Pain and inflammation. Part 1. Pathogenetic aspects

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The relief of suffering, which is associated with a rapid and complete elimination of painful sensations, is the most important challenge facing physicians of many specialties. It is obvious that it can be solved only when you understand clearly the processes governing the development and chronization of pain. Inflammation, a universal adaptive mechanism that always accompanies damage to living tissues, plays a key role. Part 1 of this review considers the main stages of development of an inflammatory response, beginning with primary damage accompanied by the release of molecules acting as an alarm and ending with the deployment of a complete picture of the inflammatory response with the involvement of many cell elements and the overexpression of cytokines and proinflammatory mediators. The biological basis of the peripheral and central nociceptive sensitization phenomenon that is rigidly associated with inflammation is presented. Particular emphasis is placed on the possible natural completion of the inflammatory response, on the adaptive mechanisms regulating this process and on the reasons that prevent this and determines inflammation chronization.

Key words: pain; inflammation; macrophages; cytokines; mediators of inflammation and pain; nociceptors; peripheral and central sensitization.
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Pain is the most bothersome manifestation of many diseases and pathological conditions, which determines severe sufferings, disability and disruption of social adaptation among hundreds of millions people on Earth. The constant increase of the number of people experiencing pronounced and long-term painful sensations seems to be one of the most serious global problems facing modern society. First of all, it is associated with the widespread prevalence of joint and spinal diseases, wherein musculoskeletal pain is the main manifestation. The scale of this problem can hardly be overestimated: according to the World Health Organization up to 2 billion of people on Earth experience sufferings associated rheumatic diseases. Only in Europe costs for the medical treatment of this pathology comprise more than 200 milliards [1]. Osteoarthritis (OA) and non-specific backache (NBA), the most common musculoskeletal pathology, are steadily the first by the DALYs index (lost years of life due to disability, «disability-adjusted life years») reflecting the negative social impact of disease [2]. The problem of joint and spinal diseases is actual for Russia also: thus, according to data for 2012–2013, the number of patients with nosological forms belonging to the class XIII of ICD (International Classification of Diseases) in our country is 16,5 milliards of people being increased by 30% in the 2000s [3].

Effective pain control is one of the primary and most important tasks of medical practice.

However for the successful treatment of pain it is necessary to clearly understand the mechanism of its development as a complicated, multifactorial system process. This is absolutely necessary for creating a system of rational and effective analgesic therapy, wherein each component of the pathogenesis of pain should be considered as a promising target for pharmacological intervention [4–6].

One of the main trends of analgesia is associated with the use of drugs that have an anti-inflammatory effect. This is justified by the surely leading role, which is played by the inflammatory process in the onset of acute and the development of chronic pain.

Inflammation is a cyclic process occurring in response to damage to living tissue of the body; it includes systemic as well as local humoral and cellular reactions directed to the elimination of a traumatic factor and to the removal of cells and intercellular substance elements (ISM) destroyed as a result of damage [7–9].

Inflammation always accompanies the pathology in humans, and is considered as its most important manifestation; however, initially, by nature it is a protective, adaptive mechanism, in the absence of which it is impossible to restore damaged tissue and protect the macroorganism from foreign genetic information. Moreover, the elements of inflammatory activity (in particular, the local activity of macrophage-line cells) naturally accompany the normal vital activity of living tissue [7–9]. Indeed, cells and ICM constantly experience the negative effect of external factors which cause their graduate damage. Thus, the structures of the musculoskeletal system – bones, muscles, ligaments, articular cartilage and synovial membrane of the joints, are subjected to mechanical stress under physical stress and under the influence of gravity, which leads to their gradual «wear» [10, 11]. The high organization of a living organism does not imply a significant reparative potential of specialized cells: their serious structural failure inevitably triggers a program of cell death – apoptosis. The process of regeneration of damaged tissues proceeds by replacement of cellular elements with new specialized cells originating from respective cell line progenitors capable for controlled division. However, effective repair is possible only on a «clean» background after removal of cell debris and degraded intercellular substance. The resident macrophage line cells – the descendants of peripheral blood monocyte or tissue-located embryonic cells, such as synovial macrophages, Kupffer cells of the liver, Langerhans cells of the epidermis, osteoclasts, cells of the microglia of the nervous tissue and others, function to utilize the cell debris. Macrophages destroy dead cells and ICM elements by means of reactive oxygen species, organic acids and different enzymes (in this case the most important role is played by matrix metalloproteinases, MMP), phagocyte them and «digest» the remaining biological substrate [9, 12, 13]. This action which invisibly accompanies vital activities of organs and tissues is a prototype of the clinically relevant inflammatory reaction, «inflammation in miniature».

If the damage is significant, and the extent of tissue deterioration is clearly exceeds adaptive possibilities of resident macrophages, the local with the following systemic reaction develops [14].

Key elements of inflammation development

The primary triggering factor of non-infective inflammation is a disruption of the integrity of cell membrane, thereby the internal contents of the cell saturated with proteins and non-proteinaceous molecules, «poured» into the intercellular space. For cells of the inflammatory response, a sharp change in the biochemical composition of the extracellular liquid becomes an alarm signal, and the main role is played by substances referred to as DAMP (Damage-associated molecular pattern) [7, 8, 14].

These include several classes of intracellular proteins: heat shock proteins (HSP), regulators of functions of complex protein molecules, such as tridimensional structure formation (folding), HMGB1 (high-mobility group protein B1), chromosomal non-histone proteins with a high electrophoretic mobility, involved in the construction of DNA-protein complexes, as well as the family of low molecular weight proteins S100. In addition to proteins, ATP, DNA and RNA (as well as their fragments and metabolic products), that normally could be found only in the nucleus and cell organelles, purine bases and their main metabolite uric acid, if its local concentration is significantly higher than the concentration corresponding to the normal metabolism, can act as a «mediator of damage». An important proinflammatory stimulus is also the appearance of a large number of fragments of macromolecules, which form the basis of ICM. Thus, as DAMP glycans and glucoconjugates – the products of degradation of the cartilage and synovial glycoproteid complex, as well as fibrinogen, can act [7, 14, 15].

DAMP interacts with special receptors referred to as PRR (pattern-recognition receptors) of macrophages and a number of other cells (dendrite cells, epithelial cells, fibroblasts and others) involved in the adaptive immunity, which results in their activation; and that becomes the first triggering element of the inflammatory reaction. PRR include receptors located on cellular membranes – Toll-like receptors – and intracellular Nod-like receptors – NOD1, NOD2, NALP family and others, interacting with phagocytic «molecules of damage» within cellular endosomes [15–17].

Activation of PRR leads to the modification of specific intracellular proteins – «signaling molecules» by protein kinase enzymes, such as IKK (IκB kinase), IRAK1 and 4 (Interleukin-1 receptor-associated kinase 1), TBK1 (TANK-binding kinase 1) and others. This biochemical signaling triggers genetic programs for the synthesis of cytokines, specific regulatory molecules, which controls the further development of the inflammatory reaction. Transcription of cytokine genes proceeds by specific proteins, among them nuclear factor «kappa B» (NF-κB), mitogen-activated protein kinase p38 (MAPK p38), as well as STAT (signal transducers and activators of transcription) should be particularly mentioned [15, 19].

It is NF-κB which causes transcription of the most important cytokine interleukin (IL) 1β, which triggers the subsequent immune inflammatory process. Its generation from its inactive precursor occurs with the participation of the enzyme caspase-1, which in turn forms within the special organelle – inflammosome. Such a complicated two-phase system is necessary for the intracellular control of the development of the inflammatory response as well as for maximally rapid production and activation of IL1β. The overexpression of IL1β attracts monocytes (which become new, active macrophages), neutrophils to the damaged site, stimulates the proliferation of lymphocytes and endotheliocytes, promoting the development of neoangiogenesis [20, 21].

Among cytokines playing the central role in the development of inflammation tumor necrosis factor (TNF) α, IL-6 as well as interferon (IFN) γ should be particularly mentioned.

Their expression is triggered by the action of IL-1β or is stimulated by activation of PRR (Toll- and Nod-like). The main «suppliers» of TNF α and IL-6, of course, are macrophage line cells as well as T-lymphocytes and other cells involved in the formation of an inflammatory response [22–24].

Biological effects of TNF α and IL-6 are exerted after their interaction with respective cellular receptors. For TNF αthese receptors are TNF 1 and TNF 2 receptors, which with excitation through the adapter protein TRADD conducts an intracellular signal by means of NF-κB, MAPK p38 and also activates killer enzymes caspases, triggering cell apoptosis. Implementation of the action of IL-6 occurs after its interaction with receptor glycoprotein 130, gp130, the intracellular signaling pathway of which is carried out with the participation of tyrosine kinases, such as Janus kinase. It is necessary to note that the TNF family also include RANKL, the synthesized by cells of the inflammatory response ligand interacting with osteoprotegerin and RANK (receptor activating NF-κB). This signaling pathway induces the differentiation and activation of osteoclasts carrying out the resorption of bone tissue; this process is considered to be responsible for the development of local and systemic osteoporosis associated with the severe acute or chronic inflammatory reaction [22–24].

A local increase in the concentration of cytokines results in the attraction of monocytes to the tissue damage site; the leading significance here is the expression of monocyte chemotactic factor (MCP-1 or CCL2), which, interacting with the corresponding monocyte receptor, promotes their differentiation into tissue macrophages. These effector cells («big eaters» according to I.I. Mechnikov who discovered them) are the most potent force of the non-specific and immune-mediated inflammatory reaction. Being activated through the «classic pathway» (involving proinflammatory cytokines TNF-α, IL-1β, IL-6, IFN-γ), so called M-1 macrophages potently produce reactive oxygen forms and NO (by means of the expression of an inducible form of NO-synthase), synthesize and activate proteases, mainly MMP (such as collagenase and aggrecanase), which induce the destruction of cellular elements and ICM [25, 26].

It should be noted that local overproduction of proinflammatory cytokines and mediators is also can be noted in situations, wherein obvious signs of systemic inflammation, such as a significant increase in ESR and the level of C-reactive protein, may be absent, for example, with OA [27, 28]. Thus, a series of studies shows an increase in the expression and the synthesis of TNF-α, IL-1β and IL-6, as well as cyclooxygenase (COX) -2 and prostaglandin (PG) E2, in patients with severe knee OA. An increase in the concentration of proinflammatory cytokines and mediators correlated with the pain severity and the high rates of disease progression [29–31].

A similar situation can be noted with backache, wherein there is also no marked systemic inflammatory activity [32, 33]. For example, Igarashi A. et al. estimated the concentration of proinflammatory cytokines in the synovium of the arcuate joints in 40 patients (14 with hernia of intervertebral disc and 26 with spinal stenosis), who underwent surgery. In the synovial membrane and the cartilage of the facet joints, a significant increase in the concentration of IL-1, 6 and TNF-α was noted [34]. Similar data were obtained by Genevay S. et al. examining the concentration of proinflammatory mediators in the epidural fat harvested during the spine surgery from patients with radiculopathy (totally 23 specimens) and without radiculopathy (14 discs, 10 fat specimens). The authors found the significant difference in the overproduction of TNF-α: thus, the concentration of this substance in the epidural fat of individuals with radiculopathy was 6.6 (1.6–16.3) pg/ml, in individuals without radiculopathy it was – 2.3 (1.3–5.0) pg/ml with only 0.35 (0–2.28) pg/ml in the subcutaneous fat ($p < 0.001$) [35]. Cuellar J. et al. determined the concentration of IFN-γ in the punctate harvested during the discography procedure from 21 patients with degenerative changes in discs and axial pain, and 3 individuals with scoliosis without backache comprising the control. The concentration of this mediator was found to be significantly higher at intervertebral discs in individuals, experiencing pain [36].

Inflammation and sensitization of the nociceptive system

Pain is the inevitable companion of injury and inflammatory reaction. The destruction of living tissue caused by injury, infectious agent invasion or autoimmune attack leads to the direct stimulation of algetic receptors [37]. Algetic receptors – nociceptors – are free terminals of nerve fibers Aδ and C, possessing the sensing specificity for physical and chemical factors: mechanical pressure, temperature increase, changes in the pH of the extracellular media and the impact of a number of chemical substances (algogens). The primary stimulation of nociceptors underlined by the mechanism of transduction – depolarization of the cellular membrane by opening the ion canals in response to specific receptor activation, forms the sensation of acute pain. However, subsequently, if the traumatic effect stops, the nociceptors gradually come to the resting condition [37, 38]. Of fundamental importance for the extinction of noxious stimulation is the «gate control» system at the level of the gelatinous substance of the spinal cord posterior horns, where the neurons of the nociceptive system «switch» and interact with the neurons of the analgesic (anti-nociceptive) system [39, 40].

However, if the damage is significant, and accompanied by the severe inflammatory reaction, and the repair process takes a long time, the «tailoring» of changes in the nociceptive system, and the mechanism of the progressive reduction in the neuron accommodation of the algetic system swings into action, and so called ***peripheral and central sensitization*** takes place. The physiological role of these processes for a macroorganism appears to be related to the need to maintain prolonged functional dormancy in the damaged site of the body. Painful sensations that can occur with a much smaller stimulus compared with the normal state (hyperalgesia) in this situation represent a very efficient means for limiting excessive physical activity and protecting the injured part of the body from further traumatization. But, unfortunately, it is the central sensitization of the nociceptive system that becomes the most important element of the chronization of pain in pathological conditions [37, 38, 41].

The development of sensitization is tightly related to active inflammation. The change in the threshold of nociceptors arises by the action of substances, different in their nature – pain and inflammatory mediators (Table), which action translates to neurons after contacting them with corresponding membrane receptors [37, 38, 41].

There are several sources of pain and inflammatory mediators. Thus, polyunsaturated fat acid derivatives (eicosanoids) – PGE2 and leukotriene (LTE) B4 – are synthesized by a number of cellular elements in the damaged site of a tissue by the action of cytokines and DAMP. TNF-α, IL-1β

Mediators of pain and inflammation

Mediator	Source	Receptor	Physiological action	Inhibitor
Prostaglandin E2	Eicosanoid, is produced under the action of COX-2 and prostaglandin E2 synthetase in a number of cells	EP1-4	Sensitization of pain receptors, pyrogenic effect	Paracetamol, NSAID, investigational PGE-2 synthetase and EP* receptor inhibitors
Leukotriene B4	Eicosanoid, are formed from FFA under the influence of 5-LOX and leukotriene A4 hydrolase in various cells	G-protein coupled receptors (GPCRs), serpentines	Induces the chemotaxis of neutrophils, the plasma exudation, the cytokine formation	Licofelone*
Platelet activation factor	Phospholipid, forms in monocytes, neutrophils, basophils, platelets and endothelium	GPCRs	Vasodilator, thrombosis, blood pressure lowering, bronchoconstriction	Israpafant*
Bradykinin	Plasmatic polypeptide, is synthesized in liver	B1 and B2	Vasodilator, smooth muscle relaxation, plasma exudation, direct stimulation of pain receptors; causes dry cough in the treatment with inhibitors ACE**, plays the key role in the development of angioneurotic edema	Icatibant
Histamine	Amine, is synthesized and released by basophils and mast cells	H1-4	Different functions, including the pain modulation, the plasma exudation, the chemotaxis of leukocytes, the itching occurrence and others.	Anti-histamine drugs (H1-receptor antagonists, such as ketotifen), investigational H4 JNJ 7777120* inhibitor and others.
Serotonin	Amine, is synthesized by various cells	5-HT1-7	Different functions, including the pain modulation, the plasma exudation, the chemotaxis of leukocytes and others.	Antiemetics — metoclopramid, ondansetron, granisetron, tropisetron
Glutamate	Amino acid is synthesized in neurons from glutamine	AMPA (alpha-amino-3-hydroxy-5-methyl-isoxazole-4-propionic-acid) - receptors	The membrane depolarization of spinal posterior horn neurons and the spike potential formation	NBQX (AMPA/KA GluR antagonist)*
Substance P, neurokinin A (tachykinins)	Polypeptide, is synthesized in neurons	Receptors for neurokinins (NK1,2)	The nociceptive signaling on the CNS level, contributes to the «neurogenic inflammation» development, vasodilator, promotes nausea and emesis, regulates the cell proliferation and migration	Aprepitant, fosaprepitant
Calcitonin gene related peptide	Polypeptide, is synthesized in neurons	CALCRL and RAMP1	The nociceptive signaling on the CNS level (particularly important with migraine) Vasodilator	Telcagepant, Olcegepant*: MAb**: ALD-403, AMG 334, LY2951742* and others.
Nerve growth factor	Protein, is synthesized be neurons and immune system cells	Tropomyosin receptor kinase A (TrkA) and low-affinity receptor NGFR	Various functions, the main of which is the neuron proliferation, growth and apoptosis suppression; with the inflammatory reaction neoneurogenesis and sensitization of nociceptors	MAb**: tanezumab and others.*

* Drugs are not used in clinical practice (are investigational or undergo a phase of clinical trials). ** ACE — angiotensin converting enzyme, MAb — monoclonal antibodies

and IL-6 trigger the expression of key enzymes producing precursors of PGE2 and LTE B4 – COX-2 and 5-lipoxygenase (LOX), respectively. Besides, the same proinflammatory stimulus also induces the expression of membrane-associated receptors for PGE2 and LTE B4 [42, 43]. Biochemically similar is the platelet-activating factor (PAF), a phospholipid derivative synthesized by a number of inflammatory response cells [37, 42, 43].

The other source of inflammatory mediators is blood plasma penetrating the intercellular space by means of exudation: thereby nociceptors contact with bradykinin [44, 45]. Histamine – the known trigger of pain, itching and inflammatory edema, accesses the damaged site with degranulation of activated basophils and mast cells attracted by the chemotactic action of proinflammatory cytokines [46, 47]. A part of mediators is released by neurons, wherein the synthesis of these substances arises both by the action of proinflammatory cytokines and with repeated noxious impulses. These include serotonin, tachykinins (P substance and neurokinin A), calcitonin gene related peptide (CGRP), nervous growth factor (NGF), brain neurotrophic factor, glial cell line neurotrophic factor and others [48–51].

Therefore, during the inflammatory reaction the intercellular space in the damaged site is being saturated with proinflammatory mediators forming so called «inflammatory» or «sensitizing broth» [37, 52, 53]. It's effect on nociceptors is exerted through the change in the sensitivity of ion channels, penetrating the membrane of nerve terminals [41, 54]. Particularly, non-selective cation channel TRPV1, also known as capsaicin or vanilloid receptor, becomes one of the main targets of proinflammatory mediators. Normally TRPV1 responds to a temperature rise or the contact with H+ ions, providing the action of thermo- and chemoreceptors. However, with activation of membrane-associated receptors for PGE2 (here EP-4 plays the crucial role) or bradykinin, which signaling pathway occurs by means of protein kinase C, TRPV1 begins to actively pass Ca^{2+} ions into the neuron [41, 55]. The similar effect is observed during activation of potential-dependent calcium channels. Entering the cell Ca2 +, as an active cation, not only changes the transmembrane potential, but primarily acts as a biological «transmitter», activating signaling pathways by increasing the concentration of cAMP and by phosphorylating regulatory intracellular proteins, essentially changing their properties. A consequence of this is the increase of the suscep-

tibility of potential-dependent sodium (Na V 1.1-1.9) and potassium membrane channels (K2P – TREK1 and 2, TRAAK), which facilitates the depolarization of the cellular membrane and reduces the excitability threshold of the nociceptor, Figure [41, 54–56].

This process results in that the algetic receptors become more sensitive for typical for their nature stimuli (for example, mechanical or chemical irritation), and subsequently lose their specificity at all, becoming polymodal, i. e. gaining the capability to perceive any external stimuli [37, 38]. In addition, so called «silent» nociceptors, which don't perceive the primary damaging stimulus, but start to act only after the stimulation by proinflammatory mediators, are also activated [57, 58].

Finally, the phenomena of primary hyperalgesia develop (short and not high intensiveness noxious stimulus is perceived as the longer and highly intensive one; the development of primary hyperalgesia is strictly limited at damaged tissues), secondary hyperalgesia (it is located more widely, than the site of the primary damage, and covers healthy tissues), as well as allodynia (the painful sensation with the exposure of non-noxious stimuli) [37, 38, 41].

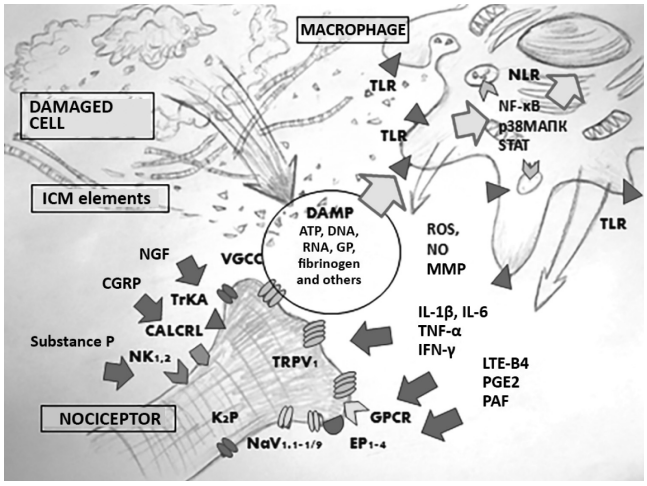
An increased excitability of neurons of the nociceptive system occurs not only at the level of nociceptive terminals, i. e. at the periphery, but also at the level of the central nervous system (CNS). The potent and long-term noxious stimulation maintaining by the inflammation-associated peripheral sensitization leads to a modification in sensitivity of posterior horn neurons and upstream parts – thalamus and cortex – of the brain. The molecular mechanism underlying this process is also associated with the effect of inflammatory mediators. In the response to the noxious stimulation neuroglia cells and neurons themselves synthesize cytokines: TNF-α, IL-1β and IL-6, and also a number of inflammatory mediators, such as PGE2, NO, substance P, CGRP, glutamate, NGF [37, 41, 59, 60].

Cytokines can directly affect neuronal cells, promoting their sensitization. This mechanism is exerted by the action of IL-1β, TNF-α as well as chemokines, particularly CCL2 and CXCL1, by activation of membrane receptors of neurons, and opening potential-dependent potassium and calcium channels. In addition, cytokines and chemokines can induce the sensitization of neurons indirectly by activation of glial cells, such as astrocytes. The latter becomes the source of cytokines and proinflammatory mediators, supporting neurogenic inflammation [61, 62].

It should be noted that the sensitization of nociceptive neurons is possibly determined by a different immune mechanism unrelated to the inflammatory reaction. The main role is played here by autoantibodies, occurring under exposure of the external tissue damage or as a consequence of autoimmune process. Autoantibodies as such, even without prominent inflammation, may cause pain, when their Fab-fragment binds to receptors of nervous cells or changes the spatial conformation of ion channels («autoimmune canalopathy»), leading to their opening and the depolarization of the nociceptive neurons' membrane. This mechanism is considered to be an important element of the development of three syndromes, presenting with nociceptive and neuropathic pain: complex regional pain syndrome, chronic pain associated with antibodies against potential-dependent potassium channels, and chronic fatigue syndrome [63]. The similar immune mechanism is described also as an element of the development of joint pain with RA, when anticitrulline antibodies directly or indirectly interact with membrane structures of nociceptors by activation of the synthesis of CXCL8 and IL-8 (the latter signal is transmitted through CXCR1 and 2 receptors) [64].

A series of experimental studies, wherein the modeling of peripheral hyperalgesia and arthritis was performed, demonstrates the significant and rapid increase of proliferative and metabolic activity of glial cells as well as a clear increase in the concentration of cytokines and inflammatory mediators in the liquor with severe local pain [65–67].

An increase in the concentration of inflammatory mediators in the CNS in the response to the strong peripheral noxious stimulation was shown for humans as well. This fact is confirmed by investigations of the efficacy of non-steroid anti-inflammatory drugs (NSAID) in surgical patients undergoing the complex anesthetic support with the use of spinal or epidural anesthesia, which allowed to collect samples of the liquor prior and after the surgical intervention. Thus, Harney D. et al. estimated the influence of nimesulide and placebo on the severity of pain, the need in morphine and the concentration of inflammatory mediators in the liquor of 92 patients underwent traumatic surgery on the chest (thoracotomy or medial sternotomy). In the placebo group the clear and significant increase of the concentration of eicosanoids was noted: the level of 6-keto PGF1-α had increased after the surgery by 54.7±25.7 pg/ml while decreased in the active treatment group by 0.6±18.2 pg/ml [68]. Buvanendran A. et al. estimated the effect of the treatment with rofecoxib and placebo on the efficacy of perioperative analgesia in 30 patients with OA, who



The molecular mechanism for sensitization of a peripheral pain receptor with inflammation. The cell and the intercellular matrix (ICM) induce the release of the «alarm molecule» (DAMP). They in turn activate Toll- and Nod-like receptors (TLR, NRL) of macrophages. This triggers the NF-κB, p38МАПК, STAT signaling pathways leading to the expression and the synthesis of cytokines (IL1, 6, TNF-α), as well as pain and inflammatory mediators (PGE2, LTE B4, PAF), the synthesis of reactive oxygen species (ROS), nitrogen oxide (NO), activation of matrix metalloproteinase (MMP). Macrophages and neurons release calcitonin gene related peptide (CGRP), substance P, nerve growth factor and others. Through respective receptors on the nerve terminal surface (EP for PGE2, GPCR for LTE B4, CALCRL for CGRP, NK1,2 for substance P, TrKA for NGF) they increase the sensitivity of ion channels TRPV1, VGCC, NaV1.1-1.9, K2P. This decreases the excitation threshold and induces the sensitization of the nociceptor.

underwent the hip replacement surgery. The researchers noted the increase in the concentration of IL6 and PGE2 in liquor samples taken after 24 h of the operation, as compared with samples taken before the operation. True, it was impossible to determine the increase in the level of IL-1β and TNF-α [69]. Similar data were obtained by Piirainen A. et al., comparing the analgesic effect of dexketoprofen and etoricoxib and their effect on the concentration of inflammatory mediators. The study group consisted of 24 patients, who underwent the hip replacement surgery. According to the results obtained both treatments efficiently decreased the level of IL-1 and IL-6 receptor antagonist in liquor, which confirmed the capability of anti-inflammatory drugs to affect the central mechanisms of pain [70].

One of the principal mechanisms, maintaining the central sensitization, is the phenomenon of neuroplasticity, comprising the ability of neurons of the nociceptive system to stably modify (decrease) the perception threshold for noxious stimuli. It is the phenomenon of «string up», that is the increase in the effectiveness of the synaptic transmission [37, 38, 71]. An important role in this process is played by purinergic receptors P1, P2X, P2Y, responding to ATP and adenosine (acting as DAMP in inflammation). The signal pathway, being triggered after activation of this receptor, results in the increase in the concentration of intracellular calcium [72, 73]. The more interesting in an aspect of the formation of the long-term memory of neurons is the receptor controlled by glutamate and glycine, NMDA (N-methyl D-aspartate). This is the membrane channel, consisting of two glycoproteid subunits NR1 and NR2 normally blocked by Mg^{2+} or Zn^{2+} ion. When interacting with glutamate, as well as the persistent depolarization of the membrane during the long-term noxious excitation (NMDA is a potential-dependent receptor), this channel opens, passing calcium ion into the cell and loosing potassium ions. The Ca^{2+} entrance in turn induces the intracellular signaling pathway by activation of calmodulin-dependent protein kinase CaMK-II followed by the phosphorylation of regulatory proteins [74, 75].

Inflammation resolution

So, an inflammatory process is the key element in the development of the peripheral and central sensitization. However, as mentioned above, inflammation is a cyclic process; its cascade, including primary damage, formation of DAMP, activation of PRR, attraction of new macrophages and other cells of the «inflammatory response», expression of cytokines and mediators, ***simultaneously*** triggers also the mechanism of gradual suppression of the inflammatory reaction [7, 76, 77]. With a normal, favorable course of inflammation, when a macroorganism «manages» with the occurred damage, the elimination of foreign material as well as own destroyed cells and degraded ICM (and as a consequence, DAMP) leads to the gradual cessation of PRR activation. This decreases the synthesis of new proinflammatory cytokines and inflammatory mediators, and previously formed molecules are subjected to the natural destruction. Accordingly, the chemotaxis of new aggressive cells of the «inflammatory response» to the damaged site gradually ceases, and already involved in this process macrophages, neutrophils and lymphocytes without the biochemical excitation («cytokine deprivation») lose their activity and undergo apoptosis. Against this background, anti-inflammatory effects begin to dominate [76, 77]. The key role in the process of the natural inhibition of the inflammatory reaction is played by two subpopulations of immune cells: regulatory T-lymphocytes (T_{per}) and type 2 macrophages (M2) [78, 79].

The former are a T-helper species (CD4+ lymphocytes), carrying the receptor for IL-2 on their surface (CD25), as well as the transcription factor Foxp3. Whereas the differentiation of CD4+CD25+T_{per} is induced by proinflammatory stimuli, this cells previously referred as «T-suppressors» function to cease immune inflammation. For this they use such tools as the synthesis of proinflammatory cytokines, particularly IL-10 and transforming growth factor (TGF)-β, as well as enzymes (granzymes, perforin), inducing the local destruction of cells of the «inflammatory response». CD4+CD25+T_{per} interrupts the interaction between antigen presenting cells (APC) and T-lymphocytes, blocking the costimulation factor CD28 by means of CTLA-4 [78].

As noted above, macrophages represents the most potent force in the development of the inflammatory reaction. It is macrophages that trigger inflammation, becoming the main suppliers of proinflammatory cytokines and mediators as well as the main tool for the destruction of damaged cells and ICM. But this concerns «classic» macrophages (M1), activated by DAMP and proinflammatory mediators. Macrophages (M2) activated by the alternative pathway — by means of proinflammatory mediators IL-4, 10 and 13, against the background of increased levels of endogenous cortisol, carry fully different responsibilities. According to the metaphor by D. L. Laskin, the author of the review devoted to this question, M2 acts during the inflammatory reaction as representatives of «The Light Side of The Force» [79]. They provide a «way out» from inflammation, synthesizing anti-inflammatory mediators and growth factors. M2 phagocytize and destroy immune complexes as well as neutrophils and lymphocytes penetrated into the damaged site, stimulate the differentiation of fibroblasts and myofibroblasts, promoting the development of fibrosis with serious tissue damage [79, 80].

The synthesis of a particular class of substances, possessing a clear anti-inflammatory potential – SPM (specialized proresolving mediators) – has the essential meaning for the successful «way out» from inflammation. SPM are derivatives of polyunsaturated fat acids, such as eicosapentaenic acid and docosahexaenic acid, and comprise several classes, having different structures and biological properties: E and D-series of resolvins (RvE1-3 and RvD1-3), protectins (PD) and maresins (MaR). They may include also derivatives of arachidonic acid (15-LOX metabolite), lipoxines A4 and B4. The main source of SPM become macrophages, and a variety of other cells involved in the inflammatory response: dendrite cells, fibroblasts, endotheliocytes and others. Effects of SPM are opposite in their nature to the action of PGE2 and LTE B4: they constrain intracellular signaling pathways (in particular, related to NF-kB), the chemotaxis, induce apoptosis of neutrophils, eosinophils and lymphocytes, decrease the permeability of endothelium and reduce pain [81–83].

It should be also noted, that natural systems of the pain control, such as the endorphin and endocannabinoid system (ECS), exert their effects not only through the decrease of the excitation of nociceptive neurons, but also the inhibition of inflammation. Thus, the ability of endorphins EM-1 and EM-2 to block the synthesis of cytokines IL-1 and IL-8 with OA and rheumatoid arthritis (RA) was shown. Furthermore, activation of the endorphin analgesic system decreases the formation of proinflammatory neuromediators, such as GPCR, tachykinins and NGF [84].

ECS (anadamide, 2-arachnoglycerol, 9-tetrahydrocannabinol) ligands exert their action through type 2 receptors – CB1 and CB2. Activation of CB1, widely represented on the synaptic membrane of neurons of the algetic system, decreases the sensitivity of vanylloid (TRPV1) receptor and inhibits the synthesis of neurotransmitters. The same receptor can be found as well on immune cells, and their interaction with endocannabinoids results in constraining the expression of proinflammatory cytokines. CB2 is predominantly localized on cells of the inflammatory response (among them it is widely represented on cells of the synovial membrane with OA and RA), and its activation exerts various anti-inflammatory effects. Thus, besides the decrease of the synthesis of cytokines, the inhibition of the chemotaxis of monocytes, the decrease in the M1-macrophage activity as well as in the MMP formation and activation are noted. In addition, ECS acts as an inhibitor of COX-2 and COX-3 (the effect similar to the effect of paracetamol). It's interesting to note, that ECS ligands, in particular 2-arachnoglycerol, are found in the synovial liquid with OA and RA, but not in healthy volunteers [85, 86]. This confirms the value of ECS activation with chronic diseases as a natural adaptive mechanism.

As seen, a macroorganism has a potent potential for the effective inflammation control, the persistent feedback system based on the interrelated action of specialized cellular elements and humoral factors. Nevertheless, with many diseases inflammation ***becomes chronic***, generating a background for maintaining the peripheral and central sensitization of the nociceptive system.

Causes of inflammation chronization

An inflammatory reaction can take a protracted or chronic character due to the constant presence of a damaging factor, provoking the inflammatory cascade [7, 14]. With infectious diseases this is the persistence of a causative agent (commonly intracellular) resistant to the immune protection of a macroorganism, as can be observed, for example, with tuberculosis or viral B and C hepatitis. With diseases of the autoimmune or immunoinflammatory nature, such as RA, systemic lupus erythematosus and ankylosing spondylitis, chronic inflammation is caused by the reaction of the aggressive immune system against own cellular elements. The development of these diseases is associated with the dysregulation of the autoantibody synthesis and with the dysfunction of the interaction of different populations of effector cells – APC, T-helpers and B-lymphocytes. Herein own antigens of various tissues of an organism and formed with their participation immune complexes are perceived as foreign, thus provoking the attack of macrophages and T-killer cells, destroying target cells. This in turn results in the appearance of large amounts of DAMP, including modified proteins, fragments of RNA and DNA, and stimulates the further autoantibody formation and the chronization of immune inflammation [78, 87, 88].

The different situation is observed with as common disease as OA. As noted above, inflammatory elements are necessary for remodeling tissues, experiencing the mechanical stress and subjected to gradual «wearing». Herein the damaged cells (chondrocytes, osteocytes, synovial fibroblasts) and ICM become the source of DAMP, which in turn stimulate PRR – Toll- and Nod-like receptors of the synovial macrophages, inducing the respective intracellular signal pathway, wherein the main transmitter is NF-kB. The subsequent expression of cytokines, and then COX-2 induces the subclinical inflammatory reaction («catabolic inflammation»), which should precede reparation processes and complete after restoring the tissue structures. However here the game enter other pathological factors. These can be a genetically determined or acquired dysregulation of inflammation, wherein proinflammatory stimuli – TNF-α, IL-1β, IL-6, PGE2 and LTE B4, activation of M1 macrophages — clearly prevail over cellular and humoral anti-inflammatory effects [42, 43, 89, 90]. The causes of this can be persistent structural and biomechanical disorders, promoting the development of the mechanical cellular stress within joint structures, even with the physiological loads, as well as metabolic disorders, such as obesity and diabetes mellitus.

Currently obesity represents one of the main sources of the systemic inflammatory activity. As is known, fat cells (adipocytes) are producers of various biologically active substances, such as leptin and adiponectin hormones, aspirin, hemerin and others, as well as a series of proinflammatory cytokines [91–95]. A massive fat pad («white» subcutaneous fat located subcutaneously and around abdominal organs), especially against the background of the insulin resistance, disturbing the natural cellular metabolism, inevitably results in hypoxia and apoptosis of a large number of adipocytes [93, 94]. This induces the expression of so called «hypoxia-associated genes», in particular, regulatory molecules HIF1α and HIF2α, stimulating angiogenesis, the adipose tissue fibrotic remodeling, and acting as potent inducers of the inflammatory reaction [95]. Free fat acids when entering blood plasma possess their own proinflammatory potential, acting as DAMP. Of course, necrobiotic modifications in adipocytes result in the constant release of other signaling molecules as well, such as HMGB1, inducing the proinflammatory signaling pathway, as already described above, through activation of Toll-like receptors. Thus, adipose tissue becomes the constant «attractant» for monocytes (besides, adipocytes as such actively express the chemoattractant MCP-1/CCL2), where they undergo the differentiation to M1-macrophages by the classic pathway. These effector cells produce large pads in adipose tissue forming characteristic crown-like structures (CLS). A «work» of the wide subpopulation of adipose tissue-associated M1 macrophages stipulates not only the local but systemic increase also in the detectable concentration of proinflammatory cytokines in blood plasma [96, 97].

Obesity is tightly connected with the problem of immune resistance and type 2 diabetes mellitus (DM2). DM2 is yet another cause for the development of systemic inflammation. A new confirmation of this fact was a large-scale study by de Rekeneire N. et al., who carried out an analysis of the concentration of inflammatory mediators in 3075 patients aged from 70 to 79 years, suffering from type 2 DM, impaired glucose tolerance, and those without these problems. The authors clearly showed, that concentrations of CRP, TNF-α and IL-6 in individuals with DM2 and impaired glucose tolerance were significantly higher (on the average nearly 2-fold, $p < 0.001$), than in the control group. Herein the more severe course of DM, wherein an increase in the glycosylated hemoglobin HbA(1c) was noted, was associated with the highest increase in inflammatory markers [98].

The development of inflammation against the background of hyperglycemia was associated with the phenomenon of the oxidative stress, occurring with the disturbance of energy metabolism in cellular mitochondria. This process is caused by the accumulation of polyols (polyhydric alcohols), the formation of

glycosylated proteins (AGE, Advanced glycation end products), the connection of alternative pathways providing energy to the cells in conditions of insulin resistance (hexosamine pathway), activation of protein kinase C upon the exposure of diacylglycerol etc. Reactive oxygen species cause the damage of DNA and regulatory proteins, thereby triggering proinflammatory signaling pathways (in particular, activation of NF-κB) and the apoptotic program. Necrobiotic modifications of the cell become, respectively, a signal for resident macrophage cells, triggering the inflammatory cascade [99–102].

The intervention of systemic metabolic inflammation accompanied by the overproduction of cytokines and other proinflammatory mediators, to the natural course of the local inflammatory reaction is able to disturb its cycling and block the feedback mechanism, including the synthesis of anti-inflammatory substances and the differentiation of «alternative» M2 macrophages. Furthermore, the development of diabetic micro- and macroangiopathy as well as polyneuropathy makes the process of the damaged tissue remodeling difficult, and creates additional conditions for the transition of an acute to a chronic inflammatory reaction.

The elderly patients are of great importance for the chronization of inflammation. As known, one of the most common theories of aging of a living organism connects this process with the oxidative stress experienced by all of the cells of an organism, including stem cells responsible for the reproduction of all lines of specialized cellular elements. The accumulation of damaged with an oxidation DNA segments acts as a «biological clock»: it results in the decrease of the effectiveness of transcription and translation of the genetic information, and errors in the synthesis of important macromolecules. This delays reparation processes, and consequently remodeling processes no longer have time to compensate for damage, and against the background of maintaining inflammation, the amount of DAMP, keeping the synthesis of proinflammatory substances going, consistently grows. Furthermore, proteins damaged by reactive oxygen species and/or incorrectly folded proteins (for example, if their tertiary structure is disturbed) become a subject of the attack of immune cells, the formation of antibodies and immune complexes.

Conclusion of the first part

Inflammation and pain are closely related processes. A primary tissue damage causes the release of particular substances, «damage witnesses» DAMP (HSP, HMGB1, S100, ATP, DNA, RNA, glycoproteids, fibrinogen and others), stimulating the specific receptors (PRR) of resident macrophages (Toll- and Nod-like). Activation of these receptors through the system of signaling pathways (NF-κB, MAPK p38, STAT and others) triggers the action of genes responsible for the mRNA expression of proinflammatory cytokines, such as TNF-α, IL-1β, IL-6, IFN-γ. The «inflammatory cascade» develops – cytokines and chemotactic factors synthesized by macrophages attract new «inflammatory response» cells (M1 macrophages, neutrophils, T and B-lymphocytes, basophils, mast cells) to the damaged site and promote their differentiation and activation. The synthesis of proinflammatory mediators such as PGE2, LTE B4, NO, CGRP, substance P, glutamate, NGF becomes a response to the primary damage. They in turn induce sensitization of peripheral pain receptors and neurons of the nociceptive system thereby drastically increasing their excitability and promoting chronization of pain. The molecular basis of the phenomenon of peripheral and central sensitization is activation of particular potential-dependent (such as TRPV1), purinergic and glutamate (NMDA) receptors on the neuronal membrane.

Transparency

The review was performed without any sponsor's support. The authors are fully responsible for the submission of the final version of this paper.

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