Chapter

Inflammatory Mediators Leading to Edema Formation through Plasma Membrane Receptors

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Abstract

Edema is a swelling from liquid accumulation in body tissues. Injuries in tissues or organs may cause this disorder leading to chemical mediators releasing and triggering the inflammatory process. Inflammatory mediators, when released in response to injuries, promote biological reactions at the affected site. Furthermore, plasma membrane receptors modulate the inflammatory chemical agent synthesis and release. Pattern recognition receptors, such as Toll Like is an example of plasma membrane receptors associated with chemical agents recognizing and cascade amplification. Therefore, these plasma membrane proteins exhibit essential roles during injuries and immunologic response. Thus, this review discusses the plasma membrane receptors modulation in the inflammatory area, focusing on edema formation.

Keywords: membrane receptors, edema, inflammation, cytokines, vascular permeability

1. Introduction

Edema is characterized as a swelling caused by an increase of fluids in the interstitial space. Interstitial liquid deregulation causes liquid accumulation in the body with harmful consequences to tissues and organs [1, 2]. The physiologist Ernest Starling defined the interaction between the fluids forces in blood vessels. The fluid movement (FM) in the blood vessel is correlated with blood vessel wall permeability (constant Kf) and the difference between hydrostatic pressure variations (ΔP) and colloid osmotic pressure ($\Delta \pi$) forces [1, 3]. The following mathematical equation (Starling's equation) describes this interaction: $FM = Kf. (\Delta P- \Delta \pi)$.

The liquid retention becomes harmful to tissues affecting the cellular balance and homeostasis. Several factors induce this phenomenon: hormones, plasma proteins, inflammation, infectious diseases, and disturbs in some organs [3–5]. After an injury, inflammatory mediators cause physiological reactions in the lesioned region. Some of these inflammatory molecules include interleukins (IL-1β, IL-6, and IL-18), tumor necrosis factor-alpha (TNF-α), vasodilators, arachidonic acid metabolites, nitric oxide (NO), among others [6–8]. The inflammatory agent overproduction mediates increase in vascular permeability and leukocyte recruitment, causing edema formation and hyperalgesia [2, 9].

Membrane receptors are a group of functional proteins located in the plasma and organelles membranes. These receptors are able to trigger intracellular chemical cascades [10]. Approaches in the pharmacological field investigated several plasma membrane receptors modulating inflammation [11], such as the purinergic system, TRP channels, and pattern recognition receptors (PRRs), are commonly associated with inflammatory pathways [12–16]. Therefore, this chapter will address the plasma membrane receptors modulation on inflammatory agents and subsequent edema formation.

2. Inflammation and edema: influence in the vascular permeability

Inflammation is a natural defense mechanism to Pathogen-associated molecular pattern (PAMPs) or Damage-associated molecular pattern (DAMPs) involving cells and blood vessels. In this process, local and immune cells (macrophages, neutrophils, and lymphocytes) promote the release of pro-inflammatory mediators, such as those mentioned earlier. Although the inflammatory response is a natural mechanism, this process may become harmful to tissues and organs when persistently stimulated [17, 18]. The inflammation course and edema formation are linked because edema is one of inflammation cardinal signs [2].

After a trauma or injury, intracellular components are released, modifying the inflammatory site characteristics (**Figure 1**). Migrant and local cells, such as mast cells and basophils, release vasoactive amines, serotonin, and histamine. These molecules initially cause increase in blood vessel permeability and vasodilation [19–21]. Thus, these vascular changes cause liquid leakage from the vascular environment. Plasma protein, such as albumin, in the extravascular medium may modulate the vascular pressures. The press alteration favors the fluid and electrolyte passage to interstitial space generating swelling [3, 22].

Coagulation factor activation, such as the Hangeman factor, induces bradykinin and proteases synthesis stimulation. Bradykinin is a kinin involved in vascular permeability and other vascular mechanisms [23–25]. Additionally, the complement system fragments exhibit a crucial role in the immunity and vascular processes. The anaphylatoxins, such as C3a, C4a, and C5a, act on leukocyte recruitment and also in bradykinin signaling [23, 26–29].

The pro-inflammatory cytokines participate in pain mechanisms and also promotes increase in vascular permeability [23]. Stamacovic [30] described cytokines participating in the central nervous system inflammation and Blood–brain barrier

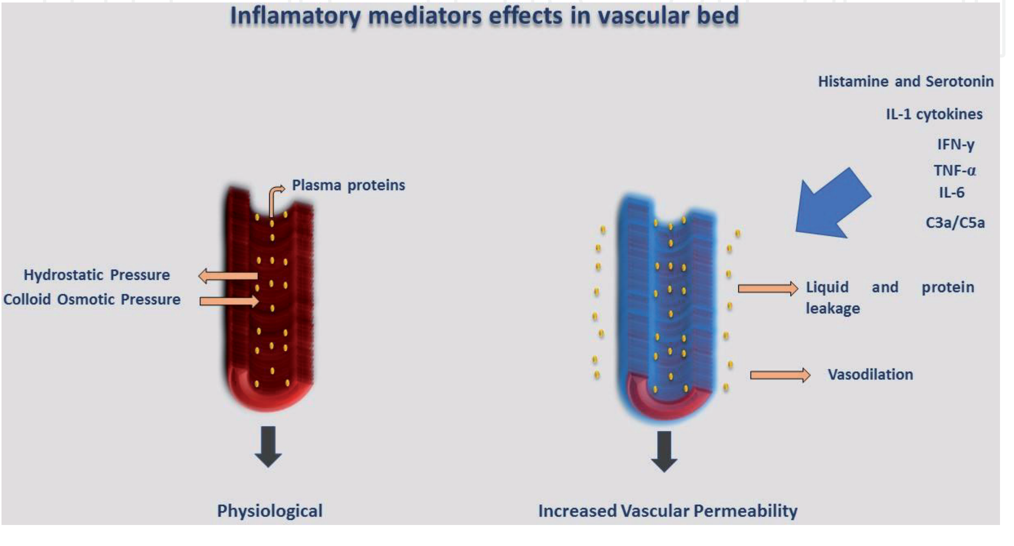

Figure 1.
Inflammatory mediators are acting on vascular permeability.

permeability. The increase in IL-1β, IL-6, and TNF-α may cooperate for brain edema emergence. Martin et al. [31] showed vascular increase induced by IL-1 and IFN-y in Wistar rats. IL-1β is very approached in a mechanism involving nociception and sensibility to pain, as well as bradykinin [32, 33]. Furthermore, increase of IL-1β and TNF-α induct arachidonic acid metabolites [34]. Arachidonic acid metabolites like prostaglandins, leukotrienes, prostacyclin, and thromboxane also mediate vascular changes [35]. Prostaglandins is directly involved in the modulation of pain mechanisms [9, 36].

IL-18 is another IL-1 family member involved in pain mechanisms. The IL-1β and IL-18 synthesis possess similarities in their signaling [37]. Pilat and colleagues' study involving the IL-18 inhibition [38] showed nociception reduction in a neuropathic pain model. Besides, IL-18 is also notorious as the IFN-y-inducing factor [37, 39].

Additionally, inflammatory mediators modulate inflammatory diseases, and some data confirms this actuation in organ pathophysiology such as lung, liver, heart, and others [40–43]. Thus, vital organ disturbs promote vascular fluids imbalance. Additional data about cytokines modulation at vascular mechanisms can be found in the following works [23, 44, 45].

3. Membrane receptors participation in the inflammation and edema pathophysiology modulation

Scientific advances provide new discoveries about plasma membrane receptors function and identity. Molecules impermeable to the membrane can selectivity cross to the intracellular environment through these receptors. Many receptors characteristics are investigated in the physicochemical field, including biophysical properties and structure. Membrane receptors generally have three classifications: receptors coupled to enzymes such as tyrosine kinase (RTKs), G protein-coupled receptors (GPCRs), and ion channels [46]. Interestingly, there is a group of membrane proteins that are widely addressed in scientific research for modulating inflammatory mediators release and search for new anti-inflammatory drugs. Based on this, the following topics exhibit some of studied plasma membrane receptors related to the inflammatory response.

3.1 Toll-like receptors

The host defense against infections and tissue damage is a complex mechanism. In this process, the cells must recognize PAMPs and DAMPs to initiate a specific intracellular response against infectious agents, such as viruses and bacteria or dangerous signs, such as burn injuries [47].

The Toll-Like Receptors (TLRs) are a group of membrane proteins involved in inflammation and immunity. They act on PRRs expressed in macrophages, neutrophils, and dendritic cells [47, 48]. TLRs compose the interleukin 1 receptors superfamily (IL-1Rs) with slight structural differences. Ten TLRs subtypes were described in humans (TLR1–10), although other species may exhibit variations.

TLRs are located in different compartments in the cell. For instance, the subtypes 1, 2, 4, 5, and 6 are located at the cell plasma membrane, whereas subtypes 3, 7, 8, 9, and 10 are in the intracellular compartment, located in endosomes. [RF1] TLR2 and TLR4 are the best-studied receptors of this family [49, 50].

TLRs, when activated, are essential for the host response to harmful agents, since these receptors modulate the inflammatory mediators release. The factor nuclear kappa β (NF-kβ) and mitogen-activated protein kinase (MAPKs) are classical pathways activated by Toll-Like Receptors (**Figure 2**) [48]. When stimulated

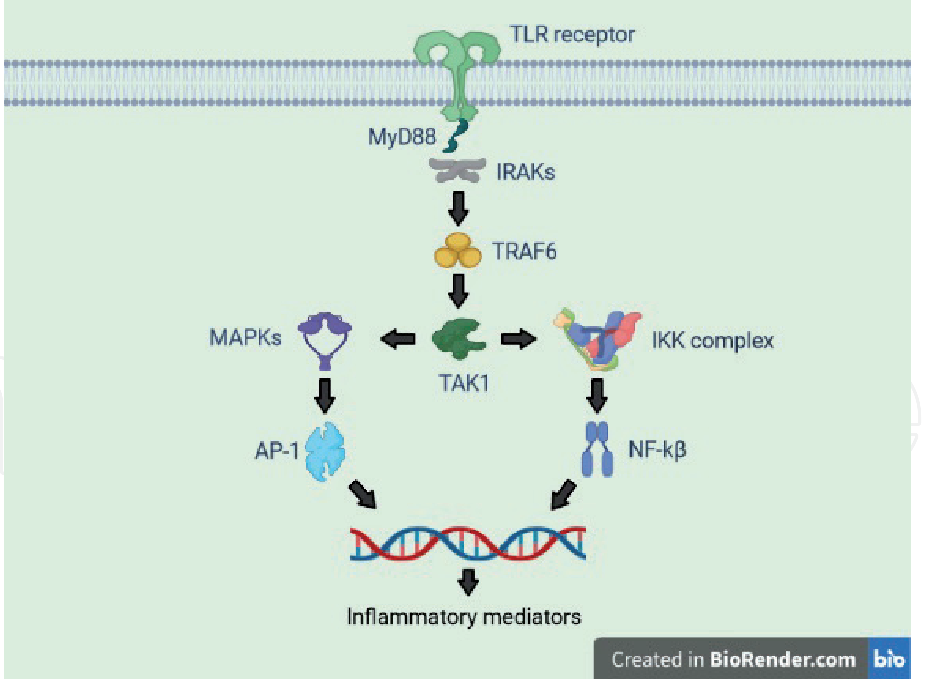

Figure 2.
Plasma membrane TLR signaling pathway. TLR receptor activation triggers AP-1 and NF-kβ transcription factors.

by a ligand, such as lipopolysaccharides (LPS), TLRs transduces the signal through adaptor molecules in the intracellular environment. Myeloid differentiation primary response 88 (MyD88) is an adaptor molecule of the interleukin- 1 receptor-associated kinases (IRKs) signaling with subsequent TNF receptor-associated factor 6 (TRAF6) activation. TRAF6 activates the growth factor β-activated kinase 1 (TAK1), which triggers an enzymatic complex associated with NF-kβ translocation to the cell nucleus. TAK1 signaling also activates the MAPKs pathway with activator protein 1 (AP-1) nuclear factor translocation. This pathway leads to various pro-inflammatory mediators transcription, such as cytokines (IL-1 family, IL-6, TNF-α), **COX-2** stimulation (prostaglandin E2), and interferons [50, 51].

TLR activation may exhibit a crucial role in edema formation through inflammatory mediator production (**Table 1**). In a recent paper, Okada and colleagues [55] described brain edema reduction in a subarachnoid hemorrhage model (SAH) mouse after treatment with TAK-242, a TLR4 receptor inhibitor. The molecular mechanism by which this occur was not evaluated. However, the pathophysiology development of brain edema shows association with TLR4 function. In liver diseases, such as acute liver failure, astrocyte swelling is a notable characteristic that promotes brain edema formation. Interestingly, NF-kβ and MAPKs-induced cytokine release are crucial mechanisms for astrocyte swelling development [56, 57]. Jayakumar et al. [58] have demonstrated LPS and cytokines-induced astrocyte swelling increase. These data suggest TLR4 may be a target in the brain edema pathophysiology**. Table 1** represent more data about TLR receptors in the inflammatory context.

3.2 Histamine receptors

Histamine constitutes an essential molecule in cell biology, edema pathophysiology, and the inflammatory process. The histamine synthesis occurs with the amino acid L-histidine decarboxylation through the histidine decarboxylase enzyme (HDC). Other inflammatory mediators can lead to increase HDC activity, such as IL-1 cytokines [60]. Histamine synthesis occurs in different body cells, although this production primordially occurs in mast cells and basophils [61]. In these cells, histamine is

Receptor	Ligand	Involvement in inflammation and edema	References
TLR1	Tri-acyl lipopeptides	TLR1 works together with TLR2 as a heterodimer. This subtype also mediates the intracellular cytokines transcription	[47, 52]
TLR2	Peptidoglycan	TLR2 signaling intracellular transcription of inflammatory mediators Cytokine gene expression such as IL-1β, TNF-α, and IL-6 decrease in TLR2 Knock out mice in vascular injury model TLR2 plays a role in mast cells degranulation and cytokine release stimulated by peptidoglycan	[47, 53, 54]
TLR4	LPS	TLR4 activation leads to inflammatory mediators transcription involved in pain and edema, such as **COX-2** metabolites, IL-1 cytokines, and TNF-α LPS induces astrocyte swelling and brain edema pathogenesis. TLR4 also increases TNF-α and IL-1β in LPS-induced mast cells	[47, 50, 54–58]
TLR5	Flagellin	TLR5 can be activated by high mobility group box 1 (HMGB1), a protein that plays a role in inflammation. The HMGB1 action on TLR5 induced the pro-inflammatory mediators intracellular signaling. TLR5 also plays a protective role in intestinal cells.	[47, 52, 59]
TLR6	Di-acyl lipopeptides	TLR6 functions are interacting with TLR2 and TLR4 as a heterodimer.	[47, 52]

Table 1.
Plasma membrane TLRs modulate inflammatory mediators.

stored in cytoplasmatic granules and released according to the stimulus presented. Histamine interacts with GPCRs membrane receptors classified as histamine receptors (HRs) and divided into four subtypes: HR1, HR2, HR3, and HR4 (**Table 2**) [61].

The histamine action is remarkable in the vascular modulation mechanism, including vascular permeability increase. HRs actuate as a second messenger, leading to intracellular signal and cytokine synthesis [68]. A study by Delaunois and co-authors [69] showed a protective HR3 agonist role in pulmonary edema stimulated by inflammation-promoting molecules. In addition, HR3 stimulation appears to play a significant role in perfusion in post-burn tissues [70]. HRs also participate in the mechanisms related to antinociception [61].

Among HRs, HR4 has become a new antihistamines studies target. The HR4 activation triggers MAPK, which leads to pro-inflammatory mediators synthesis [60]. Coruzzi and collaborates [66] showed promising results in inhibiting paw edema by HR4 in acute inflammation. After carrageenan-induced edema, two selective HR4 inhibitors, JNJ7777120, and VUF6002, respectively, were evaluated. Inhibition by JNJ7777120 after two hours of carrageenan induction has shown notable values compared to VUF6002. Another study using JNJ7777120 described the anti-nociceptive role in a pain inflammation model through HR4 antagonism. Additionally, HR4 inhibition decreases neutrophilic influx to stimulated area pretreated with JNJ7777120 [67]. These findings suggest HR4 with a crucial role in edema and pain mechanism.

3.3 Serotonin receptors

Diseases involving the psychiatric area have been widely addressed in scientific research, such as depression. [RF2] Factors involving mood and mental disorders,

Receptor	Ligand	Involvement in inflammation and edema	References
HR1	Histamine	HR1 is involved in allergic response HR1 influences MPAK signaling and modulates Th1 response.	[61–63]
HR2	Histamine	HR2 modulates Th2 response HR2 regulates IL-10 and antinociceptive activity	[61, 62, 64]
HR3	Histamine	HR3 exhibits an essential role in neuronal inflammation and neuropathic pain. HR3 inhibition has been shown to be beneficial in inflammation and edema stimulated by formalin	[61, 65]
HR4	Histamine	HR4 also participates in MAPK signaling. HR4 inhibition shows to reduce neutrophil infiltration, edema, and hyperalgesia in acute inflammation	[60, 63, 66, 67]

Table 2.
Histamine receptors.

include serotonin, a critical functional amine in this disease. Interestingly, serotonin regulates inflammatory signaling, playing a role in vascular permeability. Therefore, serotonin becomes a multifunctional molecule modulating many body processes [71–73].

5-hydroxytryptamine (5-HT), serotonin is synthesized from the amino acid tryptophan. The enzymes tryptophan hydroxylase and tryptophan decarboxylase are responsible for 5-HT production. Serotonin may be found in various body tissues, such as enterochromaffin, platelets, brain, and lung [71]. 5-HT interacts with membrane receptors (5-HT receptors), divided into seven families (5-HT1–7), where these receptors are GPCRs, except for 5HT3, which belongs to ion channels. These receptors possess fourteen subtypes: 5-HT1 (A, B, D, E, and F), 5-HT2 (A, B, and C), 5-HT3 (A, B), 5-HT4, 5-HT5 (A), 5-HT6, and 5-HT7 [74, 75].

The 5-HT role in other systems has been studied over the years. During inflammation, 5-HT plays an essential role in vascular permeability, as well as histamine, in addition to participating in pro-inflammatory mediator production [72]. In this context, serotonergic receptor subtypes act on inflammation process biochemistry. 5-HT7 is influential in peripheral inflammatory modulation, according to Albayrak and co-authors [76]. The 5-HT7 participates in the nociception mechanism with other 5-HT receptors, such as 5-HT1 and 5-HT2 [77, 78]. The 5-HT2 subtype (A) subtype also modulates the inflammatory process. Nishiyama studies [79] have demonstrated a role for 5-HT2A in cytokines synthesis during an inflammation model induced by endotoxin shock. The 5-HT2A inhibition reduced TNF-α, IL-1β, IL-8, and IL-6 levels. Interestingly, IL-10 levels (cytokine with anti-inflammatory function) increased due to 5-HT2A inhibition. Additionally, 5-HT2A shows to play a function in body temperature control [80]. These data demonstrate a relevant role for 5-HT2A receptors in inflammation pathophysiology (**Table 3**).

3.4 Purinergic receptors

The purinergic system is a group of transmembrane proteins activated by extracellular purine ligands, such as adenosine and other derivatives, adenosine triphosphate and diphosphate (ATP and ADP). Interestingly, when the ATP molecule is found in elevated concentration in the extracellular environment (eATP), this nucleotide may become a DAMP and regulates the inflammatory process. Purinergic receptors are formed by two groups (P1 and P2) differing in structure and activation ligands on mammalian cells [93, 94].

Receptor	Ligand	Involvement in inflammation and edema	References
5-HT1	Serotonin	5-HT1 receptors stimulation induces a role in neurogenic inflammation Intrathecal 5-HT1A, 5-HT1B, and 5-HT1D receptor agonists administration decreased the peripheral inflammatory edema induced by carrageenan.	[81, 82]
5-HT2	Serotonin	5-HT2A subtype inhibition increased IL-10 in inflammation induced by shock with endotoxins. 5-HT2A receptor activation decrease TNF-α-induced inflammation 5-HT2A regulates the body temperature 5-HT2B subtype shows the immunomodulatory function in dendritic cells	[79, 80, 83, 84]
5-HT3	Serotonin	5-HT3 inhibition decreased inflammatory cytokines and neutrophilic action in a colitis model 5-HT3 decreases pain in carrageenan-induced inflammation	[72, 85, 86]
5-HT4	Serotonin	Spinal 5-HT4 receptor antagonism decreased hyperalgesia effects 5-HT4 induced IL-1β and IL-8 release in mature dendritic cells.	[72, 87, 88]
5-HT5	Serotonin	Intrathecal administration appears to show an anti-nociceptive role for spinal 5-HT5A receptors	[89, 90]
5-HT6	Serotonin	Like 5-HT4, 5-HT6 receptor antagonism is also beneficial in hyperalgesia	[87, 91]
5-HT7	Serotonin	5-HT7 receptor stimulation has an anti-inflammatory role in the periphery carrageenan-induced inflammation 5-HT7 agonist decreased **COX-2** levels. Like 5-HT4, 5-HT7 activation also induces IL-1β and IL-8 secretion in dendritic cells.	[76, 88, 92]

Table 3.
Serotonin receptors.

The adenosine molecule activates the P1 group and possesses four subtypes (A1, A2a, A2b, and A3). The P1 group comprises GPCRs receptors, and the P2 group is extensive and divided into two families, P2X and P2Y. The P2X receptors form ATP-activated ion channel receptors with seven subtypes (P2X1–7). P2Y receptors are GPCRs, like the P1 group. Interestingly, ATP and their derivatives activate the P2Y receptors, although, pyrimidine molecules, such as uridine diphosphate (UDP and UDP-glucose), also modulate some subtypes activation. This family consists in eight subtypes (P2Y1, P2Y2, P2Y4, P2Y6, P2Y11, P2Y12, P213, and P2Y14) in mammals. The purinergic receptors participate in inflammation and immune response and are expressed in several tissues [14].

In the purinergic group, the receptor of great scientific notoriety is the P2X7 receptor (P2X7R), addressed in several mechanisms, such as cell death and inflammatory cytokines release [14]. P2X7R have the capacity to increase membrane permeability for large solutes after prolonged ATP activation. The prolonged P2X7R stimulation induces a pore opening that allows the molecules of up to 900 Da. This mechanism highlights the P2X7R as a pore-forming protein, similar to other membrane receptors, such as some TRP channels [95].

However, a striking P2X7R feature is the participation in the maturation of IL-1 cytokine family (IL-1β and IL-18) release. The IL-1β and IL-18 production and maturation require two signaling mechanisms, one mediated by pattern recognition receptors (via TLRs family activation) and a second by a danger signal, such as eATP. The activation of TLRs induces nuclear transcription through NF-kβ of the immature forms of these cytokines (ProIL-1β and ProIL-18), concluding the first stage.The eATP activates the P2X7R, beginning the cascade signaling that compose the Nod-like receptor protein-3 (NLRP3) inflammasome complex with subsequent IL-1β and IL-18 maturation and release [48, 96]. The following figure illustrates this mechanism more clearly (**Figure 3**).

The IL-1β inhibition in inflammation and pain has been addressed in several inflammation studies. Experiments in vivo using P2X7R antagonist have demonstrated improvements in the swelling caused by inflammation in a model of paw edema [97, 98]. The pain sensibility mechanism is linked to vascular permeability, causing edema [2]. Furthermore, P2X7R inhibition reduces pro-inflammatory cytokines, such as IL-1β and other mediators, since the P2X7R is responsible for these mechanisms [96]. Additionally, the P2X4 receptor has participated in IL-1β and IL-18 signaling based on Chen et al. [99]. Further, other purinergic receptors data in edema and inflammation have already been approached in the literature (**Table 4**).

3.5 TRP channels

The physiological mechanisms of pain and temperature stimuli indicate the transient receptor potential (TRP) as a target in this regard [110]. The TRP channels superfamily is constituted of transmembrane cationic ionotropic receptors. In mammals, six subfamilies classify the TRP channels into two groups. The first group: TRPC (canonical), TRPV (vanilloid), TRPA (ankyrin), and TRPM (melastatin). The second group is composed of TRPML (mucolipin) and TRPP (polycystic). This chapter will discuss the most addressed subfamilies in the scientific literature: TRPV, TRPM, and TRPA based on their involvement in inflammation and pain. These subfamilies are classified in TRPV1–6, TRPM1–8, and TRPA1 receptors [111, 112].

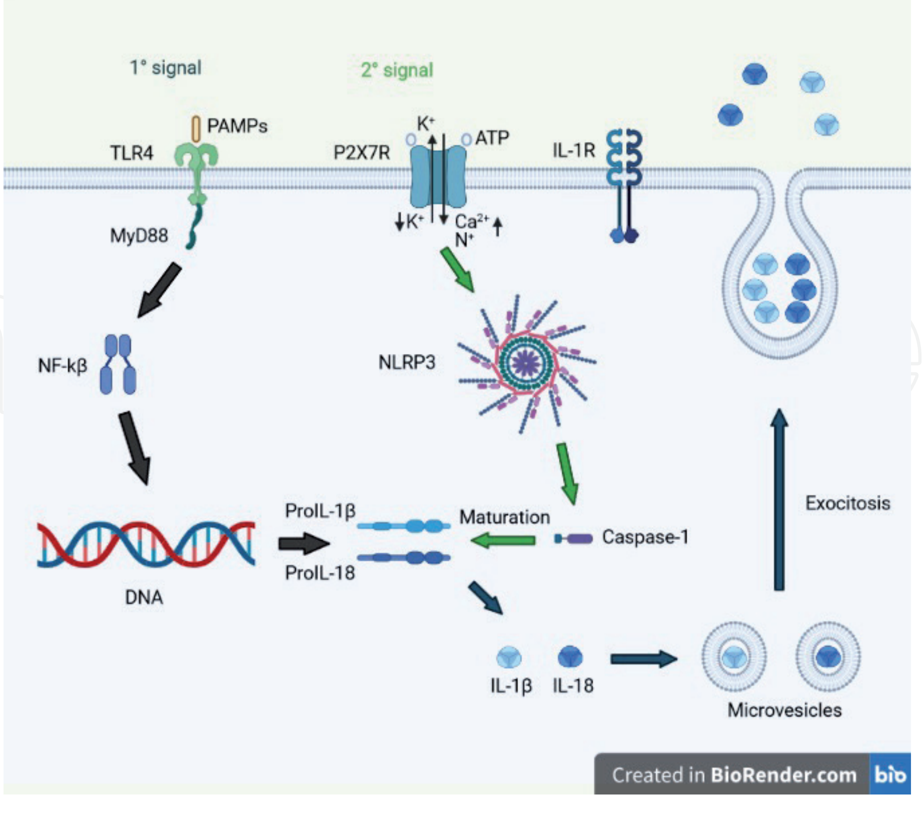

Figure 3.
IL-1β and IL-18 synthesis after P2X7R activation. The first signaling occurs with the ProIL-1β and ProIL-18 transcription after TLRs receptor activation (TLR4). The second signal arrives with the eATP stimulating the P2X7R. The receptor activation induces the NLRP3 inflammasome complex, and finally, IL-1β and IL-18 conversion for mature form.

Receptor	Ligand	Involvement in inflammation and edema	References
A1R	Adenosine	A1R receptor stimulation increased leukocyte recruitment and edema formation in acute pancreatitis disease. A1R participates in pulmonary inflammation and influence vascular permeability through inflammatory cytokines release in monocytes and neutrophils	[100, 101]
A2R	Adenosine	A2aR decreases cytokine synthesis (IFN-γ, IL-4, and IL-2) in lymphocytes and influence platelet aggregation. A2bR mediates several pro-inflammatory cytokines (IL-1β, TNF-α) synthesis In contrast, A2bR also exerts an anti-inflammatory action, as observed for IL-10 release in macrophages.	[101]
A3R	Adenosine	A3R stimulation induces histamine and serotonin release and inflammation in rat paw. A3R seems to mediate benefits in control hyperalgesia	[102, 103]
P2X4R	ATP	P2X4 induces IL-1β and IL-18 cytokines maturation through NRLP3 inflammasome P2X4R is involved in prostaglandin E2 release and pain	[14, 99, 104]
P2X7R	ATP	P2X7R activation produces cytokines, such as IL-1β and IL-18 maturation through NRLP3 inflammasome and TNF-α P2X7R regulates prostaglandin E2 release P2X7R antagonism reversed edema and hyperalgesia P2X7R stimulation leads to vascular bed inflammation through IL-1β release	[14, 96–98, 105, 106]
P2YR	ATP/UDP/UDP-glucose	P2Y1R, P2Y2R, and P2Y6R are associated with leukocyte chemotaxis. P2Y1R, together with P2Y12R, have a function in platelet aggregation Like P2X7R, P2Y6R activation in endothelial cells promotes vascular inflammation and fluids leakage.	[107–109]

Table 4.
Purinergic receptors.

TRPV1 is the most studied TRP channel because of its noxious heat and inflammation perception. TRPV1 is a pore-forming protein, like P2X7R and other TRPs, such as TRPV2–4, TRPA1, and TRPM8 (**Table 5**). All these channels promote pore opening, and molecules flux up to 900 Da [117]. Capsaicin is one TRPV1 receptor agonist and plays a critical role in nociception pathogenesis [124].

The TRPV1 receptor (heat sensor) together with TRPA1 (cold sensor) can modulate the neuropeptide molecules release like substance P. This molecule encompasses many biochemical processes involved in inflammation, such as histamine and serotonin released by mast cells, which leads to increased vascular permeability and hyperalgesia [113]. Hoffmeister and co-authors [125] described a reversion in edema and pain caused by monosodium urate crystals after TRPV1 inhibition. These findings may be associated with the mechanism mentioned above with TRPV1 participation. Additionally, TRPV1 and TRPA1 receptor inhibition

Receptor	Ligand	Involvement in inflammation and edema	References
TRPV1	Capsaicin/Protons/Heat sensor	TRPV1 channel is involved in the release of the neuropeptide like substance P in sensory fibers Capsaicin administration showed painful effects in mouse paws, which were diminished by TRPV1 inhibitors TRPV1 increased intracellular Ca^{+2} concentration inducing the cytokines transcription such as IL-1β and TNF-α through the NF-kβ pathway In the endotoxin-induced lung injury model, TRPV1 reduced the pro-inflammatory cytokines levels	[113–116]
TRPV4	4α-Phorbol 12,13-didecanoate/ Osmotic sensor	TRPV4 activation in vascular endothelial cells caused an increase in vascular permeability. TRPV4 is sensitive to hypo-osmotic stress in chondrocytes	[117–119]
TRPA1	Allyl Isothiocyanate (AITC)/ Cold sensor	Like TRPV1 channels, TRPA1 acts on neuropeptides molecules regulation and nociception. TRPA1 induced edema in an acute inflammation model using AITC TRPA1 stimulation by AITC has been shown to influence the **COX-2** regulation in HEK 293 cells	[113, 116, 120]
TRPM8	Menthol/Eucalyptol/Cold sensor	TRPM8 channels inhibited edema and inflammation by decreasing pro-inflammatory cytokines (TNF-α and IL-1β) Menthol produced analgesic effects on inflammatory pain through the TRPM8 channel	[16, 121–123]

Table 5.
Transient receptors potential.

decreased pro-inflammatory cytokines levels, such as TNF-α, IL-1β, and IL-6 in an endotoxin-induced lung injury model [114]. Interestingly, Li et al. [115] demonstrated TRPV1 activation associated with NF-kβ phosphorylation through the intracellular Ca^{2+} influx. Based on this data, TRPV1 receptors play a critical role in the modulation of the pro-inflammatory cytokines.

Another notorious receptor involved in the low temperatures detection in conjunction with TRPA1 is the TRPM8 receptor. TRPM8 exhibits an essential role in neuropathic pain and anti-inflammatory effects [111]. TRPM8 is the most studied receptor in cold physiology. TRPM8 activation reverses the hyperalgesia caused by TRPV1 and TRPA1 stimuli [16]. Experiments using eucalyptol, a TRPM8 agonist, show promising results in reducing pro-inflammatory cytokines in paw edema [121]. Studies with cold therapy can have analgesic and anti-edema effects [122]. These findings make the TRPM8 receptor a target in this context.

3.6 Other receptors involved

A large quantity of plasma membrane receptors modulates the inflammation and immune response processes. In this work, we discuss the membrane receptor groups as therapeutic targets for inflammation and edema processes. The connection between the receptor systems is vast, and the response can vary according to the stimulus. Thus, other receptors can fit this context, such as cholinergic, dopaminergic, and adrenergic receptors. These are other examples of membrane receptors that can also be addressed in this context [126–128].

Additionally, bradykinin also promotes a role in vascular permeability. Bradykinin receptors divide into B1, and B2 (GPCRs) play a crucial role in edema pathogenesis [129, 130]. Further, cytokines receptors are also involved in inflammation mechanisms, such as IL-1 family and TNF-α receptor [131].

4. Therapeutic perspective of membrane receptors for inflammatory diseases

The inflammatory process (edema, cell migration, pain, and other) treatment mainly uses non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids.

Receptor	Compound	Disease	Clinical study	Results	References
TLR4	NI-0101	Rheumatoid arthritis (RA)	Phase II	Insufficient therapeutic effects	[133]
HR4	JNJ-39758979	Asthma	Phase IIa	Potential in patients with eosinophilic inflammation	[134]
	Toreforant	RA	Phase IIa and IIb	No improvement in Phase IIb study	[135]
		Eosinophilic asthma	Phase IIa	No significant effects on the applied dose	[136]
	ZPL-3893787	Atopic dermatites (DA)	Phase IIa	Improvement in skin lesions	[137]
P2X7R	AZD9056	RA	Phase IIa and IIb	Insufficient therapeutic effects	[138]
		Crohn's disease (DC)	Phase IIa	Good effects in improving symptoms in moderate and severe DC	[139]
	CE-224.535	RA	Phase IIa	Insufficient therapeutic effects	[140]
TRPV1	JNJ-38893777	Not available	Phase I	Tolerable and safe for future investigations	[141]
	PAC-14028	DA	Phase IIb	Effectiveness for the treatment of mild and moderate AD	[142]

Table 6.
Receptor antagonist compounds highlighted in clinical trials for inflammatory diseases.

NSAIDs inhibit eicosanoid metabolites produced for the COX pathway, whereas corticosteroids are based on hormones released by the endocrine glands [132]. On the other hand, the more serious problem with these drugs is their prolonged use in treatments, presenting toxicity to organs. Based on this, the membrane receptors discussed in this chapter are promisor candidates for inflammation treatment. In addition, some classes possess agonists and antagonists commercially available among these receptors, such as 5-HT receptors and HRs.

Interestingly, clinical trials have already been realized and described in the literature concerning other membrane receptor types for reducing inflammatory diseases and their symptoms (**Table 6**). Therefore, we highlight four receptors discussed in this chapter with great potential in modulating the inflammation (TLR4, HR4, P2X7R, and TRPV1).

5. Conclusion

The inflammation field encompasses broad aspects, such as chemical mediators (cytokines, vasoactive amines, and lipid mediators), pain, and edema. The plasma membrane receptors influence on the inflammatory process is widely explored in scientific research. Concerning data discussed in this chapter, membrane receptors are promising and directly involved in the inflammatory mediators modulation in the edema and hyperalgesia pathophysiology. Thus, these new data open a horizon in the search for new pharmacological targets with anti-edema and analgesic effects in the therapeutic perspective of the inflammatory process.

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Conflict of interest

The authors declare no conflict of interest.

Notes/thanks/other declarations.

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