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ACTIVATION OF THE NEURO-IMMUNO-ENDOCRINE SYSTEM FOR PAIN TREATMENT

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Abstract: Pain is always subjective, and everyone learns to use the word through their own experience. The sensation of pain has a physiological role and serves as a warning signal for the perception of something that threatens the physical integrity of an organism. The ability of the central nervous system (CNS) to modulate the immune system has been extensively studied and established. This regulation is mediated by complex signaling networks that exist in the communication between three systems that generate biological mediators that interact and/or influence the cellular components of the immune response. Currently, research is carried out in order to elucidate the physiological and emotional mechanisms of pain, aiming at the discovery of new drugs that can reduce or even eliminate the painful process. The objective of this article is to elucidate concepts involved in the activation of the neuro-immuno-endocrine system to treat pain from a literature review, in databases of scientific productions such as SciELO and Google academic. As such, it becomes a field with vast knowledge and future perspectives to better understand these relationships, in order to better understand and develop new methods to control this phenomenon.
Keywords: Nneuro-immuno-endocrine system; pain treatment. Neuro-immuno-endocrine system in pain.

INTRODUCTION

The immune system (IS) includes all the mechanisms by which the human body defends against external and endogenous attacks and helps maintain the integrity of the body. There is a close interrelationship between the immune, nervous and endocrine systems, which are mediated by complex networks of receptors and substances produced and shared. (MOREIRA, 2010).

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential harm, or described in terms of such harm. Pain is always subjective, and everyone learns to use the word through their own experience. Persistent pain can cause significant damage to health, work, and daily life. It has also been associated with low health and disability indicators, interfering with quality of life, including social, family and professional aspects. (MIGUEL, 2013).

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with or described in terms of actual or potential tissue damage". The sensation of pain has a physiological role and serves as a warning signal for the perception of something that threatens the physical integrity of an organism. In this sense, pain is a clinically important symptom for the detection and evaluation of the disease, as well as for inducing preventive behaviors that limit possible damage. (VITOR; BRIDGE, 2008).

The complexity of the pathophysiological mechanisms that explain the onset and maintenance of pain often makes it difficult to assess, diagnose and treat pain syndromes that may have inflammatory, neuropathic or mixed components (ARAÚJO; SENA, 2011; MIGUEL, 2013).

Research over the years has increasingly demonstrated the complex two-way interactions between the nervous, endocrine,

and immune systems. The ability of the central nervous system (CNS) to modulate the immune system has been extensively studied and established. This regulation is mediated by complex signaling networks that exist in the communication between three systems that generate biological mediators that interact and/or influence the cellular components of the immune response. Research in the field of psychoneuroimmunology has shown that responses to stressful stimuli are mediated by activation of the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system (ANS), which, when unbalanced, lead to changes in the immune response. As a result, in addition to being more susceptible to infections caused by microorganisms, diseases such as depression, cancer and chronic inflammatory diseases also develop. Therefore, the study of the so-called "stress hormones" and the regulation of the HPA axis has received special attention. (PAGLIARONE; SFORCIN, 2009).

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LITERATURE REVIEW

Pain is not a disease, but a specific symptom that, although common to many diseases, has the ability to induce intense aggression, leading to a series of unpleasant consequences, it is the manifestation of most conditions. The most effective way to eliminate pain is to remove the pathological cause, but this is not always feasible and is sometimes a difficult task, requiring specific treatment for the symptoms. Since almost everyone feels or has experienced pain, and since chronic pain affects more than 3 million Portuguese, it has become imperative to develop pharmacological treatments for pain (VARANDAS, 2013).

Since 1984, Blalock has referred to the immune system as an organic "sixth sense" that receives information from the environment and makes it available to the brain's senses. Evidence of interactions between the immune system and elements of the central nervous system (CNS) includes psychological changes that can occur in infectious and cancerous diseases, allergies, and autoimmune diseases; and stress hormones (cortisol and adrenaline), neurotransmitters and immunological abnormalities in psycho-emotional disorders, such as neuropeptides, psychotropic drugs, depression, stress and schizophrenia (MOREIRA, 2010).

Interactions between inflammatory mediators produced by afferent neurons and immune system activation exist in persistent pain states such as complex regional pain syndrome (CRPS). The cytokine transport system allows these proteins to pass through the blood-brain barrier, directly affecting

the function of the central nervous system. Peripheral blood pro-inflammatory cytokines act as humoral mediators, leading to central sensitization by inducing cyclooxygenase 2 (COX-2) and prostaglandin E synthase in blood-brain barrier cells (MIGUEL, 2013).

Some mood swings can occur during certain illnesses, where there is intense tension, insecurities, social withdrawal, difficulty expressing feelings, and greatly increased emotional sensitivity. These mood changes are also observed in psychotic depression, immunosuppression is common in both conditions, where this relationship between psycho-mood and the immune system would be exacerbated and/or trigger a cascade of physical illness. This mind-body integration was described by Aristotle (384-322 BC), who reported that mind (soul) and body respond to each other (MOREIRA, 2010).

Thus, the phenomenon of pain has two components: one distinguishes painful stimuli in terms of time, space and intensity, called perceptual discrimination (the sensory part); the other, which attributes emotion to the painful experience, is responsible for the behavior in relation to the painful reaction. This is characterized by defensive behaviors, such as the reflexive withdrawal of limbs or flight/fight behavior, known as the aversive-cognitive-motivational component (VITOR; PONTE, 2008).

Emotions are expressed through physiological changes in the body, triggering the production of substances that cause specific changes in the body. These changes include T lymphocyte function, natural killer (NK) cell activity, antibody responses, macrophage function, and more, with serious consequences for physical health (MAIA, 2002). The endocrine system, especially the hypothalamic-pituitary-adrenal axis, is one of the systems responsible for regulating the immune response through nervous system stimuli such as stress, where the combined action between the nervous, endocrine and immune systems occurs during recovery (MOREIRA, 2010).

The sensory component involves the mechanism by which pain impulses generated by actual or potential tissue damage reach the central nervous system (CNS). This mechanism is called nociception. On the other hand, the motivational components concern the individual's emotional characteristics, the symbolic meanings attributed to sensitive phenomena and cultural and emotional aspects (VITOR; PONTE, 2008).

These signs and symptoms are manifestations of vasodilation and increased permeability of the microcirculation, resulting in increased local supply of nutrients and oxygen; production of energy, infiltration of fluid in the interstitium, causing swelling and edema, and irritation of the nerve endings causing pain (JÚNIOR, 2003).

Pain is important because through it the warning signs of imminent danger are perceived and, therefore, related to the protection of the organism, showing insurmountable limits. Although the sensation of pain is an alert used by the body to signal an aggressive process, the problem of pain accompanies the human being, as it interferes with the individual's homeostasis and their relationship with others (VITOR; PONTE, 2008).

Cardiovascular, respiratory and neuroendocrine changes can also be more dynamically noticed by the body's natural response - increased cardiac function (tachycardia, increased contractility, which leads to increased cardiac output), increased respiratory rate (tachypnea) and increased hormonal function (catecholamines, cortisol, antidiuretics, hormones, growth hormone, glucagon and insulin) (JUNIOR, 2003).

Pain is a signal used by the central nervous

system to signal an aggressive process to the body and represents a threat to its bodily integrity. This alarm triggers a series of adaptive responses, of a psychological, autonomic and motor nature, aimed at keeping the organism away from the cause of the attack, protecting it (VITOR; PONTE, 2008).

If the initial stimulus is strong or sustained, the body's response is amplified and it loses control over interacting and integrating systems, a feature of a systemic inflammatory response in which changes cluster together in a process called systemic inflammation response syndrome. (SIRS). In some cases, cytokines are the main physiological messengers of the inflammatory response, even before the breakdown, including tumor necrosis factor (TNF), interleukins (IL-1, IL-6), interferon, colon stimulating factor (CSF) and effector cells such as polymorphonuclear cells (PMN), monocytes and endothelial cells (JÚNIOR, 2003).

Pain is characterized by an organ protection response, as it alerts the individual to imminent or actual tissue damage, inducing the emergence of coordinated reflexes and behavioral responses to control tissue damage as much as possible. This pain is classified as acute. However, when pain starts to repeat itself or last longer, it ceases to have biological dominance and starts to cause suffering, classified as chronic pain, produced by small amplitude impulses produced by abnormal neural activity (VITOR; PONTE, 2008).

The pain process begins with nociceptors, which are morphologically differentiated receptors present at the free ends of afferent nerve fibers. They become sensitive when a stimulus is potentially dangerous, that is, it exceeds a certain physiological range (harmless stimulus). Nociceptors are located distal to sensory afferent neurons (first-order neurons) and are widely distributed in the skin, blood vessels, muscles, joints, and internal organs. They fall into three categories: mechanoreceptors, which are sensitive to strong mechanical stimuli; thermoreceptors, which are sensitive to thermal stimuli (above 45°C) and multimodal nociceptors, which are sensitive to mechanical, thermal and chemical stimuli. As an essential characteristic, these receptors do not show adaptation, in addition, they present facilitation and increased sensitivity when continuously stimulated (VITOR; PONTE, 2008).

Like all pathophysiological concepts, this concept has evolved several times throughout human history, starting with the belief that pain is a cosmic phenomenon that can be treated with magic. In Judeo-Christian civilization, suffering is understood as God's punishment for the author of original sin, allowing him to purify his soul. According to Hippocrates, pain becomes a necessary marker for the diagnosis of a disease, so it is necessary to understand the underlying origin of pain (VARANDAS, 2013).

Nociceptors transmit pain information to the spinal cord through three types of sensory afferent fibers: Aβ fibers, a myelinated fiber larger than 10 μm in diameter with a conduction velocity of 30-100 m/s, which respond to stimuli. ; Aδ fibers, myelinated, with a mean diameter of 2-6 μm and a conduction velocity of 12-30 m/s, responsible for the rapid conduction of painful stimuli; C-fibers, unmyelinated, with a diameter of 0.4-1.2 μm and a conduction velocity of 0.5-2 m/s, is the reason for the slow conduction of pain impulses. C fibers constitute the majority of sensory fibers (VITOR; PONTE, 2008).

Pain is one of the biggest challenges that science faces today. The presentation of pain has become one of the most studied aspects by health professionals, with contributions from professionals from the most diverse areas to develop a multidisciplinary approach. As pain is the link between body and mind,

an unbearable mixture of painful sensations, an experience of all human beings, it is not difficult to understand the interest of the pharmaceutical industry in this. its research and the development of new treatments for its treatment (VARANDAS, 2013).

Peripheral nociceptors are located at the outer ends of primary neurons, whose cell bodies constitute the dorsal root ganglia. They transmit nociceptive information to neurons in the dorsal horn of the spinal cord. The main neurotransmitters responsible for transmitting nerve impulses from primary afferent fibers to neurons in the dorsal horn of the spinal cord are substance P and glutamate. This process also depends on calcium and sodium channels, the former being the main regulators of neurotransmitter release (VITOR; PONTE, 2008).

Pain is the subject of considerable research in the medical field, and the fact that it is a global problem further increases the need to effectively assess patients suffering from this problem. In this regard, the American Institute for Public Health Research and Quality and the American Pain Association list pain as the fifth most important vital sign, as important as body temperature, pulse, breathing, and blood pressure. In 1993, Portugal also recognized that pain is the fifth most important vital sign, which must be given a position of extreme clinical importance. (VARANDAS, 2013).

After interacting directly or indirectly with primary afferent neurons in the dorsal horn, axons of secondary neurons form afferent tracts that transmit nociceptive impulses to structures in the brainstem and diencephalon, including the thalamus, periaqueductal gray, spinal cord formation, amygdala complex, hypothalamus, and more. Pain information is sent to higher centers via the pain projection pathway or the anterolateral spinal tract. The main pain conduction pathways in the central nervous system are the spinothalamic tracts, spinoreticular tracts and spinomesencephalic tracts (VITOR; PONTE, 2008).

According to the International Association for the Study of Pain (IASP), describing this feeling is as difficult as describing a color to a person who was born blind, so the IASP defines pain as an "unpleasant sensation", and emotional experiences associated with pain. tissue damage, actual or potential, or described in the form of such damage". The difficult definition of pain is related to the difficult interpretation of the neural phenomena involved, but something is true always has a cause, there is always a way to feel. Pain is an aversive experience. (VARANDAS, 2013).Numerosos neurotransmissores e moduladores estão sendo descobertos que

are involved in the transmission of nociceptive signals from the spinal cord to higher centers. However, electrophysiological studies have shown that glutamate and other excitatory amino acids act through ionotropic and metabotropic receptors for glutamate and are involved in injury from the spinothalamic tract to the thalamus and from the spinomesencephalic tract to the SCPV (VITOR; PONTE, 2008).

In each type of pain, we can observe four properties: nociception, which can detect noxious stimuli; perception, which consists of the way the organism feels the stimuli; Suffering; and behavior. These characteristics are always present in pain, but they vary according to the type, but in different proportions, however, it is necessary to know that there is a threshold below which no pain is felt, called the threshold of perception, and there is also a threshold above which pain cannot be felt. the pain becomes unbearable called tolerance threshold (VARANDAS, 2013).

The descending pathway leaves the midbrain through the rostral ventromedial end and reaches the dorsal horn of the

spinal cord in the exact opposite direction of the ascending sensory pathway. They exert inhibitory and modulatory effects on distal structures, particularly in the posterior medulla, where the balance between nociceptive and non-nociceptive afferents can control the transmission of pain information to higher centers (VITOR; PONTE, 2008).

We know that all organisms are susceptible to pain, however, according to Grunenthal, women are more susceptible to pain than men due to hormonal factors, as estrogen increases sensitivity to pain, and by stimulating the nervous system, testosterone reduces pain sensitivity. (VARANDAS, 2013).

It is known that painful impulses are subject to central regulation and that painful stimuli are tolerable in situations of physical stress or high concentration. Therefore, it has been proposed that there is a physiological system for central pain control. After painful injury, two behaviors can be activated: restorative behaviors, which are responsible for the individual's recovery, or defensive behaviors, which inhibit restorative behaviors and pain and promote environmental perception and defense. That is, fear activates endogenous opioid mechanisms that inhibit the pain motivational system, as the expression of this system can compete or even be incompatible with defensive behavior (VITOR; PONTE, 2008).

RESULTS AND DISCUSSION

INTERACTION BETWEEN IMMUNE, NEUROLOGICAL AND ENDOCRINE SYSTEMS

The innate immune response is the body's first line of defense against tissue infection and involves several mechanisms, such as phagocytosis, in which granulocytes, monocytes, macrophages and NK lymphocytes participate. Acquired immunity is characterized by response specificity, in which antigen-presenting cells (APCs) (macrophages, dendritic cells) capture and process foreign substances, and then the particles that express that substance (antigens) bind to their own. surfaces in the molecular histocompatibility complex. Class II (MHC-II), which is then presented to T lymphocytes that are activated and undergo a process of differentiation and proliferation, resulting in the emergence of memory T lymphocytes that recognize specific antigens and respond more rapidly and robustly in the second contact (MOREIRA, 2010).

Changes in serum cytokine levels were found in neuropathic pain, fibromyalgia, migraine and low back pain, suggesting that pain intensity is directly related to the increase in pro-inflammatory cytokines in peripheral blood. Just as peripheral mediators are altered in chronic pain states, subsets of lymphocytes associated with the production of inflammatory cytokines also appear to be involved in persistent pain, including CD4, CD8 T lymphocytes and natural killer (NK) cells (MIGUEL, 2013).

Functionally, the central nervous system is divided into: cortical areas, which develop the conscious functions of logical and rational thinking and store long-term memory; subcortical areas that carry out the subconscious functions of the organism, including emotion and emotional processing, and carry out the unconscious, reflex, and instinctive functions of the organism in balance, stimulation assessment, and spinal cord areas. To maintain the homeostasis of an organism, several regions can be used simultaneously that communicate with each other from synapses, transmitting information via neurotransmitters and neuropeptides. Once the information is interpreted by the central nervous system, the thalamus (the main information distribution center) at the subcortical level sends the

information to the hypothalamus, one of the 12 main parts responsible for connecting the NS and the endocrine system (SE) Causes activation of various endocrine glands. In the hypothalamus, there are neurons that do not perform typical synapses, but release their chemical mediators directly into the bloodstream to act on target cells, facilitating their action. Among the neurohormones or hypothalamic hormones are corticotropin-releasing hormone (CRH); thyrotropin releasing hormone (TRH) and antidiuretic hormone (ADH) (MOREIRA, 2010).

Despite this knowledge, there are still few human studies and controversial results that still lead to inconsistent conclusions. Therefore, a better understanding of how the immune system influences the persistence of chronic pain is critical to finding answers to the ineffectiveness of current treatments, understanding the causes of refractoriness in large numbers of patients, and finding new therapeutic targets. Treatment options are effective (MIGUEL, 2013).

The endocrine system (ES) produces chemical mediators (hormones) that regulate different metabolic functions of organisms, is a communication system parallel to the SN and plays a role in the regulation of cell growth, reproduction and metabolism. It is involved in prenatal sexual differentiation, sexual maturation in adolescence, reproduction, growth, digestion, cardiovascular function, and excretion in adulthood. In addition to transporting substances across cell membranes. Endocrine glands form SE and are hormone producing centers, classified as exocrine glands that secrete their products (hormones) in ducts and are directed to body cavities such as the lumens of organs or to the external surface of the body (sweat), sebaceous glands, digestive glands and endocrine glands, which secrete into the interstitial fluid that surrounds the secretory cells that diffuse into capillaries and blood (eg, thyroid) (MOREIRA, 2010).

Normally, pain processing consists of a series of chemical events triggered by positive thermal, mechanical, or chemical stimuli that activate the nerve endings of surrounding sensory fibers, known as nociceptors. This generates excitatory impulses along afferent axons to the posterior horn of the spinal cord, where sensory fibers cross and ascend to the cerebral cortex. However, painful stimulus processing constitutes a dynamic system with multiple pathways in which inhibition or amplification can occur at any level of synaptic communication (MIGUEL, 2013).

The connection between the nervous, endocrine and immune systems occurs through the HPA axis, which is controlled by corticotropin-releasing hormone and vasopressin secreted by the hypothalamus, which in turn activates the secretion of adrenocorticotropic hormone (ACTH). The pituitary gland, "also known as the pituitary gland", stimulates the secretion of mineralocorticoids, androgens and the release of glucocorticoids: hydrocortisone, corticosterone and cortisol, the latter being the main glucocorticoid in humans. The anti-inflammatory and immunosuppressive effects of glucocorticoids are evident at pharmacological doses and, physiologically, these hormones have important regulatory functions in the IS. Since inactive lymphocytes are more sensitive to the inhibitory effects of glucocorticoids, it has been suggested that the HPA axis may play a role in preventing the excessive increase in lymphocytes with low affinity for the antigen, maintaining or even improving the specificity of the immune response (MOREIRA, 2010).

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Some authors even suggest that suppressing negative emotions increases the risk of cancer and one is more likely to develop upper respiratory tract infections and develop inflammatory diseases after viral exposure. Positive relationships are associated with lower levels of stress, better immune responses, and a lower risk of infection and development of inflammatory diseases. Some behaviors, such as smoking, inadequate diet and sleep disorders, can affect the SI, making it depressed (MOREIRA, 2010).

Acute pain has protective and adaptive functions that induce behavioral and physiological changes suitable for the recovery and preservation of the individual. When the injury or inflammation is prolonged, the permanent excitation of primary neurons causes a pathological response, chronic pain, which has no apparent biological value and persists beyond the normal time for tissue recovery (MIGUEL, 2013).

Few studies have examined the relationship between psychosocial variables and neuroendocrine and immunological processes in disease progression. However, the results to date suggest that psychosocial factors may contribute to the susceptibility and exacerbation of the disease, influencing immunological mechanisms in body processes (MOREIRA, 2010).

History of trauma, viral infection, vascular disease, endocrine or metabolic disorders, nutritional deficiencies, and inflammatory or autoimmune processes contribute to injury or stimulation of nociceptive pathways. Thus, changes in ion channels, receptors and synapses, as well as changes in the distribution of neurotransmitters and neuromediators, allow peripheral and central neurons to reach depolarization thresholds earlier, producing ectopic triggers that amplify and activate neighboring cells, characterizing chronic pain.(MIGUEL, 2013).

There is evidence of a correlation between the neuroendocrine and immune systems, the latter being partly regulated by the HPA axis and the ANS (25). As this interaction is bidirectional, the immune system can also send messages to the central nervous system via pro-inflammatory cytokines. Cytokines present in the bloodstream can activate the CNS by crossing the blood-brain barrier. They also induce brain endothelial cells to produce nitric oxide synthase and cyclooxygenase, indirectly stimulating central nervous system activity. For example, we can mention IL-1β, which acts in the paraventricular nucleus of the hypothalamus, which contains neurons for CRH. This way, CRH is released, leading to the secretion of ACTH, which in turn induces the release of glucocorticoids from the adrenal cortex(PAGLIARONE; SFORCIN, 2009).

Structural and chemical changes in nerve fibers are not the only reason neuropathic pain persists. It has been thought for some time that inflammatory mediators produced by immune cells may contribute to the persistence of pain, but only recently has evidence of this relationship emerged, suggesting that there is communication between the immune and nervous systems described above. The interference of immune cells in the inflammatory process, characterized by heat, redness, swelling and pain, has long been understood, and anti-inflammatories have successfully become part of the therapeutic arsenal since then. However, recent data suggest that these cells

may play an important role in regulating pain associated with peripheral nerve and central nervous system damage (MIGUEL, 2013).

Any imbalance between the production of pro- and anti-inflammatory cytokines, dominated by inflammatory cytokines, can lead to increased inflammatory responses in immune and brain cells, in the latter case affecting behavior and mood, and even the progression of neurodegenerative diseases. Another fact that demonstrates the relationship between the different systems in the stress response is that in addition to the HPA axis, primary and secondary lymphoid organs are also innervated by ANS noradrenergic fibers. The close association of these nerve endings with immune cells facilitates direct neuroimmune interactions through neural connections. Norepinephrine, substance P and other neurotransmitters are released at these junctions, which can subsequently alter the activity of remote and nearby immune cells.

The initial damage to nerve fibers also follows an inflammatory cascade that leads to increased local perfusion, increased capillary permeability, and enrichment and activation of innate immune cells. However, immunoreactive substances released at the site of injury can trigger a systemic immune response by activating microglia and astrocytes, glial cells located in the spinal cord and brain, which appear to be important in nociception. Activation of mast cells in injured peripheral nerves triggers the release of histamines, proteases, cytokines, and neurotrophic factors that directly stimulate nociceptors and dorsal root ganglion cells and promote substance P (SP) and calcitonin genes and other related peptide products. pain-causing. (CGRP), causing spontaneous burning pain and depletion of circulating neutrophils before experimental peripheral nerve injury attenuates hyperalgesia (MIGUEL, 2013).

The disease is triggered by an imbalance caused by inappropriate (intensified or less than normal) activation of the neuroendocrine system, which reflects the function and activity of the immune system. The main feature of this dysfunction is an unbalanced pattern of cytokine production, and the glucocorticoids and catecholamines released during stress are considered the main contributors to this immune imbalance, as when released in high concentrations, they can inhibit the Th1 response. It causes autoimmune diseases, depression and cancer. On the other hand, the production of Th2 cytokines is prevalent when produced at levels below baseline, favoring allergies and infectious diseases (PAGLIARONE; SFORCIN, 2009).

The administration of antagonists or agonists of these hormone receptors has been widely used by researchers to try to reverse or prevent this imbalance between immune responses. In addition, the administration of cytokines (anti- or pro-inflammatory) and the use of natural products have been investigated for exerting immunomodulatory activities. For example, a research group studied the effects of propolis on the immune system of stressed mice, looking for an alternative that could actually be used as a treatment in humans to control the effects of stress on the immune system. These studies are also important for a better understanding of stress response mechanisms that have not yet been fully elucidated (PAGLIARONE; SFORCIN, 2009).

CONCLUSION

Upon investigation, it appears that the study of pain is very complex, since, in addition to the sensory aspect (depending on the transmission route) presenting its functional anatomical nature, it is also related to pathways involved in motivation. Behavior,

which may incorporate your responses to different individuals. This makes its treatment difficult, such as the non-exclusive use of analgesics. As such, it becomes a field with vast knowledge and future perspectives to better understand these relationships, in order to better understand and develop new methods to control this phenomenon.

REFERENCES

ALEIXO, G., Tudury, E., Coelho, M., Andrade, L., & Bessa, A. (2017). **Tratamento da dor em pequenos animais: fisiopatologia e reconhecimento da dor (revisão de literatura: parte I).** Medicina Veterinária (UFRPE), 10(1-4), 19–24.

ARAÚJO, Arão Nogueira de; SENA, Eduardo Pondé de. **Interações dos sistemas nervoso, endócrino e imune na fisiopatologia da esquizofrenia.** R. Ci. med. biol., Salvador, v.10, n.3 p.223-230, set./dez. 2011.

MOREIRA, Jôsimar Dornelas**. A inter-relação entre sistema imuno-neuroendócrino na artrite reumatóide.** Monografia apresentada ao II Curso de Especialização em Análises Clínicas e Toxicológicas da Faculdade de Farmácia da Universidade Federal de Minas Gerais. 2010.

MIGUEL, Marcia de. **Aspectos imunológicos de pacientes com dor crônica.** Dissertação (Mestrado em Processos Interativos dos Órgãos e Sistemas) – Universidade Federal da Bahia. Instituto de Ciências da Saúde – Salvador: 2013. 87 f. : il.

PAGLIARONE, Ana Caroline; SFORCIN, José Mauricio. **Estresse: revisão sobre seus efeitos no sistema imunológico**. Biosaúde, Londrina, v. 11, n. 1, p. 57-90, jan./jun. 2009.

SANTOS JÚNIOR JCM.Rubor, **Calor, Tumor e Dor e o Paciente Grave**. Rev bras coloproct, 2003; 23(3):206-210.

VARANDAS, Cláudia Maria Brás. **Fisiopatologia da Dor.** Universidade Fernando Pessoa, 2013.

VITOR, Aline Oliveira; PONTE, Edson Lopes da. **Psicofisiologia da dor: uma revisão bibliográfica**. RECIIS – R. Eletr. de Com. Inf. Inov. Saúde. Rio de Janeiro, v.2, n.1, p.87-96, jan.-jun., 2008.