents Chemother 53:1581–1585

Pazgiera M, Hoover DM, Yang D et al (2006) Human beta-defensins. Cell Mol Life Sci 63:1294–1313

Pereira HA, Moore P, Grammas P (1996) CAP37, a neutrophil granule-derived protein stimulates protein kinase C activity in endothelial cells. J Leukoc Biol 60:415–422

Pestonjamasp VK, Huttner KH, Gallo RL (2001) Processing site and gene structure for the murine antimicrobial peptide CRAMP. Peptides 22:1643–1650

Polazzi E, Contestabile A (2002) Reciprocal interactions between microglia and neurons: from survival to neuropathology. Rev Neurosci 13:221–242

Porter D, Weremowicz S, Chin K et al (2003) A neural survival factor is a candidate oncogene in breast cancer. Proc Nat Acad Sci USA 100:10931–10936

Qian ZM, Wang Q (1998) Expression of iron transport proteins and excessive iron accumulation in the brain in neurodegenerative disorders. Brain Res Brain Res Rev 27:257–267

Radek K, Gallo R (2007) Antimicrobial peptides: natural effectors of the innate immune system. Semin Immunopathol 29:27–43

Ramasundara M, Leach ST, Lemberg DA et al (2009) Defensins and inflammation: the role of defensins in inflammatory bowel disease. J Gastroenterol Hepatol 24:202–208

Ransohoff RM, Kivisäkk P, Kidd G (2003) Three or more routes for leukocyte migration into the central nervous system. Nat Rev Immunol 3:569–581

Rotem S, Mor A (2009) Antimicrobial peptide mimics for improved therapeutic properties. Biochim Biophys Acta 1788:1582–1592

Salzet M (2002) Antimicrobial peptides are signaling molecules. Trends Immunol 23:283–284

Salzet M, Tasiemski A (2001) Involvement of pro-enkephalin-derived peptides in immunity. Dev Comp Immunol 25:177–185

Sang Y, Blecha F (2008) Antimicrobial peptides and bacteriocins: alternatives to traditional antibiotics. Anim Health Res Rev 9:227–235

Scapini P, Lapinet-Vera JA, Gasperini S et al (2000) The neutrophil as a cellular source of chemokines. Immunol Rev 177:195–203

Schauber J, Gallo RL (2008) Antimicrobial peptides and the skin immune defense system. J Allergy Clin Immunol 122:261–266

Schauber J, Gallo RL (2009) Antimicrobial peptides and the skin immune defense system. J Allergy Clin Immunol 124(3 suppl 2):R13–R18

Schikorski D, Cuvillier-Hot V, Leippe M et al (2008) Microbial challenge promotes the regenerative process of the injured central nervous system of the medicinal leech by inducing the synthesis of antimicrobial peptides in neurons and microglia. J Immunol 181:1083–1095

Schittek B, Hipfel R, Sauer B et al (2001) Dermcidin: a novel human antibiotic peptide secreted by sweat glands. Nat Immunol 2:1133–1137

Schluesener H, Meyermann R (1995) Neutrophilic defensins penetrate the blood-brain barrier. J Neurosci Res 42:718–723

Schneider JJ, Unholzer A, Schaller M et al (2005) Human defensins. J Mol Med 83:587–595

Scholzen T, Armstrong CA, Bunnett NW et al (1998) Neuropeptides in the skin: interactions between the neuroendocrine and the skin immune systems. Exp Dermatol 7:81–96

Selsted ME, Ouellete AJ (2005) Mammalian defensins in the antimicrobial immune response. Nat Immunol 6:551–557

Senyürek I, Paulmann M, Sinnberg T et al (2009) Dermcidin-derived peptides show a different mode of action than the cathelicidin LL-37 against Staphylococcus aureus. Antimicrob Agents Chemother 53:2499–2509

Shaykhiev R, Beisswenger C, Kandler K et al (2005) Human endogenous antibiotic LL-37 stimulates airway epithelial cell proliferation and wound closure. Am J Physiol Lung Cell Mol Physiol 289:L842–L848

Simard AR, Soulet D, Gowing G et al (2006) Bone marrow-derived microglia play a critical role in restricting senile plaque formation in Alzheimer's disease. Neuron 49:489–502

Skalicky JJ, Selsted ME, Pardi A (1994) Structure and dynamics of the neutrophil defensins NP-2, NP-5, and HNP-1: NMR studies of amide hydrogen exchange kinetics. Proteins 20:52–67

Steiner H, Hultmark D, Engstrom A et al (2009) Sequence and specificity of two antibacterial proteins involved in insect immunity. J Immunol 182:6635–6637

Stolzenberg ED, Anderson GM, Ackermann MR et al (1997) Epithelial antibiotic induced in states of disease. Proc Natl Acad Sci USA 94:8686–8690

van 't Hof W, Veerman EC, Helmerhorst EJ et al (2001) Antimicrobial peptides: properties and applicability. Biol Chem 382:597–619

van Wetering S, Tjabringa GS, Hiemstra PS (2005) Interactions between neutrophil-derived antimicrobial peptides and airway epithelial cells. J Leukoc Biol 77:444–450

Vouldoukis I, Shai Y, Nicolas P et al (1996) Broad spectrum antibiotic activity of the skin-PYY. FEBS Lett 380:237–240

Wang Z, Corey E, Hass GM et al (2003) Expression of the human cachexia-associated protein (HCAP) in prostate cancer and in a prostate cancer animal model of cachexia. Int J Cancer 105:123–129

Wang Q, Du F, Qian ZM et al (2008) Lipopolysaccharide induces a significant increase in expression of iron regulatory hormone hepcidin in the cortex and substantia nigra in rat brain. Endocrinology 149:3920–3925

Wehkamp J, Schmid M, Stange EF (2007) Defensins and other antimicrobial peptides in inflammatory bowel disease. Curr Opin Gastroenterol 23:370–378

Weinberg A, Krisanaprakornkit S, Dale BA (1998) Epithelial antimicrobial peptides: review and significance for oral applications. Crit Rev Oral Biol Med 9:399–414

Welling MM, Hiemstra PS, van den Barselaar MT et al (1998) Antibacterial activity of human neutrophil defensins in experimental infections in mice is accompanied by increased leukocyte accumulation. J Clin Invest 102:1583–1590

Wu Q, Wen T, Lee G et al (2003) Developmental control of foraging and social behavior by the Drosophila neuropeptide Y-like system. Neuron 39:147–161

Yamasaki K, Gallo RL (2008) Antimicrobial peptides in human skin disease. Eur J Dermatol 18:11–21

Yang De, Chen Q, Schmidt AP et al (2000) LL-37, the neutrophil granule- and epithelial cell-derived cathelicidin, utilizes formyl peptide receptor-like 1 (FPRL1) as a receptor to chemoattract human peripheral blood neutrophils, monocytes, and T cells. J Exp Med 192:1069–1074

Yang D, Biragyn A, Kwak LW et al (2002) Mammalian defensins in immunity: more than just microbicidal. Trends Immunol 23:291–296

Yang D, Liu ZH, Tewary P et al (2007) Defensin participation in innate and adaptive immunity. Curr Pharm Des 13:3131–3139

Zaiou M (2007) Multifunctional antimicrobial peptides: therapeutic targets in several human diseases. J Mol Med 85:317–329

Zanetti M (2004) Cathelicidins, multifunctional peptides of the innate immunity. J Leukoc Biol 75:39–48

Zanetti M (2005) The role of cathelicidins in the innate host defenses of mammals. Curr Issues Mol Biol 7:179–196

Zasloff M (2002) Antimicrobial peptides of multicellular organisms. Nature 415:389–395

Zecca L, Youdim MB, Riederer P et al (2004) Iron, brain aging and neurodegenerative disorders. Nat Rev Neurosci 5:863–873

Zechel S, Huber-Wittmer K, und Halbach O (2006) Distribution of the iron-regulating protein hepcidin in the murine central nervous system. J Neurosci Res 84:790–800

Zhang L, Falla TJ (2009) Host defense peptides for use as potential therapeutics. Curr Opin Investig Drugs 10:164–171

Zhang G, Wu H, Shi J et al (1998) Molecular cloning and tissue expression of porcine beta-defensin-1. FEBS Lett 424:37–40

Zhu S (2008) Discovery of six families of fungal defensin-like peptides provides insights into origin and evolution of the CSalphabeta defensins. Mol Immunol 45:828–838

Zuo Y, Perkins NM, Tracey DJ et al (2003) Inflammation and hyperalgesia induced by nerve injury in the rat: a key role of mast cells. Pain 105:467–479