INTRODUCTION

Although almost three years have passed since the World Health Organization (WHO) declared a pandemic, COVID-19 is still an unsolved problem, thereby attracting great scientific interest. The disease has a heterogeneous clinical picture with multiple manifestations from different organs and systems. Currently, COVID-19 is perceived as a polysyndromic inflammatory disease involving not only the respiratory system, but also the musculoskeletal system, the cardiovascular system, the skin, the excretory and the nervous system, and is accompanied by a number of hematological, gastrohepatoenterological and endocrine disorders. Various pain phenomena also appear in the clinical presentation of the disease, often as a single manifestation or in combination with symptoms from different organs and systems. The pathogenesis of pain is complex and there is still no consensus on the exact driving mechanisms. Several different signaling pathways play an important role in the generation of pain impulses and perception. They are different for different types of pain. At this stage, the role of angiotensin-converting enzyme 2 (ACE), the renin-angiotensin system (RAS), angiotensin 2 receptors (AT2R), direct neuronal invasion of the virus, the involvement of pro-inflammatory cytokines, hypoxia, the involvement of macrophages, is discussed, as well as the role of overactivity of the immune system, causing the so-called “cytokine storm”. Pain is the result of complex biochemical processes influenced to varying degrees by biological, physiological and social factors. Our knowledge at this stage remains scarce and is the subject of many studies on the key pathogenic mechanisms. Therefore, the purpose of this review is to describe the known mechanisms for the occurrence and persistence of pain in patients with COVID-19, as well as to classify the pain phenomena and present its most common localizations. The diagnosis and treatment of COVID-19 and associated pain should be carried out by a multidisciplinary team of specialists, given the heterogeneous clinical presentation of the disease.

Key words: COVID-19, pain, pathogenetic mechanisms
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**Pathogenetic aspects of pain in COVID-19**

The pathogenesis of pain is complex and there is still no consensus on the exact driving mechanisms. There are several different signaling pathways that have been implicated in the generation of pain impulses and pain perception, presented in Figure 1.

**ACE2 involvement**

At this point, we know that the SARS-CoV-2 virus uses angiotensin-converting enzyme 2 (ACE2) as a cellular entry receptor. The entry “spike protein” – S, consists of subunits S1 and S2, which are responsible for membrane attachment and fusion, respectively. Spike protein binds to the human ACE2 (hACE2) receptor in the cell membrane via the S1 subunit of the receptor-binding domain (RBD) [2]. The transmembrane protease serine protease-2 (TMPRSS-2) and the host cell ADAM metallopeptidase domain 17 (ADAM17) are required for the capture of the S protein to enable viral and host membrane fusion via the S2 subunit [3]. Consequently, SARS-CoV-2 enters the cell by endocytosis and the viral RNA is released for replication and translation from the host cell. Subsequently, viral assembly and exocytosis of the new viral particles that will infect new cells take place.

ACE2 is a metalloproteinas a ectoenzyme that is found in almost all human organs. Its expression varies in different organs and tissues and is greatest in epithelial cells of the lower respiratory tract, such as type II alveolocytes, secretory cells, vascular endothelium, nasal cilia and olfactory cells [4]. It is also found in gastrointestinal tract, cardiac muscle, corneal epithelium, synovial membrane, kidney epithelium, bile duct, gallbladder epithelium, testicular Sertoli cells, and alveolar macrophages [5]. ACE2 plays an essential role in the renin-angiotensin system (RAS) maintaining the fluid and electrolyte balance.

**RAS involvement**

All the elements involved in the renin-angiotensin (RAS) system are targets of viral damage, therefore in the genesis of disease symptoms, including pain.

Serum renin, which is synthesized by the kidneys, is converted into angiotensin I (Ang I) under the influence of angiotensinogen. The main function of angiotensin-converting enzyme (ACE) is to convert angiotensin I to angiotensin II (Ang II). The active form is actually angiotensin 1-7 (Ang-(1-7)). It is an octapeptide hormone that acts by binding to two types of G-protein coupled receptors (GPCRs), Ang I type 1 (AT1) receptor (AT1R) and Ang type 2 (AT2) receptor (AT2R) [6]. Viral interactions with GPCR and Mas receptors are the most relevant to pain from the perspective of this review. Furthermore, octapeptide Ang-(1-7) has a very high affinity for the Mas receptor and is about 100 times more se-

**Fig. 1. Pathogenetic mechanisms of pain in COVID-19**

Abbreviations: ACE2 = angiotensin-converting enzyme 2, RAS = renin-angiotensin system, AT2R = angiotensin 2 receptors
Angiotensin 2 receptors (AT2R) involvement

Angiotensin 2 receptors (AT2R) are also involved in the pathogenesis of pain. This receptor subtype is directly related to pain control and may act as a co-protagonist, especially in acute pain [8]. In case of SARS-CoV-2 binding, the host AT2R and Mas-mediated Ang-(1-7) effects have essential roles in the pathogenesis of pain. The activation of angiotensin 2 (Ang-II) receptor pathways may trigger a pathogenic cascade that affects the spinal transmission of nociceptive information can take place. Thus, SARS-CoV-2 infection may directly affect these mechanisms be altering the balance between the neuromodulatory systems of nociception leading to the onset of pain.

Activation of angiotensin 1 receptors (AT1R) affects nociception by phosphorylation of p38 mitogen-activated protein kinase (MAPK) (10). Furthermore, the Ang II octapeptide is not the only cleavage product derived from the action of ACE2. Angiotensin III (Ang III), which is a C-terminal metabolite of angiotensin II, can also bind to AT1R and participate in spinal nociceptive transmission [11]. Therefore, SARS-CoV-2 infection in the human dorsal horn may disrupt the balance between two opposing systems: the ACE/Ang II/AT1 receptor axis and the ACE2/Ang-(1-7)/Mas axis [12].

AT2R is also involved in pain control and may play a protagonist/co-protagonist role [13]. The exact signaling pathway still remains unclear, but the coupling of AT2R with the G-protein is discussed as a working hypothesis. It ensures the activation of serine/threonine protein phosphatase 2A (PP2A) in neurons, the generation of prostaglandin E2 from arachidonic acid by the enzyme cyclooxygenase-1 (COX-1). This ultimately stimulates K+ channels and causes hyperpolarization of plasma membranes [14]. There are other signaling pathways such as the release of bradykinin and nitric oxide (NO). There is evidence that angiotensin II can induce COX-2 induction. This activates the inflammatory cascade, various cytokines, metalloproteinases and pro-inflammatory mediators are released.

CNS involvement

The pain may also be the result of the direct neuronal invasion of the virus because it has a pronounced tropism to the nervous tissue. SARS-CoV-2 has also been detected in cerebrospinal fluid [15]. The central nervous system (CNS) can also be affected by a retrograde mechanism. Respiratory droplets containing SARS-CoV-2 reach the nasal mucosa, and the virus can directly infect olfactory sensory neurons, then enter the brain via the olfactory nerve [16]. SARS-CoV-2 can spread to the CNS through the vessels because the capillaries (blood and lymphatic) found in the nasal mucosa express ACE2 receptors. ACE2 receptors are also expressed in glial cells as well as in neurons. The high affinity of the virus for these receptors can cause direct damage to neuronal cells, most commonly sensory neurons [17]. In support of the fact that SARS-CoV-2 possesses neurotropism is that part of the clinical manifestations of the disease is neuropathy, accompanied with or without neuropathic pain [18]. Namely, the ability to invade the central nervous system [19] is considered to be the cause of one of the most common symptoms of the disease – anosmia and dysgeusia [20]. It is assumed that it is actually dysautonomia [21] due to brainstem invasion [22].

One of the hallmarks of the disease is the dissociation between oxygen desaturation and the absence of overt dyspnea, which is currently attributed to brainstem dysfunction [23]. The propensity of the virus for neuronal invasion may result in those who recover from the acute stage of the disease not only experiencing chronic respiratory symptoms (cough, shortness of breath) and difficulty returning to their usual motor capacity (so-called prolonged COVID) [24], but also with long-term neurological consequences such as dysautonomia, neuromuscular weakness, easy fatigue, cognitive impairment and anxiety [25]. The presence of the virus and its replication in nervous tissue is difficult to prove in clinical
practice. Therefore, virus/ACE2 binding and receptor expression in neural tissue does not necessarily mean that SARS-CoV-2 causes direct CNS and/or PNS damage in all patients. Chronic pain manifestations manifesting as diffuse myalgias and arthralgias could be an expression of nociceptive pain, which from a pathophysiological point of view usually refers to the presence of tissue damage.

**Cytokines involvement**

The involvement of pro-inflammatory cytokines is also discussed [26]. From the studies done to date, it is clear that the levels of cytokines in the serum of patients with COVID-19 are elevated, including tumor necrosis factor (TNF), interleukin 2 (IL-2) and granulocyte-macrophage-colony stimulating factor (GM-CSF) [27]. This is discussed as one of the pathophysiological mechanisms of the occurrence of one of the most common pain symptoms in the disease, namely headache.

**Hypoxia involvement**

Hypoxia, which occurs as a result of the viral invasion of the lung parenchyma, also has an influence. Theoretically, impaired gas exchange leading to cerebral hypoxia increases anaerobic cerebral metabolism, leading to the accumulation of acidic metabolites. This can lead to changes in cerebral blood flow, with dilatation of cerebral vessels and cerebral edema, which clinically manifests with headache and varying degrees of quantitative and/or qualitative changes in consciousness.

**Macrophages involvement**

Macrophages are also involved in the pathogenesis of pain. They, as cells of the immune system, stimulate the production of inflammatory mediators, such as IL-1β, TNF and bradykinins. These mediators primarily affect the function of sensory neurons in the dorsal root ganglion (DRG) region and through complex processes of sensitization (activation) can induce pain and hyperalgesia [28]. Macrophages contribute to both the initiation of pain symptoms (acute type of pain) and the maintenance of pain (a chronic type of pain) [29]. These cells can adopt different phenotypes: an inflammatory (M1) phenotype when they infiltrate the DRG during acute inflammatory pain, and a divisive (M2) phenotype that probably works by restoring the mitochondrial functions of neurons, i.e. to participate in reparative functions [30]. Their effect is determined by several complex axes (signaling pathways). The membrane glycoprotein OX-2 (CD200), which is expressed on cells of the myeloid lineage, and its receptor (CD200R) act as important checkpoints of the immune response by inhibiting the signaling pathways of mitogen-activated protein kinase (MAPK) and lipid kinases (PI3K/Akt) [31]. Thus, the inhibitory CD200/CD200R axis works to prevent excessive inflammatory stimulus, even when secondary to infectious agents. Through signaling networks involving molecules and transcription factors, it can promote the polarization of macrophages towards the beneficial M2 phenotype.

**Involvement of the hyperactivated immune system**

Last but not least, the role of overactivity of the immune system, which is observed in part of the patients infected with SARS-CoV-2, is also discussed. A “cytokine storm” resulting from active immune-mediated inflammation occurs as a result of dysregulation in the production of soluble immune mediators. There is activation and inhibition of different subtypes of immune cells and, therefore, a dysregulation between the production of mediators with anti-inflammatory action and substances that cause extraction of other cellular elements, damage to the endothelium and alteration of the microcirculation. Proinflammatory cytokines such as IL-6, TNF-α, IL-1β, IL-8, and IL-12 are released, as well as IFN-γ inducible protein (IP10; also called chemokine motif ligand 10, CXCL10), macrophage inflammatory protein 1A (MIP1A) and monocyte chemoattractant protein 1 (MCP1) [33].

**Types of pain in COVID-19**

The spectrum of pain in patients with COVID-19 is heterogeneous and the most common symptoms are headache, sore throat (angina), arthralgias, myalgias, chest pain (including pleurodynia), abdominal pain, neuropathic pain and others.

Sore throat is one of the most common symptoms. Its frequency varies within 12.5-23.2% of patients [34]. It is assumed that the mechanisms for the appearance of this symptom are similar to those of other respiratory viruses. The role of inflammatory mediators (e.g., prostaglandins and bradykinin) in the airways in response to SARS-CoV-2 infection is central, thereby affecting sensory nerves in tissue structures of the throat [35]. Another factor is the binding of the virus to its receptor which is also ex-
pressed on the epithelial cells of the pharynx, leading to cell destruction and subsequent inflammation.

Patients with COVID-19 may also experience chest pain. Chest pain is defined as discomfort or pain in the area between the neck and upper abdomen. According to different authors, the frequency of this symptom varies between 1.6-17.7% [36]. Chest pain may be a risk factor for developing severe COVID-19 or death [37]. It has been suggested that chest pain may result from cardiac damage or pleural inflammatory infection [38]. Cardiomyocytes possess ACE2 receptors, and the virus can directly invade them and cause myocardial damage, leading to an increase in biomarkers of myocardial necrosis [39]. The damage can also occur in the course of a severe inflammatory reaction, the so-called “cytokine storm”. Also, certain inflammatory mediators released into the pleural space can activate pain receptors in the pleura, thereby causing chest pain [40]. Cardiac damage may also result from respiratory dysfunction and hypoxemia induced by COVID-19 [41].

Abdominal pain is also present in the spectrum of pain manifestations. In patients with COVID-19, abdominal pain may be one of the first symptoms of the disease. Its frequency ranges from 1.9-14.5% [42]. Several factors are involved in the pathogenesis of abdominal pain. ACE2 is abundantly expressed in the gastrointestinal tract, especially in the small and large intestines, therefore SARS-CoV-2 can attack the digestive system by binding to ACE2 and cause pain through direct viral invasion [43]. Pneumonia is the most common extra-abdominal cause of abdominal pain, especially in childhood, and enlarged mesenteric lymph nodes are considered a potential contributing mechanism in the presence of abdominal pain [44].

In patients with SARS-CoV 2, pains from the musculoskeletal system – arthralgias and myalgias – are often found. Myalgia is a symptom of muscle pain or discomfort and is also manifested in systemic or local infection [45]. It is usually diffuse rather than localized. According to different sources, the incidence varies from 49.3 to 60.9% in patients with COVID-19 [46]. Myalgia during SARS-CoV 2 infection is associated with elevated levels of interleukin-6. ACE2 is expressed by skeletal muscle myocytes, i.e., the virus can directly infect muscle cells and lead to cell destruction, which is established by an increase in the values of CPK and LDH in the serum of patients [47]. Also, inflammatory cytokines stimulate the production of prostaglandin E2, and prostaglandin E2 mediates pain through peripheral pain receptors. Involvement of the peripheral nervous system in SARS-CoV 2 infection can also lead to muscle pain [48]. Arthralgias are joint pains. They are not a common symptom, and approximately 2.5% of patients with COVID-19 report arthralgia [49]. Arthralgia during SARS-CoV 2 infection is associated with increased levels of pro-inflammatory cytokines such as interleukin-6, interleukin-1 and TNF alpha. Synoviocytes express ACE2, i.e., the virus can enter the synovial membrane. Like myalgias, inflammatory cytokines stimulate the production of prostaglandin E2, which mediates pain through peripheral pain receptors.

The most common pain symptom in patients with COVID-19 is a headache. The mechanism of headaches caused by COVID-19 remains unclear. Its frequency varies from 35.4 to 55.8% of patients [50]. Several reasons are possible. In patients with COVID-19 who report headaches, elevated serum levels of cytokines [51] such as tumor necrosis factor (TNF), interleukin 2 (IL-2), and granulocyte-macrophage-colony stimulating factor (GM-CSF) have been found [52]. These cytokines, released by immune cells in response to other viral infections, have been implicated as a cause of headache [53]. Also, when SARS-CoV-2 invades the lung tissue, it can cause disorders of alveolar gas exchange, leading to hypoxia in the brain, an increase in the anaerobic metabolism of mitochondria in brain cells, and the accumulation of acidic metabolites. This leads to cerebral blood flow obstruction, brain cell edema, cerebrovascular dilatation, and headache due to ischemia and congestion [54]. Additionally, headaches may result from direct invasion of the nervous system by SARS-CoV-2. This often leads to neurological symptoms other than headache, such as dizziness, nausea, and vomiting [55].

Pathoanatomically, brain tissue congestion and edema as well as neuronal degeneration were observed at autopsy of patients with COVID-19. SARS-CoV-2 is also found in cerebrospinal fluid. The neuronal pathway is an important way for neurotropic viruses to enter the central nervous system. Experimental studies have been done in transgenic mice that show that members of the coronavirus family, such as SARS-CoV or the Middle East respiratory syndrome coronavirus (MERS-COV), can enter some areas of the brain via the olfactory nerves when administered intranasally. Retrograde infiltration of the virus into CNS areas such as the trigeminal nerve through the conjunctiva of the eye or through the taste buds of the tongue upon exposure to aerosol droplets containing SARS-CoV-2 is also possible.
Conclusion

Pain is a subjective symptom associated with a very wide range of diseases, including COVID-19. Pathogenetic mechanisms of pain in different diseases are not identical. Complex interactions at the cellular and intercellular levels are discussed and explored, some of which have been elucidated.

The pain puzzle is yet to be clarified in light of COVID-19. The psycho-emotional state and the function of the immune system are closely related and determine a significant part of pain sensations. Personalized medicine and individual care for each patient, including those from COVID-19, is a necessity.

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