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Review

C5a and pain development: An old molecule, a new target

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ABSTRACT

Pain is a distressing sensation, resulting from real or potential tissue damage. It is crucial to protect our body, but it can be so intense that it requires treatment. Furthermore, in some circumstances, pain can become persistent/chronic, such as that triggered by inflammatory disease or neuropathy. Treatments for pain are still a clinical challenge. An advance in the knowledge of the neurobiological mechanisms involved in the genesis of acute and chronic pain might be the fundamental approach for developing novel classes of analgesic drugs. In this context, there is emerging evidence indicating that C5a, a component of the complement system, and its cell membrane receptor, C5aR, play a critical role in the genesis of acute and chronic pain states. Thus, this review will describe the mechanisms by which C5a/C5aR signaling participates in the cascade of events involved in the pathophysiology of acute (postoperative), inflammatory and neuropathic pain states. Furthermore, it will also highlight the current possibilities for the development of a novel class of analgesic drugs that target C5a/C5aR signaling.

Contents

1. Introduction

Pain is a distressing sensation, resulting from real or potential tissue damage and is associated with emotional recognition. Pain is crucial for protecting our body but can be so intense that it can require treatment, as in post-operative and post-traumatic pain;it can even become a disease by itself if it becomes persistent or chronic. Importantly, pain is one of the most costly and disabling health conditions, affecting a huge percentage of people in the world [1]. Notably, the current pharmacological therapies available for acute and chronic pain control, including opioids and non-steroidal anti-inflammatory drugs (NSAIDs), are only partially effective, and prolonged exposure to these therapeutic agents can cause unwanted effects. Furthermore, the advance in the pharmacotherapy of acute and chronic pain is mostly related to the novel application of drugs created for different conditions, such

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as antidepressants and anticonvulsants or reformulations of old drugs. Nevertheless, despite the economic and life quality impacts, pain treatment is still a clinical challenge. Consequently, there is a continuous effort to identify novel therapeutics for pain control that have innovative biological mechanisms and elicit fewer side effects.

In the last decades, we have significantly advanced our knowledge of the neurobiological mechanisms of acute and chronic pain conditions [2,3]. However, there are few clinically available analgesics that were discovered in a validated target-based manner [4]. The most important example of this strategy might be the selective cyclooxygenase-2 inhibitors [5]. Another example is the N-type voltage-dependent calcium channel blocker ziconotide (Prialt®), which is one of the first examples of a compound with a novel molecular analgesic mechanism [6]. Although it is relatively disappointing, the discovery/characterization of novel and specific cellular and molecular mechanisms involved in the development of acute pain and the transition to chronic pain states might be the main way by which a novel class of analgesic will be developed, in our opinion. In this context, over the last few years there is emerging evidence in the literature indicating that C5a, a component of the complement system, and its cell membrane receptor, C5aR, participate in the pathophysiological mechanisms of acute and chronic pain. Thus, the main purpose of this review is to discuss the related aspects and mechanisms by which C5a/C5aR signaling participates in the cascade of events involved in the genesis of acute (postoperative), inflammatory and neuropathic pain states. Furthermore, this review will also highlight the possibilities for the development of a novel class of analgesic drugs that target C5a/C5aR signaling.

2. Complement system and C5a/C5aR

The complement system is a broad network of soluble and cell-surface proteins that are inactive or have little basal activity. This system is activated and amplified by proteins/enzymes in a cascade manner [7]. The constituents are mainly synthesized in the liver but can also be produced by immune and resident cells in the tissues [8–11]. In the last few years, our knowledge of the complement system has been enhanced considerably, and its biological functions have been shown to move from being only a simple supplementary mechanism of the innate immune system. Currently, we know that the complement system acts not only as a first line of defense against pathogens but is also an important line of communication between the innate and adaptive immune systems, interacting with several cell types, including dendritic cells, macrophages and T and B cells [7]. This system is also important in homeostasis, promoting the clearance of necrotic and apoptotic cells, cell debris and immunocomplexes [12,13]. In addition, it is involved in neurodevelopment [14,15], the homing of hematopoietic stem and progenitor cells to bone marrow [16], tissue regeneration [17,18] and metabolism [19,20].

There are at least five main ways to trigger/activate the complement system cascade. The best characterized ways are the classical, the alternative and the mannose-binding lectin pathways. All complement pathways lead to the activation of protease C3-convertase. The classical pathway involves antigen-antibody complexes, whereas the alternative and mannose-binding lectin pathways can be activated by C3 hydrolysis without the presence of antibodies. In all pathways, C3-convertase cleaves and activates the component C3, producing C3a and C3b that in turn cause a further cascade of proteases and activation events. C3b binds to the cell membrane of pathogens, leading to opsonization. If C3b binds to fragments of C4b from the classical pathway, a complex will be formed—the C5a convertase of the classical pathway (C4bC3b). This fragment of C3b can also bind to another C3b in the membrane, which together with Bb (B factor b) forms a C5 convertase of the alternative pathway (C3bC3bBb). Both C5 convertases will cleave C5 into C5a and C5b. This last component will bind to C6, C7, C8 and polymeric C9, forming a complex that provokes a lytic pore in the membrane—MAC (membrane attack complex).

The component C5a, also called anaphylatoxin, is a common component of all pathways of complement activation and is the most potent inflammatory mediator produced by the complement cascade [21,22]. Among its cellular effects, C5a is responsible for the production of inflammatory mediators in immune cells [23,24]. For instance, C5a is also potent at causing the release of histamine from mast cells and basophils [25]. Additionally, it promotes the expression and release of proinflammatory chemokines and cytokines and also reduces the concentration of anti-inflammatory cytokines [26–30]. C5a is well recognized by its ability to stimulate leukocyte locomotion in vitro and emigration in vivo. In fact, C5a is an important chemoattractant for neutrophils, eosinophils and monocytes/macrophages/microglia [31,32]. It also enhances the production of reactive oxygen species by phagocytes [33,34] and astrocytes [35]. C5a also increases calcium influx and activates NFkB in several cell types, including neurons [36,37].

These C5a activities are exerted by interacting with high affinity (Kd of approximately 1 nM) with its selective receptor C5aR, also called CD88, which is a class A seven-transmembrane G-protein-coupled receptor (7TM GPCR) [38–41]. C5aR was initially identified in neutrophils, eosinophils, monocytes, dendritic cells and mast cells [42–44]. It is now known that it is also expressed in non-immune cells, such as the vascular endothelium [27], astrocytes [45], microglia [46], oligodendrocytes [47], primary sensory neurons of the dorsal root ganglion [48], neural stem cells [49], synovial cells [50], articular chondrocytes [51] and others.

In addition to the importance of C5a/C5aR signaling for the defense against pathogens, it has been associated with several pathological conditions [52–54], such as rheumatoid arthritis [55,56], sepsis [57,58], autoimmune diseases [59,60], multiple sclerosis and Alzheimer's disease [61–64]. More recently, C5a/C5aR signaling has been implicated in the pathophysiological mechanism involved in the genesis of acute (post-operative), inflammatory and neuropathic pain states.

3. C5a/C5aR and pain

3.1. First evidence on the nociceptive actions of C5a

The first evidence that C5a could have nociceptive actions came from the study of Levine et al.. They found that intraplantar injection of a low dose of C5a in naive rats reduces the mechanical nociceptive threshold, indicating for the first time that C5a is a hyperalgesic mediator. Interestingly, the C5a hyperalgesic effect was not reversible with indomethacin treatment, excluding the participation of cyclooxygenase-derived products in this effect. In contrast, in neutrophil-depleted rats, C5a-induced mechanical hyperalgesia was not observed, indicating the dependence of neutrophils for the hyperalgesic effect of C5a [65,66]. Although this seminal study has indicated that C5a is a potent pro-nociceptive substance, only several years later did C5a emerge again as an important mediator of acute and chronic pain conditions.

3.2. C5a/C5aR and post-operative pain

Pain is necessary to protect the body against damage but in particular situations can be extremely intense and require treatment. One of these situations is the post-operatory pain, which is one of the most common consequences of surgeries. A high percentage (30–40%) of patients suffer moderate to severe pain