IJCNP, Volume 3, Issue 1, 2025 ISSN: 2995-536X
https://medicaljournals.eu/index.php/IJCNP

INTERNATIONAL JOURNAL OF COGNITIVE NEUROSCIENCE AND PSYCHOLOGY

Patients with Parodont Diseases Have Disorders of Vascular Endothelial Function

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Abstract: Endothelin (ET), a key regulatory peptide, plays a crucial role in various physiological and pathological processes, including the progression of periodontal diseases. This study examines the multifaceted involvement of ET in the intricate interactions between periodontal pathogens, host defense mechanisms, and the immune system. Pathogenic bacteria such as Porphyromonas gingivalis and Aggregatibacter actinomycetemcomitans release virulence factors that induce immune activation and tissue destruction. In response, innate and adaptive immune cells produce pro-inflammatory cytokines (IL-1, TNF-α, IL-8) and matrix metalloproteinases, which, while protecting against infection, can also contribute to tissue damage. ET further amplifies inflammation by promoting cytokine and chemokine production, attracting additional immune cells to the affected site. Moreover, its role in impairing microcirculation leads to hypoxia and tissue degeneration, exacerbating periodontal inflammation. These findings highlight ET as a potential therapeutic target for modulating inflammation and preventing periodontal tissue destruction.

Key words: Endothelin, periodontal disease, inflammation, cytokines, immune response, Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, matrix metalloproteinases, microcirculation, hypoxia.

Introduction.

Insufficient formation of various biologically active substances in the endothelium, leading to an imbalance of these substances, is called endothelial dysfunction (ED). This term describes the numerous changes in the functional status of the endothelium that occur in response to external stimuli. But a gradual and permanent disruption of the functioning of the endothelium occurs with prolonged exposure to damaging factors. ED is considered a condition in which the endothelium is unable to produce nitric oxide (NO) in sufficient quantities. Insufficient NO production is considered as the main sign of ED, since NO is the most damage-sensitive factor and plays an important role in the regulation of almost all endothelial functions. Inflammatory processes and atherosclerosis are among the many pathological conditions caused by this imbalance of NO production. In the modern scientific environment, the endothelium is considered dynamic, heterogeneous and widespread. It performs the most important tasks for maintaining the body's homeostasis. The endothelium is involved not only in secretory and synthetic processes, but also in metabolism and immune protection. Its cells can synthesize NO, which regulates vascular tone and blood pressure. The endothelium is also involved in metabolism, regulating the metabolism of lipids and carbohydrates and promoting the immune response, protecting the body from inflammation and pathogens. Currently, a huge amount of experimental data has been accumulated that allows us to identify a number of basic functions of the endothelium. First, angiogenesis, the process of forming new blood vessels necessary for tissue growth and healing, depends on the endothelium. Secondly, the endothelium regulates the level of lipids in the blood and prevents the development of atherosclerosis. Thirdly, the endothelium is responsible for maintaining the balance between vasoconstriction and dilation necessary to maintain normal blood pressure. Finally, the endothelium regulates the hemocoagulation potential of blood plasma, maintaining the balance of blood clotting and thinning processes; this is vital for maintaining normal blood circulation and preventing thrombosis [2.4.6.8.10].

Material and methods

The endothelium also performs an important transport function, transferring substances from two sides between the

blood and other tissues. The transport of substances through the endothelium is carried out using active and passive mechanisms, ensuring the maintenance of homeostasis and the excretion of metabolic products. In addition to its transport function, ET plays an important role in the reception of signals that regulate various processes in the body. This is due to the fact that endotheliocytes have unique receptors for various cytokines and adhesive proteins. By expressing a variety of molecules on their surface, endothelial cells play a key role in regulating inflammatory processes and the immune response.

These molecules, acting as receptors, ensure the adhesion of leukocytes to the endothelium, as well as their subsequent transmigration through the vessel wall. Substances of endothelial origin can be divided into several groups depending on the rate of their absorption in the endothelium and how they are secreted (intracellular or extracellular):

1. Factors of lifelong learning: In the endothelium, these substances are constantly synthesized and released into the bloodstream. NO and prostacyclin are examples of such factors. Due to the fact that it dilates blood vessels and lowers blood pressure, NO plays an important role in regulating vascular tone. Prostatilin promotes vasodilation and prevents platelet aggregation.
2. Factors released during stimulation: In endothelial cells, these substances accumulate and are released in response to stimuli, activation, or damage to the endothelium. Such factors are Willebrand factor (VF), which is involved in the process of blood clotting; P-selectin, which is involved in the adhesion of leukocytes to the endothelium; and tissue plasminogen activator (t-PA), which is involved in fibrinolysis.
3. Activation factors: These substances are mainly synthesized in the endothelium during activation. Their synthesis is usually minimal, but when the endothelium is activated, their concentration increases dramatically. E-selectin, ICAM-1, VCAM-1, and ET-1 are examples of cell adhesion processes and inflammatory reactions. Fibrinolysis is controlled by an inhibitor of plasminogen activator-1 (PAI-1), which also helps to prevent excessive dissolution of blood clots.
4. Endothelial cells not only synthesize and accumulate a number of substances, such as t-PA, which plays a key role in the dissolution of blood clots, but also contain membrane receptor proteins on their surface. Such receptors include thrombomodulin and the protein C receptor, which are involved in regulating blood clotting and maintaining its fluid state, preventing the formation of blood clots.

Results and discussion

Inflammation can manifest itself as a small focus or a large area covering large areas of tissue. It can be not only focal, but also spread over a larger area or even over the entire organ. In some cases, the inflammation can lead to systemic inflammation such as vasculitis or systemic lupus erythematosus. Even localized inflammation can cause systemic reactions affecting the entire body, which makes it difficult to distinguish systemic from localized inflammation. For example, an increase in body temperature, changes in blood composition, and other systemic manifestations may be caused by local inflammation [1.3.5.7.9.11].

The inflammatory process localized in the histione (connective tissue) is a multi-stage phenomenon characterized by a sequential change of phases, each of which has unique features and mechanisms of development.: Alteration: This is an injury to cells and tissues at the beginning of the inflammatory process. Physical, chemical, and biological agents are among the many sources of alteration. Damaged cells secrete prostaglandins and cytokines, one of the inflammatory mediators that trigger a number of inflammatory reactions. At this stage, the first damage to cellular structure and function occurs. This gives reason to expect further inflammatory changes.

The next stage involves the release of blood cells, fluid, and proteins from blood vessels into surrounding tissues. Increased permeability of the vascular wall during inflammation ensures the penetration of immune cells, such as neutrophils and macrophages, into damaged tissues, accompanied by exudation. These cells play a key role in protecting the body by phagocytosing pathogens and removing dead cells. In addition, they secrete additional inflammatory mediators, which enhances the immune response. Proliferation: The active proliferation of cells, more often hematogenous and histiogenic, less often parenchymal and epithelial, characterizes the final phase of inflammation. Proliferation improves the healing of damaged tissues and eliminates inflammatory foci. At this stage, the following processes occur:: active cell division, synthesis of matrix proteins and creation of a new vascular network. Proliferative processes contribute to the completion of the inflammatory process, restoring the structure and function of damaged tissues.

One of the most noticeable signs of inflammation is a change in blood microcirculation, accompanied by a violation of its rheological properties. Initially, a reflex spasm of small vessels occurs, narrowing the lumen of the arterioles and precapillaries. However, this spasm is quickly replaced by an expansion of the entire vascular network in the area of

inflammation, especially venules and postcapillary vessels. As a result, the permeability of the vascular wall increases, which leads to the release of plasma and blood cells into the surrounding tissues. This increases the inflammatory process, causing swelling and redness of the inflamed area [7.9.11.13].

Research initiated in 2010 by F.D. Aiuto has opened a new chapter in understanding the pathogenesis of arterial hypertension (AH), revealing a close relationship between this disease and impaired endothelium-dependent vascular relaxation. This disorder has been found both in animals with various experimental models of hypertension (for example, spontaneously hypertensive rats) and in humans with various types of hypertension, including essential (primary), renovascular (caused by narrowing of the renal arteries) and others [48; p. 35]. The endothelium plays an important role in the regulation of vascular tone, blood clotting, inflammatory reactions, and other processes. Endothelium-dependent vascular relaxation is a mechanism by which endothelial cells release substances such as NO, prostacyclin, and endothelial hyperpolarizing factor (EDHF), which cause vasodilation and a decrease in blood pressure. With hypertension, ED is observed, that is, a violation of its ability to produce a sufficient number of vasodilators and / or excessive production of vasoconstrictors. This leads to an increase in vascular tone, an increase in peripheral resistance and, as a result, an increase in blood pressure [6.8.10.12.14].

One of the mechanisms leading to ED in hypertension is an increase in intracapillary pressure, which occurs following an increase in systemic blood pressure. This creates an additional mechanical load on the endothelial cells, which leads to their damage and impaired function. The damaged endothelium produces fewer vasodilators and more vasoconstrictors, such as ET-1, which contributes to a further increase in blood pressure and the formation of a vicious circle. Further studies have shown that ED is not only a consequence, but also the cause of the development and progression of hypertension. Patients with metabolic syndrome, which is characterized by obesity, insulin resistance, and dyslipidemia, have impaired endothelial function even before hypertension develops. This disorder contributes to the development of atherosclerosis, thrombosis, and other cardiovascular complications.

The formation of radicals, especially the superoxide anion, stimulates an increase in intramural pressure. This radical bond binds to the endothelium produced by NO and leads to the formation of peroxynitrite, which has a cytotoxic effect on endothelial cells and stimulates mitogenesis of smooth muscle cells. As a result of this radical bioavailability, he was pulled out. NO and prostacyclin lead to the formation of vasoconstrictor factors. Thus, ED increases the formation of these components, in particular ET-1, thromboxane A2 and prostaglandin H2. In addition, increased angiotensin II formation promotes vasoconstriction and increased ET-1 synthesis. The key function of the endothelium of postcapillary venules is to trigger and ensure the migration of leukocytes from the bloodstream into the tissues to the site of potential damage or infection. However, when the endothelial layer is damaged, the migration of leukocytes is disrupted, which leads to platelet activation. Platelets, using adhesion molecules, attach to the exposed collagen fibers of the vascular wall, forming aggregates called "rosettes". These "sockets" are able to penetrate through the damaged endothelium into the focus of inflammation, performing their protective functions. This process is necessary to enhance the inflammatory response and the involvement of platelets in the body's immune responses. The formation and migration of such cellular complexes increases the efficiency and speed of healing of damaged tissues, ensuring the delivery of necessary cells and substances to the site of inflammation. Moreover, the normal functioning of the endothelium and its interaction with platelets and other blood cells plays a critical role in protecting the body from infectious agents and various damaging factors. In addition, endothelial cells are indispensable in the process of inflammation and tissue repair after damage, because they play an important role in regulating vascular tone, coagulation, and maintaining homeostasis. Damage to the endothelium causes a protective reaction of the body, including activation of blood clotting and vasospasm to prevent blood loss. However, in pathological conditions, this reaction can cause or worsen the course of the disease. Several main factors determine the predominance of aggregation and vasoconstriction. The first step is to reduce the secretion of substances that prevent aggregation, coagulation and vasoconstriction. Secondly, under such conditions, the endothelium enhances the release of aggregates, coagulants, and vasoconstrictors.

The interaction of ET-1 with ET-B receptors suppresses apoptosis of mature dendritic cells. Blocking of these receptors leads to increased sensitivity of dendritic cells to apoptosis, which impairs their ability to present antigens and produce IL-12. ET-1 promotes the adhesion and rolling of leukocytes along the walls of blood vessels, which is the initial stage of their migration to the focus of inflammation. This process is mediated by the interaction of ET-1 with two types of receptors on the surface of endothelial cells: P-selectin receptors and ET-B receptors. P-selectin binds to carbohydrate ligands on the surface of leukocytes, ensuring their primary adhesion to the vessel wall. ET-B receptors, in turn, are

G-protein-coupled receptors, the activation of which leads to a number of intracellular signaling cascades that enhance the expression of P-selectin and other adhesion molecules [108; P. 942-949]. Studies have shown that blocking P-selectin receptors or ET-B receptors with specific antibodies or antagonists leads to a significant decrease in leukocyte rolling and adhesion. For example, in animal experiments, it has been shown that the administration of antibodies against P-selectin prevents the development of an inflammatory reaction in blood vessels after ischemia-reperfusion. ET, a powerful vasoconstrictor peptide that is ten times more potent than angiotensin II, plays an important role in the regulation of vascular tone. However, its effect on the body is ambiguous and depends on concentration. Normally, at physiological concentrations, endothelin performs an important function of maintaining vascular homeostasis. By binding to endothelial receptors, it stimulates the production of vasodilators, contributing to vasodilation and lowering blood pressure. This allows you to maintain normal blood flow and ensure adequate blood supply to organs and tissues. However, in pathological conditions accompanied by endothelial damage, such as atherosclerosis, inflammation, or injury, endothelin levels can increase significantly. Under such conditions, ET begins to interact not only with endothelial receptors, but also with receptors of vascular smooth muscle cells. This leads to activation of signaling pathways that cause smooth muscle contraction and vasoconstriction, which in turn contributes to increased blood pressure and impaired blood supply to organs and tissues.

ET-1 plays an important role not only in the regulation of vascular tone, but also in the modulation of inflammatory processes. It is able to affect lymphocytes, changing their ability to produce cytokines, which are key mediators of inflammation. ET-1 production is enhanced by various factors, including pro-inflammatory cytokines such as TNF-α and IL-1, as well as thrombin, vasopressin and angiotensin II. This leads to an increase in the expression of endothelin mRNA and its receptors, which in turn enhances the inflammatory response. It is interesting to note that inflamed gums are also characterized by high immunoreactivity to ET-1, which indicates its active participation in the pathogenesis of inflammatory periodontal diseases. Although ET-1 has the ability to attract neutrophils and monocytes to the site of inflammation, acting as a chemoattractant, its effect on the migration of these cells is significantly weaker compared to other chemokines such as IL-8 and MCP. They are produced by various cells in response to inflammation or infection and create a concentration gradient that directs white blood cells to the site of injury. Unlike these chemokines, ET-1 exhibits a weaker chemotactic effect on leukocytes. Activation of these receptors leads to a number of intracellular signaling cascades that can have both stimulating and inhibitory effects on leukocyte migration.

Conclusion

Thus, ET, being one of the key regulatory peptides, plays a multifaceted role in the body, participating in a variety of physiological and pathological processes. In the context of periodontal diseases, ET acts as an active participant in the complex interaction between pathogenic microorganisms, periodontal defense mechanisms, and the immune system. In particular, in periodontal diseases, ET acts as an active participant in the complex interaction between pathogenic microorganisms, periodontal defense mechanisms, and the immune system. Periodontal pathogenic bacteria such as Porphyromonas gingivalis and Aggregatibacter actinomycetemcomitans produce a variety of virulence factors that can damage periodontal tissue and activate the immune response. In response to bacterial invasion, cells of innate and adaptive immunity migrate to the inflammatory site and begin to produce pro-inflammatory cytokines such as IL-1, TNF-α and IL-8, as well as lytic enzymes such as matrix metalloproteinase. These molecules play an important role in protecting the body from infection, but their excessive production can lead to damage to the body's own periodontal tissues. ET, in turn, enhances the inflammatory response by stimulating the production of pro-inflammatory cytokines and chemokines that attract additional immune cells to the inflammatory site. In addition, endothelin contributes to impaired microcirculation in periodontal tissues, which leads to hypoxia and impaired tissue trophy, exacerbating the inflammatory process.

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