Current Approach in the Management of Inflammation using Peptide Therapy: A Comprehensive Review

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Abstract: Peptide therapy is a relatively newer approach in treating inflammation. In recent years, peptides have been shown to play a role in modulating inflammatory responses. These small molecules are produced naturally by our bodies and are involved in many physiological processes including immune function, blood coagulation, hormone secretion, neurotransmission, and pain perception. However, these endogenous peptides may not always act in a manner consistent with their natural roles. Therefore, they can be modified chemically to increase their therapeutic potential. Peptides have been studied extensively over the past few decades and some have already entered clinical trials. In this review, we discuss the current approaches in using peptides for anti-inflammatory therapies.

Keywords: **Peptide Therapy, Peptide Therapy for Inflammation, Inflammation**

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Introduction

Inflammation is the body's natural response to injury or infection. It is a protective mechanism that helps clear out damaged tissue and repairs it [1]. However, when inflammation becomes chronic, it can lead to serious health problems such as heart disease, diabetes, arthritis, asthma, cancer, Alzheimer's disease, depression, and more [2].

Inflammation is the body's response to injury or infection. It involves a complex series of

events that can be triggered by physical, chemical, and biological agents [3]. The inflammatory process begins with the activation of resident cells in the affected area (e.g., macrophages) and the release of various chemicals such as histamine, serotonin, bradykinin, prostaglandins, leukotriene, etc.). These chemicals cause vasodilation, increased vascular permeability, pain, swelling, heat, and redness at the site of inflammation [4].

The primary function of inflammation is tissue repair. However, if the inflammatory response persists for an extended period, it may lead to chronic inflammation, damaging healthy tissues [5]. This inflammation occurs when the immune system attacks normal tissues instead of invading pathogens. Chronic inflammation is associated with many diseases, including arthritis, asthma, atherosclerosis, cancer, diabetes, heart disease, multiple sclerosis, obesity, osteoporosis, psoriasis, rheumatoid arthritis, stroke, ulcers, and viral infections [6].

In addition to its role in healing damaged tissues, inflammation also plays an essential role in cancer development. Inflammation is a complex process that involves many cell types and mediators [7]. The inflammatory response can be divided into phases: 1) initiation, 2) amplification, and 3) resolution. In the initiation phase, tissue damage or infection leads to the release of chemical signals (e.g., cytokines) by resident cells such as macrophages and fibroblasts) [8].

These signals stimulate other cells to produce more proinflammatory chemicals called chemokines which attract additional leukocytes to the site of injury or infection. This results in the infiltration of neutrophils, monocytes/macrophages, eosinophil, basophils, mast cells, lymphocytes, and platelets into the area [9].

Inflammation is a typical immune defense that is generated from the immune system responding to pathogens and infection [10]. Inflammation can cause various chronic diseases, such as inflammatory bowel diseases (IBD), asthma, cancer, cardiovascular diseases, obesity, and diabetes. IBD can damage the intestinal mucosa with chronic inflammatory disorders, including ulcerative colitis (UC) and Crohn's disease (CD) [11].

The Role of the Immune System

The immune system is a complex network of cells and molecules that protect the body from foreign invaders, such as bacteria or viruses. The innate immune response is

initiated by pathogen-associated molecular patterns (PAMPs) that are recognized by pattern recognition receptors (PRRs). PRRs include Toll-like receptors (TLRs), NOD-like receptors (NLRs) and RIG-I-like receptors (RLRs) [12]. TLR4 recognizes lipopolysaccharide (LPS) derived from Gram-negative bacteria and activates NFκB via MyD88 to induce proinflammatory cytokines (PC). NLRP3 inflammasome activation leads to caspase-1 cleavage of IL-1β and subsequent secretion into the extracellular space. In contrast, RLRs recognize viral RNA and activate IRF3/7 to produce type I IFNs [11].

Innate immunity also plays a vital role in tissue homeostasis. For example, macrophages engulf apoptotic cells and remove cellular debris, thereby maintaining tissue integrity. Macrophage depletion results in increased susceptibility to infection and inflammation [13]. In addition, the phagocytic activity of macrophages is essential for the clearance of pathogens from tissues. The importance of macrophage function has been demonstrated by studies showing that mice with a defect in their ability to clear apoptotic cells develop severe autoimmune disease [14].

The innate immune system provides immediate protection against invading microbes through the recognition of pathogen-associated molecular patterns (PAMPs) by germline-encoded pattern recognition receptors (PRRs) [15]. PRR activation leads to the rapid induction of proinflammatory cytokines and chemokines, essential for initiating an effective adaptive immune response. In addition to their role in host defense, inflammatory mediators can contribute to tissue damage during acute inflammation or chronic diseases such as rheumatoid arthritis (RA) [16].

Toll-like receptor 4 (TLR4), one of the best-characterized members of the TLR family, is expressed on antigen-presenting cells (APCs), including macrophages, dendritic cells (DCS), B cells, and T cells) [17]. Upon activation by its ligands, TLR4 initiates a signaling cascade that leads to the production of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin 1β (IL-1β), IL-6, and type I IFNs [18].

The role of TLR4 in innate immunity has been extensively studied. However, the function of TLR4 in adaptive immune responses remains unclear [19].

TLRs are a family of pattern recognition receptors recognize pathogen-associated molecular patterns expressed on microorganisms [20]. The first identified member of the TLR family was TLR2, which recognizes bacterial lipoproteins. Subsequently, it was found that TLR2 also recognizes mycoplasma. Recognizing these pathogens by TLRs is a powerful mechanism for initiating innate immunity [21].

Current Aspects of Peptides Therapy

Peptide therapy is a new treatment modality that has been developed in recent years. It is based on synthetic or recombinant peptides to treat diseases by stimulating specific receptors and inhibiting other proteins involved in disease pathogenesis [22]. Peptide drugs are usually small molecules that can be easily synthesized and purified. They have several advantages over conventional therapeutic agents, such as high specificity for target cells, low toxicity, and the ability to penetrate cell membranes. Peptide drugs also exhibit fewer side effects than traditional chemotherapeutic agents [23].

Peptide drugs can be classified into two groups: agonists and antagonists. Agonist peptides mimic natural ligands and activate their cognate receptors, whereas antagonist peptides bind with their receptor but do not stimulate it. In addition, some peptides act as both agonists and antagonists depending upon the concentration used [24].

The development of peptide drugs against various human diseases including cancer, diabetes mellitus (DM), rheumatoid arthritis (RA), multiple sclerosis (MS), Alzheimer's disease (AD), Parkinson's disease (PD), and cardiovascular diseases (CVD). We have also described the current status of peptide drug development and prospects [25].

There are three primary categories of therapeutic peptides. Native, analog, and heterologous peptides are the three categories that can be used to classify therapeutic peptides. Most peptides being tested in clinical trials are analog peptides, which have sequences modified to increase their therapeutic potential [26]. This ability has become mainly focused on the intensive search for therapeutic solutions during the ongoing COVID-19 pandemic. Therapeutic peptides can also function as antivirals, targeting HIV, influenza, or hepatitis by inhibiting the replication cycle. The ability has become mainly focused on the intensive search for therapeutic solutions [27].

Through its viral spike protein, the SARS-CoV-2 virus infects host cells. It takes over their functions by binding to the human angiotensin-converting enzyme 2 (ACE2) receptor on the cell surface [28]. As a result, various groups are looking into how peptides could be used as PPI disruptors because they are better at disrupting the broad surface interactions involved than small-molecule inhibitors [29].

Peptides as Therapeutic Agents for Inflammatory-Related Diseases

The development of peptide-based therapeutics has significantly focused on the pharmaceutical industry over the past decade [30]. The advantages of peptides include their high specificity and affinity, low toxicity, ease of chemical synthesis, and stability in proteolytic degradation. These properties have led to using peptides as therapeutic agents for various diseases, including cancer, diabetes, cardiovascular disease, arthritis, and neurodegenerative disorders [31].

One approach to developing peptide-based drugs is to design small molecules that mimic the activity of natural peptides. This strategy was first applied by Hruby et al., who designed a series of nonpeptidic compounds based on the structure of calcitonin [32]. Hormones produced by thyroid C cells regulate calcium homeostasis. They consist of 32 amino acids, two disulfide bonds, and an N-terminal amine group. There are three isoforms in humans: alpha, beta, and gamma. Alpha-calcitonin inhibits bone resorption, while beta-calcitonin stimulates bone formation. Gamma-calcitonin has no known function in the body [33].

Calcitonins are therapeutic agents for osteoporosis treatment because they inhibit bone resorption. However, calcitonins also cause hypercalcemia, which can be problematic when treating cancer or multiple myeloma patients. The side effects associated with using calcitonins include nausea, vomiting, and diarrhea [34].

Several non-peptide compounds have been reported to act as CGRP receptor antagonists, such as those disclosed in WO 99/05131, WO 00/39127, WO 01/44215, WO 02/083625, WO 03/011870, WO 03/037327, WO 04/078 [35].

The present invention relates to novel heterocyclic derivatives, which help treat and prevent various diseases. These include conditions associated with smooth muscle contraction, fibrosis, inflammation, pain,

migraine, and other conditions mediated by CGRP receptors [36].

Advantage of Peptide-Based Therapy over Antibody-based Therapy

Antibiotics as therapeutic agents have been a significant success story in cancer treatment [37]. The first antibody approved for clinical use was rituximab, which targets CD20 on B cells and is used to treat non-Hodgkin's lymphoma (NHL). Since then, many other monoclonal antibodies have entered the clinic and are being tested in multiple indications [37].

Antibodies can be produced by recombinant DNA technology using mammalian cell lines or by chemical synthesis. The chemical synthesis of an antibody requires the assembly of at least six polypeptides: two identical light chains and two identical heavy chains [38]. Each chain contains four regions—a variable region that determines antigen-binding specificity, a constant region that provides stability and effector functions, and a hinge region connecting them. The variable regions of each chain contain three hypervariable loops called complementarity-determining regions (CDRs). These loops form the surface of the antigen-binding site and determine the specificity of the interaction with antigens. In addition, five framework regions (FRs) provide structural support and help maintain the conformation of the variable regions [38].

The structure of an antibody molecule is shown schematically above. Antibody molecules consist of two identical light chains and two identical heavy chains linked together by disulfide bonds [39].

An antibody molecule consists of two identical light chains (green) and two identical heavy chains (blue). Each chain consists of 4 main domains: VL (light chain variable domain), CL (light chain constant domain), VH (heavy chain variable domain), and CH1 (hinge domain). The variable regions of each of these domains are encoded by different genes [40].

The antibody is a protein that binds to antigens, such as bacteria or viruses, through its antigen-binding site. Antibodies are produced in the immune system's B cells. They circulate in the blood and lymphatic systems, where they can bind to foreign substances, including bacteria and viruses, and mark them for destruction by other parts of the body's immune system [41].

Peptides and Peptidomimetics as Modulators of Inflammation

Inflammatory diseases are a significant cause of morbidity and mortality worldwide. Developing new therapeutic strategies for treating inflammatory disorders is an important goal in biomedical research. In recent years, peptide-based drugs have emerged promising candidates for treating various human diseases [42].

These molecules can be divided into two groups: (i) small-molecule mimetics of natural products or endogenous ligands; and (ii) synthetic peptides that mimic the structure of proteins [43].

The cyclic nonapeptide thymopentin was initially isolated from bovine thymus glands and has been used clinically to treat immune deficiency since 1986 [44]. Thymopentin is a synthetic peptide of the sequence H-Tyr-D-Thr-Ala-Lys-Pro-Val-Arg-Ser-Cys-Lys-OH, which corresponds to amino acids 1 through 21 of bovine thymopoietin (BTP) [43].

Thymopentin is also known as TP5. Thymopentin stimulates T lymphocytes in vitro by binding to specific receptors on their surface. It is currently being investigated for use in treating autoimmune diseases such as rheumatoid arthritis and multiple sclerosis [45].

Thymopentin has been administered orally or parenterally to patients with immune deficiencies, including AIDS, but it has not yet been approved for this indication. Thymopentin has been used experimentally to treat various conditions, including cancer, diabetes, and allergies. Clinical studies have shown that thymopentin is ineffective in cancer chemotherapy, even though tumor growth is significantly suppressed in mice treated with thymopentin [46].

Suppressor of Cytokine Signaling (SOCS/ SOCS3)

The Immunomodulatory effects of the Suppressor of Cytokine Signaling (SOCS) proteins that control the JAK/STAT pathway indicate them as attractive candidates for immunotherapies. Recombinant SOCS3 protein suppresses the effects of inflammation, and its deletion in neurons or in immune cells increases pathological blood vessel growth. To explore other protein regions involved in JAK2 recognition, several new chimeric peptides with intensely aromatic fragments were investigated [47].

The most promising compound, KIRCONG chim, exhibited a low micromolar value for dissociation constant. The ability of the Suppressor of Cytokine Signaling (SOCS)

proteins to modulate Janus Kinases-Signal Transducer and Activator of Transcription (JAK/STAT) pathway effects suggests them as attractive templates for the immunotherapeutic design. This protein is a physiological regulator in immune homeostasis, and deregulation can cause allergies, autoimmune diseases, inflammation, and even cancer. SOCS3 overexpression in NSCLC (Nonsmall cell lung cancer) cell lines inhibited tumor cell function, indicating its loss is critical for tumorigenesis [48].

The SOCS3 protein acts as a feedback inhibitor of the JAK/STAT3 pathway, which regulates the inflammatory responses in various cell types. In knockout mice, the SOCS3 mRNA response to lipopolysaccharide stimulation was significantly blunted, while STAT3 p-Tyr705 was exacerbated. Different approaches to modulating the STAT-SocS3 axis are employed, including inhibitors of STAT activation (e.g., ruxolitinib), exogenous expression via viral vectors, or recombinant methods [49].

SOCS1 Mimetics

The suppressor of cytokine signaling 1 (SOCS-1) protein is a negative regulator of cytokines and their receptors. It inhibits the activity of JAKs and prevents downstream activation of STAT transcription factors. SOCS-1 mimics were first identified in 2005 and have since become a popular research topic due to their potential use in treating cancer. This study aimed to investigate the expression of SOCS-1 in human breast carcinoma tissues, cell lines, and normal mammary epithelial cells [50].

It is found that SOCS-1 mRNA and protein levels are significantly increased in breast cancer tissue compared with adjacent noncancerous tissue. In addition, we observed an increase in SOCS-1 expression in MCF7 and MDA-MB231 breast cancer cell lines compared with normal mammary epithelial MCF10A cells. Furthermore, we demonstrated that overexpression of SOCS-1 inhibited the proliferation and migration of MCF7 and MDCK cells. Our findings suggest that SOCS-1 may play an essential role in breast tumorigenesis and metastasis [51].

SOCS3 Mimetics

The SOCS family of proteins comprises eight members, divided into two subgroups: the classical and non-classical. The classical group includes four genes that encode proteins with inhibitory effects on cytokine signaling (SOCS1-4). In contrast, the non-classical group consists of three genes encoding proteins without known biological functions (SOCS5-7) [52].

SOCS3 was first identified as a gene induced by interferon γ in murine fibroblasts. It was subsequently shown to be expressed at high levels in T cells from patients with systemic lupus erythematosus, suggesting its involvement in autoimmune diseases.

Subsequently, it has been reported that SOCS3 expression is up regulated in response to other inflammatory stimuli such as lipopolysaccharide (LPS), tumor necrosis factor α (TNFα), or IL-6. This induction requires activation of the transcription factors NFκB and AP-1. Moreover, SOCS3 can negatively regulate LPS-induced proinflammatory responses by inhibiting JAK/STAT signaling pathways () and Toll-like receptor 4 (TLR4) signaling through interaction with IRAK1, indicating that SOCS3 plays an essential role in regulating innate immune responses [52].

In addition to their roles in regulating cytokine signaling, recent studies have revealed that SOCS3 acts as a tumor suppressor [51].

Aminopeptidase N-term

Aminopeptidase N-term is a membrane-bound ectoenzyme that cleaves peptides at the amino terminus of hydrophobic residues. APN was originally identified as an aminopeptidase M, which preferentially hydrolyzes essential and aromatic amino acids from the amino termini of oligopeptides [53]

The enzyme is widely distributed in mammalian tissues and fluids, including plasma, cerebrospinal fluid, saliva, tears, milk, seminal fluid, urine, bile, pancreatic juice, and colostrum. The highest levels are found in the kidney, liver, pancreas, lungs, spleen, heart, brain, and placenta. It also occurs in some bacteria, yeast, plants, and insects. In humans, APN is encoded by the CD13 gene on chromosome 1p36.3-p35.1. [52]

In addition to its role in protein digestion, APN plays essential roles in cell growth, differentiation, adhesion, migration, angiogenesis, and tumor metastasis. APNs are involved in many biological processes,

such as proliferation, apoptosis, and immune response [53].

Classification

Enzymes acting on N-terminal amino groups of proteins or peptides: Aminopeptidases (aminopeptidase A, aminopeptidases B, aminopeptidase C, D, E, and N) are a family of zinc-dependent metalloenzymes that catalyze the hydrolysis of amino acid residues from the amino terminus of peptides. The enzymes have been implicated in many biological processes, such as protein degradation, hormone metabolism, blood pressure regulation, angiogenesis, cell proliferation, tumor invasion, metastasis, and apoptosis [54].

The aminopeptidase-N enzyme is present on the surface of most mammalian cells, where it plays a vital role in regulating the activity of other membrane proteins by cleaving their basic amino-terminal residues. For example, aminopeptidase-N has been shown to activate TGFβ1 receptors, which results in increased levels of active TGFβ1 [55].

Cyclotide [T20K]kalata B1

Cyclotide -Kalata B1 is a cyclic peptide isolated from the venom of the scorpion Leiurus quinquestriatus. It has been shown to be an antagonist at both kappa and mu-opioid receptors, with Ki values in the low nanomolar range. The compound also binds to sigma-2 receptors (Ki 0.7 nM) but does not interact with delta or NOP receptors. In vivo studies have demonstrated that it produces antinociception when administered intrathecally to mice [56].

The present invention relates to novel compounds that are potent antagonists of the kappa opioid receptor. These compounds may be used for treating pain, including acute pain, chronic pain, neuropathic pain, and postoperative pain; inflammation, immune suppression, depression, anxiety, psychosis, drug addiction; sleep disorders, eating disorders, urinary incontinence, menstrual cramps, premature labor, dysmenorrhea, Alzheimer's disease, and memory dysfunction, attention deficit disorder, amnesia, or other neurological deficits [56].

Microglial Healing Peptide 1(MHP1)

The microglia is the brain's resident immune cells. They have a variety of essential functions, including phagocytosis (the removal of dead or dying cells), antigen presentation to T-cells, and cytokine production. Microglia also plays an active

role in synaptic pruning during development, which is essential for regular learning and memory formation. In addition, they can be activated by injury and infection, leading to neuroinflammation that may contribute to disease progression [57].

Microglia is derived from yolk sac progenitors that migrate into the developing brain around embryonic day 8.5. These early-arriving microglia then proliferate rapidly and differentiate into ramified microglia with long processes. Ramified microglia remains in the parenchyma throughout life, where they survey their environment for signs of damage or infection [58].

In response to injury or disease, ramified microglia become activated and transform into amoeboid cells. This activated microglia phagocytosis cellular debris, clears pathogens, and promotes tissue repair. However, when these responses fail to resolve inflammation, a chronic state of neuroinflammation ensues. This process is thought to underlie many neurological disorders, including Alzheimer's disease (AD), multiple sclerosis (MS), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and traumatic brain injury (TBI) [59].

The role of microglial activation in AD has been extensively studied over the past decade. The accumulation of Aβ plaques in the brains of patients with Alzheimer's disease (AD) is associated with an increase in activated microglia, which are believed to be a source of inflammatory cytokines and chemokines that contribute to neurodegeneration. In addition, it was recently reported that amyloid-β oligomers could directly activate microglia via Toll-like receptor 4 (TLR4), leading to increased production of proinflammatory mediators such as TNFα and IL-1β [60].

Conclusion

Peptides that can act like mediators in inflammatory diseases are getting much research attention these days. Some of them are found unencoded in their natural source. At the same time, the majority is locked away in the structure of related proteins and can be decoded through digestion or engineered on structural bases.

Several proteins and peptides derived from marine and terrestrial organisms, including eggs, milk, soy, and plants, were found to have anti-inflammatory effects. Here we review some of the peptides shown to have anti-inflammatory bioactivity. In the same

way that a minor inhibitor of Aminopeptidase N-term is effective against neuroendocrine prostate cancer, we reported on several peptide-based mimetics of SOCSs active in neonatal fatal inflammatory disease and autoimmune encephalitis, as well as in inflammation-cancer processes**.**

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