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Inflammation in amebiasis and its modulation by the Autonomic Nervous System

Inflamación en la amebiasis y su modulación por el Sistema Nervioso Autónomo

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ABSTRACT

Neuroimmune regulation of inflammation is only beginning to be explored in depth. In the case of amebiasis, the inflammatory process prompted by *E. histolytica* has been well characterized, but the modulation of this process by neurotransmitters is not as well defined. Regarding the inflammatory process, it is known that neutrophils and macrophages are important cellular effectors in the host defense against *E. histolytica*. The production of proinflammatory cytokines (IL-1β, IL-8, INF-γ and TNF-α) and anti- inflammatory cytokines (IL-10 and TGF-β) is triggered by the activation of Toll-Like Receptors and two types of transcription factors: 1) nuclear factor kappa-light-chain- enhancer of activated B cells, and 2) activator of transcriptions: Toll-Like Receptors and these transcription factors are in turn modulated by the action of three neurotransmitters of the autonomous nervous system acetylcholine, adrenaline and noradrenaline that can activate cholinergic and adrenergic receptors of immune cells, and thus modify the inflammatory process induced by the parasite. A vagotomy of the liver of hamsters inoculated with *E. histolytica* induces a stronger response in tissues through a more abundant formation of collagen, together with an increase in the levels of IL-10 and INF- γ and a decrease in macrophages, which impedes the dissemination of trophozoites.

Keywords: interaction, Entamoeba histolytica, macrophages, neutrophils, cholinergic, adrenergic.

RESUMEN

La regulación neuroinmune de la inflamación apenas comienza a explorarse en profundidad. En el caso de la amebiasis, el proceso inflamatorio provocado por E. histolytica ha sido bien caracterizado, pero la modulación de este proceso por los neurotransmisores no está tan bien definida. Respecto al proceso inflamatorio, se sabe que los neutrófilos y macrófagos son importantes efectores celulares en la defensa del huésped contra E. histolytica. La producción de citocinas proinflamatorias (IL-1β, IL-8, INF-γ y TNF-α) y antiinflamatorias (IL-10 y TGF-β) se desencadena mediante la activación de los receptores Toll Like y dos tipos de transcripción. factores: 1) factor nuclear cadena ligera kappa- potenciador de células B activadas, y 2) activador de transcripciones :. Los receptores Toll Like y estos factores de transcripción están a su vez modulados por la acción de tres neurotransmisores del sistema nervioso autónomo acetilcolina, adrenalina y noradrenalina que pueden activar los receptores colinérgicos y adrenérgicos de las células inmunes, y así modificar el proceso inflamatorio inducido por el parásito. Una vagotomía del hígado de hámsteres inoculados con E. histolytica induce una respuesta más fuerte en los tejidos mediante una formación más abundante de colágeno, junto con un aumento de los niveles de IL-10 e INF-γ y una disminución de los macrófagos, lo que impide la diseminación de trofozoítos..

Palabras clave: interacción, *Entamoeba histolytica*, macrófagos, neutrófilos, colinérgicos, adrenérgicos.

INTRODUCTION

Amebiasis

Very generally speaking, inflammation is the body's immune system's response to an irritant. The irritant might be a germ, such as bacteria and viruses. This means that an inflammation already starts when the body is trying to fight against the harmful irritant. The parasite Entamoeba histolytica (E. histolytica) causes intestinal amebiasis and amebic liver abscess as its main extraintestinal manifestation. In a 1997 report involving the World Health Organization (WHO), it is explained that Entamoeba histolytica infections result in more than 100,000 deaths worldwide per year, putting it in second place after malaria within the protozoal diseases (1) It has also been reported that 10% of the world's population is infected with this protozoa (2) The parasite then enters the bloodstream and may penetrate into the liver after crossing the endothelial barrier. It lives in the hepatic tissue and prompts the formation of liver abscesses (3).

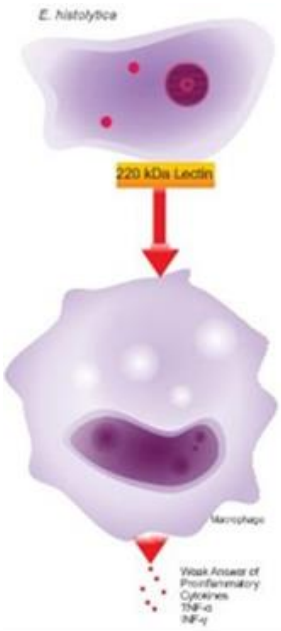
Liver abscess is a disease in which a pathogen invades the liver, proliferates, and forms pus through the body's inflammatory responses. It is the most common abscess in the abdominal cavity, and accounts for about half of all intraabdominal abscesses. Escherichia coli is the most common causative organism; however, infections due to Klebsiella

pneumoniae have been rising in recent decades. Direct contact via the biliary tract, leakage from the intestine, and hematogenous spreading can be routes for infection associated with liver abscess. The maximal diameter of liver abscess was significantly associated with prolonged hospitalization and higher in-hospital mortality rate, which may be due to the higher incidence of complications and extrahepatic manifestations as well as severe inflammatory states in patients with large liver abscesses. These findings warrant a more aggressive treatment strategy with careful monitoring in patients with large liver abscesses(4).

Upon invading humans, E. histolytica is confronted with innate mechanisms of the immune response that destroy trophozoites (5,6) Electron dense granules have been found in amebas during the formation of hepatic abscesses(7). When the parasite gets by the natural barriers of the organism, it invades the intestine (8), after that, when invade wall of blood vessels it enter to blood flow and the parasite can evade the lysis by complement due to the CD59 like protein on it surface (9) and like this, can invade liver, lungs and brain (10).

E. histolytica has a glycoprotein of 220 kDa on its membrane that participates in the process of adhesion to host cells. This glycoprotein is very immunogenic, being capable of generating high levels of antibodies (11). This lectin can suppress the proliferation of T cells in the spleen and lymph nodes of immunized mice (12).

FIGURE 1. The 220 kDa lectin from E. histolytica, from the membrane of Entamoeba histolytica activates the macrophage, inducing a weak response that produces proinflammatory cytokines IFN-γ and TNF-α (11,68).



Electron dense granules have been found in amoebas during the formation of hepatic abscesses(7). E. histolytica is also capable of downregulating some proinflammatory cytokines, such as IL-5, IL-6, INF-γ and TNF-α. Therefore, it can induce an anti- inflammatory response in select leukocytes (13) E. histolytica produces the anti-inflammatory peptide (FILM) inhibitory factor of monocyte migration produced by amoeba) as another factor that is produced by amoeba and regulates the function of host leukocytes.

TLRs are the first step in the inflammatory response to pathogens. In this sense, *E. histolytica* induces TLR activation because it has a surface molecule with the characteristics of a PAMP. This molecule, denominated lipopeptidophosphoglycan (LPPG), is recognized by TLR-2 and TLR-4, and the activation of these receptors impedes the development of amebic liver abscess (14). TLRs activate signal transduction pathways, which induce the expression of cytokines by a variety of genes of the immune response. Many TLRs promote inflammation and recruit/activate macrophages, dendritic cells and lymphocyte-specific antigens (15).

E. histolytica activation of the classic TLR pathway. TLRs are a family of 10 receptors (TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, and TLR10) (16) that recognize a variety of ligands as a part of innate and adaptive immunity. Included in these ligands are the molecular patterns associated with pathogens (PAMPs) (17,18). TLR-4 is a protein in humans that acts as a surface receptor on monocytes/macrophages, dendritic cells, myeloid, mastocytes, and B lymphocytes and in the intestinal epithelium. It is activated by lipopolysaccharides of Gram negative bacteria and has an important role in the

innate immune system (19,20). This receptor is abundant in placenta and in a sub-population of monocytes. Likewise, the expression of these receptors has been found on the surface of the epithelium of normal ovaries and ovary tumors (21).

The pro-inflammatory response mediated by NF-kB is stimulated by *E. histolytica* through its abundant secretion of cysteine proteinase 5 (PCP5). This enzyme binds through its RGD motive to α (V) β (3) of integrin in Caco-2 cells of Colon. In this way PCP5 triggers the formation of the integrin-linked kinase (ILK), mediated by phosphorylation of the Akt-473 kinase protein that binds to the NF-kB essential modulator (NEMO) and induces its ubiquitination. This modulator activates the signaling complex of NF-kB and the IkB kinase IKK-IKKβ complex. NF-kB is a protein complex that controls the transcription of DNA. It is found in almost every type of animal cell and is implicated in the cellular response to inflammation and to various stimuli, including stress, cytokines, free radicals, ultraviolet radiation, LDL, and bacterial and viral antigens (22–24).

Such events have proven to be pro-inflammatory mediators *in vitro*. These assays revealed that EhPCP5 RGD is a ligand for α (V) β (3) and regulates adherence mediated by integrins and colon cells, representing a formerly unknown mechanism by which *E. histolytica* trophozoites trigger an inflammatory response in the pathogenesis of intestinal amebiasis (25). This deregulation of NF-kB is associated not only with amebiasis, but also with inflammatory diseases and cancer (26).

STAT proteins, when in the presence of cytokines and growth factors, are phosphorylated by an associated receptor to tyrosine kinases, which permits them to form homo or heterodimers that translocate to the nucleus where they act as transcription activators (27). STAT3, belonging to this family of proteins, acts as a mediator of the expression of diverse genes in response to certain cellular stimuli. In this way it plays an important role in a multitude of cellular processes, both anti-apoptotic and proliferative (28).

STAT3 plays an important role in tumorigenesis through the positive regulation of genes implicated in the struggle against apoptosis, as well as in proliferation and angiogenesis. In the case of hepatocellular carcinoma, safe and effective pharmacological treatments can block the activation of STAT3 (29). Other functions of STAT3 include the stimulation of the proliferation of B lymphocytes as well as the activation, differentiation and growth of monocytes (30).

The interaction of *Entamoeba histolytica* trophozoites with type I collagen and calcium induces signaling from the membrane to the nucleus. It has been demonstrated that there are inducible transcription factors in the protozoo parasite *E. histolytica* that facilitate host invasion (31). These signaling pathways intervene in the inflammatory process by activating proinflammatory and anti-inflammatory cytokines. The fact that the cholinergic anti-inflammatory pathway is a mechanism by which the vagus nerve modulates inflammation further evidences the connection between the nervous and immune systems in the local stimulation of inflammation (14).

The migration inhibitor factor (MIF) of mammalian macrophages is a proinflammatory cytokine that plays an important role in the exacerbation of a wide spectrum of inflammatory diseases, including colitis. A homologue of MIF was identified in the genome of *Entamoeba histolytica* (EhMIF), expressed as a protein of 12 kDa and located in the cytoplasm of trophozoites (32).

Inflammation

It is known that neutrophils and macrophages play a pivotal role in the innate immune system (33); However, during amebiasis they are incapable of killing amoebas of virulent strains. For example, *E. histolytica* can lyse neutrophils *in vitro*, even at a ratio of 3,000 PMN per trophozoite (34). Neutrophils employ three antimicrobial strategies phagocytosis, degranulation, and the formation of extracellular traps. Phagocytosis involves the envelopment of microbes by immersion, and their subsequent elimination in specialized compartments. The degranulation of neutrophils leads to the release of antimicrobial molecules such as elastase, cathepsin G and myeloperoxidase and recently reported that activated neutrophils form neutrophil extracellular traps (NETs)(35,36) (, which consist of a network of fibers, probably nucleosomes, mainly composed of DNA but with some proteins incrusted (e.g. peptides and antimicrobial enzymes like elastase, cathepsin G and myeloperoxidase, as well as histones like H1, H2A, H2B, H3 and H4). These fibers adhere to, disarm and kill pathogens extracellularly (37). Since NETs are formed within the first 10 min after neutrophil activation, they cannot be confused with cellular apoptosis. Neither are NETs a process of necrosis, but instead netosis (36).

In general, hamster neutrophils have proven to be incapable of impeding amebic invasion. Actually, it has been proposed that these neutrophils participate in the destruction of host tissue, using novel mechanisms such as NETs (38).

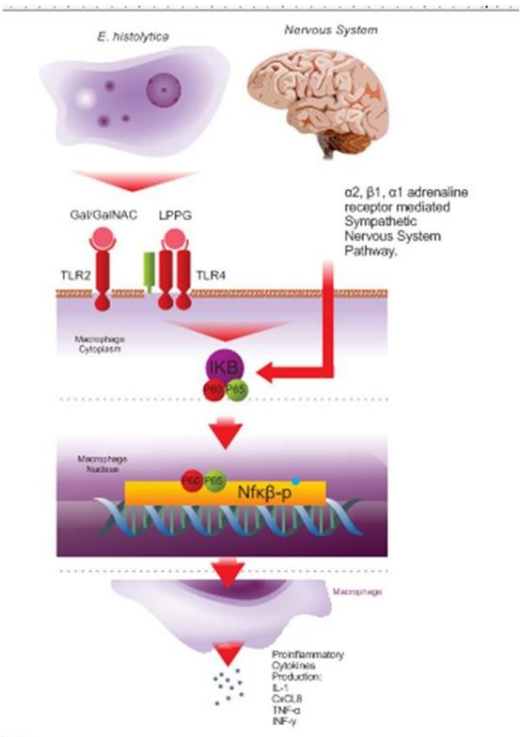
Neutrophils play a central role in the host defense against invasive microorganisms such as *E. histolytica*. The *in vitro* stimulation of neutrophils with cytokines (INF-γ and TNF-α) or LPS triggers their amebicide activity by inducing the expression of reactive oxygen species (ROS). On the other hand, macrophages in tissues represent a transitory inflammatory stage of monocytes that circulate in the blood flow (39). On the other hand, is a naturally occurring modified ribonucleoside found in the first position of the anticodon of the transfer RNAs for Asp, Asn, His, and Tyr. This impairs E. histolytica virulence by downregulating the expression of genes previously associated with virulence, including cysteine proteases, cytoskeletal proteins, and small GTPases, thus, quinine plays a dual role in promoting OS resistance and reducing parasite virulence(6).

Based on *in vitro* studies, there have been reports about the amebicide activity of human neutrophils stimulated by INF-γ and/or TNF-α. Together with macrophages, these neutrophils are capable of destroying *E. histolytica* trophozoites (40–42), even normal neutrophils can evolve *E. histolytica* trophozoites and reduce their viability(9) Additionally, INF-▪ and TNF-▪ are reportedly capable of providing significant amebicide activity to T lymphocytes derived from mouse bone marrow as well as to peritoneal macrophages (41).

On the other hand, Macrophages carry out crucial roles in innate and adaptive immunity, and are important effector cells in the elimination of microorganisms (43). The macrophages are resident phagocytic cells in lymphoid and non-lymphoid tissues. They are equipped with a wide spectrum of receptors that can recognize pathogens. Recognition is followed by phagocytosis and stimulation of proinflammatory cytokine production. Both macrophages and monocytes express various receptors that can recognize pathogens, including CD4, CD14, CD16a, CD23, CD25, CD29, CD30, CD31, CD32, CD36, CD40, CD49, CD49d, CD49e, CD49f, CD54, CD62, CD64, CD68, CD74, CD80, CD86, CD88, CD89, CD102, CD153, CD106, CD162, CD273, CD275 and CD280. These receptors induce an efficient process of phagocytosis as well as the production of proinflammatory cytokines (IL1-α, IL-8, TNF-α and INF-γ) (44). Macrophages are the dominant effector cells in the late stages of the innate immune response (an acute inflammatory response), one or two days after infection. They have a longer life than neutrophils, and unlike the latter are not terminally differentiated. Upon dividing at the site of inflammation, macrophages can specialize as M1 (classically activated by INF-γ and/or TNF-α), M2 or M3 cells.

M1 macrophages show a Th1 phenotype, are proinflammatory effectors, and have a bactericidal function. On the other hand, M2 macrophages are characterized by their low secretion of IL-12 and include at least three distinct phenotypes— M2a (induced by IL-4, IL-13 or IL-21), M2b (induced by immune complexes, IL-1, or agonists of TLRs), and M2c (induced by IL-10, TGF-β or glucocorticoids). Some researchers consider that M2b and M2c are regulated by other macrophages (45,46). M2 macrophages exhibit a Th2 phenotype and are involved in the resolution of inflammation and the healing of tissue. Although the mouse model has been useful for classifying the phenotypes of activated macrophages, it underestimates their *in vitro* activity. Under different stimuli and environmental conditions, *in vitro* experiments have shown a great diversity of the states of activated macrophages. Macrophage activation is influenced by various factors, including their form of activation and their heterogeneity (47). For example, *E. histolytica* directly lyses macrophages and other cells, meaning that infection is associated with an alteration in macrophage, but when the macrophages are activated *in vitro* by INF-γ, TNF-α or LPS have a great amebicide activity (48).

FIGURE 2. *E. histolytica* and the Autonomic Nervous System synergistically stimulate the Macrophage. The Gal/GalNAC lectin and the LPPG of *E. histolytica*, as well as the α1, α2 and β1 adrenergic receptors, activate the intracellular pathway of the nuclear transcription factor B (NFk-B) of the macrophage for the production of proinflammatory cytokines (IL- 1, CXCL8, TNFα and IFN-Y) (12,69).



Various *in vivo* and *in vitro* studies have evidenced an alteration in the effector and accessory function of

macrophages, which then become refractory to activation by INF-γ and LPS, and their ability to present antigens to T lymphocytes is reduced due to a decrease in the expression of major histocompatibility complex (MHC) (49). The importance of INF-γ in macrophage activation demonstrates that lymphocytes are responsible for this activation and the consequent transference of resistance against pathogens(46). INF-γ produced by Th1 cells activates the antimicrobial activity of macrophages (45).

Autonomous Nervous System

The first notion of the interaction between the immune and nervous systems was reported in 1930 by Hans Selye. He observed important histological changes in the cortex of adrenal glands during stress, concluding that they play a fundamental role in this interaction. In 1940 it became accepted that the interaction of the hypothalamus with the suprarenal cortex through glucocorticoids can lead to an immunosuppressive state. This discovery is the basis of controlling many systemic inflammatory processes in medicine today.

The central nervous system (CNS) regulates the immune response through hormonal and neuronal pathways. The sympathetic and parasympathetic nervous systems modulate the neuroendocrine stress response and generally inhibit the innate immune response at systemic and regional levels.

On the other hand, the peripheral nervous system tends to amplify the local innate immune response. These systems work together to activate the innate immune response so as to amplify the local inflammatory response, which contains or eliminates the invasive pathogens. After this process concludes, these same systems stop inflammation and restore homeostasis to the host. The CNS can be considered an integral part of the inflammatory response of the innate immune system in its acute phase of reaction to a pathogen (50).

The CNS has innate inflammatory cells called microglia. These modified macrophages have an important role in the reception and propagation of inflammatory signals. Recently it has been postulated that the immune system and the inflammatory process actively participate in the loss of neurons described in some diseases of the CNS, in both acute (e.g. strokes caused by cerebral infarction) and chronic (multiple sclerosis and Alzheimer's) cases (51).

The parasympathetic nervous system (PN), almost entirely cholinergic, is a division of the autonomous nervous system. The PN consists of nervous fibers that originate in cranial regions and the sacrum of the CNS and project to nerve cells (autonomic ganglions), blood vessels, glands and internal organs. This nervous system is responsible for "rest and digest" and "feed and breed" functions, which include a decrease in cardiac output, an increase in hepatic glucogenesis, contraction of the gallbladder, secretion of insulin and gastric juices, dilation of peripheral blood vessels, contraction of the bronchi, constriction of the pupil, and stimulation of peristalsis in the digestive tract (50).

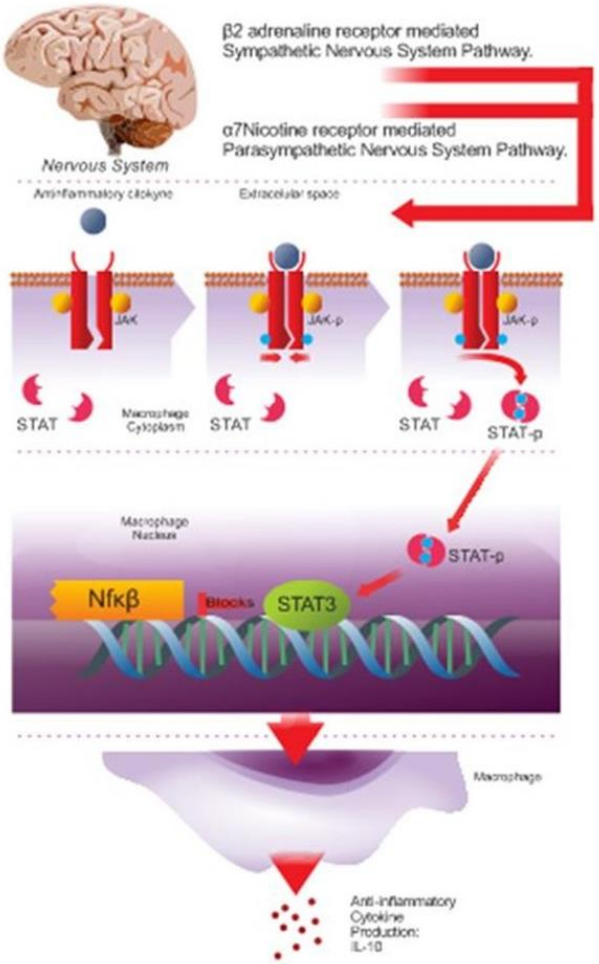
The sympathetic nervous system (SNS), which acts through adrenergic receptors, is the other division of the autonomous nervous system. The SNS consists of fibers that project from the CNS to the sympathetic gangliated cord at the side of the spinal cord in the lumbodorsal region. It is from the gangliated cord that different organs, including the heart, kidneys, intestine, spleen, and glands, are innervated. This nervous system is responsible for the "fight or flight" response, which includes dilation of the pupils, constriction of peripheral blood vessels, and increased cardiac output (52).

The main parasympathetic neurotransmitter, acetylcholine, binds to two types of cholinergic receptors nicotinic and muscarinic. Each of these receptor types has various subtypes that undergo heterodimerization in specific cells and tissues to achieve distinct cholinergic effects. Of the cholinergic receptors in immune cells, only nicotinic receptors specifically mediate anti-inflammatory effects in macrophages and neutrophils (14).

Nicotinic receptor α7 exists within cholinergic receptors, mainly expressed in macrophages and neutrophils. This receptor subtype is characterized by its role in the modulation of neurotransmission, such as its response to nicotine (53). It participates in peripheral non-neuronal systems that favor a proinflammatory response. The activity of this receptor can vary depending on where it is expressed in the organism and in what type of cell. Among its functions is the stimulation of the host defense in various tissues including the skin (53). The expression of the nicotinic receptor α7 (in response to nicotine) has been demonstrated in keratinocytes by means of *in situ* hybridization. It has also been demonstrated that nicotine increases the cell to cell adherence in a keratinocyte culture (54,55).

Stimulation of this receptor on macrophages inhibits the activation of nuclear factor kappa-light-chain-enhancer (NF-kB) of activated B cells, which in turn inhibits the synthesis of pro-inflammatory cytokines (56) as well as affecting or inhibiting Janus kinase 2 (JAK2). In this way it initiates the activity of anti-inflammatory factors like the signal transducer and activator of transcription 3 (STAT3) and the suppressor of cytokine signaling 3(SOCS3). By releasing acetylcholine, cholinergic fibers inhibit the production of tumor necrosis factor (TNF-α) by macrophages during the phase of inflammation. Acetylcholine inhibits the excessive production of proinflammatory cytokines when a macrophage makes contact with an antigen (57).

FIGURE 3. Adrenergic (β2) and cholinergic (α7 nicotinic) receptors activate the anti- inflammatory properties of the macrophage. Acetylcholine from the parasympathetic nervous system through the alpha 7 nicotinic receptor and epinephrine from the sympathetic nervous system through the beta 2 adrenergic receptor coincide in the STAT 3 signaling pathway, which is translocated to the nucleus of the macrophage, and on the other hand inactivates the STAT 3 pathway. NFk-B, thus, favor the production of the cytokine IL-10 (13).



The activation of the SNS during infections runs in parallel with the acute phase of the inflammatory response. This activation includes the massive release of its catecholamine neurotransmitters, adrenaline and noradrenaline, into the blood flow (50). Adrenaline mobilizes immune cells (leukocytes) in the blood as well as determining the specificity of stress induced by this mobilization (58). Adrenaline, a potent activator of macrophages, has been shown to regulate the increase in production of NF-κB that accompanies an acute inflammatory response. It does so through the participation of α2-adrenoreceptors (59) in adrenalectomized animals (in an experimental model used to evaluate the role of catecholamines).

Whereas it is known that noradrenaline stimulates macrophages and the functions of neutrophils (60), it has been suggested that adrenaline has an important physiological role as a mediator of stress, acting as a danger signal that reduces the innate immune response (61). On the other hand, norepinephrine stimulates the phagocytic function in neutrophils through the pathway of adrenergic signals and temporarily plays an immunomodulatory role in wound healing of the skin through alterations in the phagocytosis of neutrophils. Norepinephrine may represent a target for the therapeutic manipulation of the innate immune response (62).

In 2007 a subdiaphragmatic vagotomy was performed on adult male Wistar rats in order to determine whether or not the vagus nerve is involved in mediating the stimulation of the hypothalamic-pituitary-adrenal (HPA) axis. For this purpose muscarinic and nicotinic cholinergic agonists (carbacol and nicotine) were employed. The results suggest that carbacol evokes a considerable response of corticosterone though the stimulation of central muscarinic receptors (63).

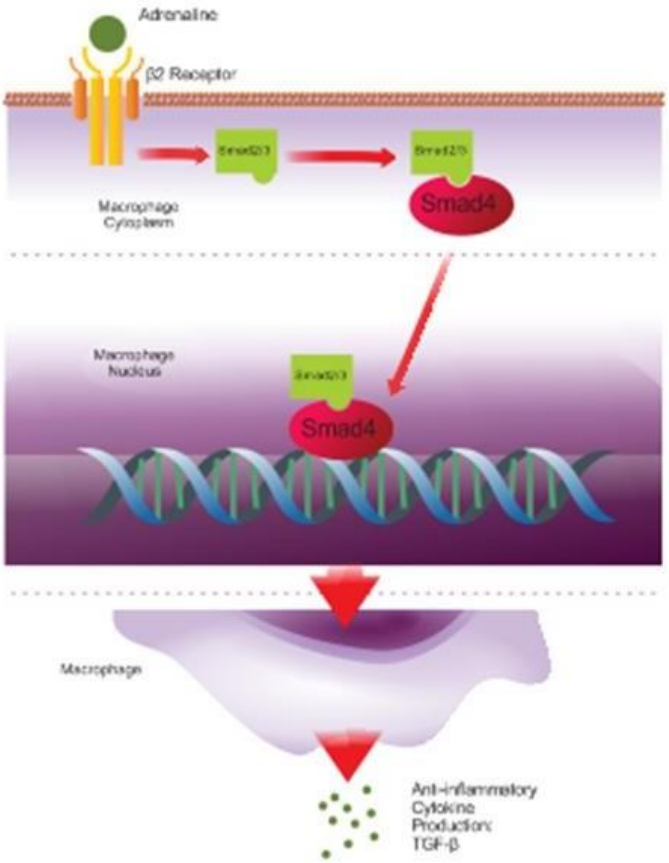
Another mechanism of immunoregulation is through pro-inflammatory cytokines such as interleukin 1 (IL-1) and their effect on the central nervous system and the HPA axis, resulting in the secretion of ACTH and corticosterone. Other cytokines, including IL-6, IL-10 and TNF-α, have the same effect (64).

Certain hormones also stimulate immune activity, including insulin-type growth factor, insulin and thyroid hormones. Contrarily, glucocorticoids (produced by the adrenal cortex, a part of the HPA axis) have an immunosuppressor effect (65) and act through nicotinic acetylcholine receptors (AChRs), in particular the subtype α7. This receptor subtype is highly expressed in cerebral regions related to cognitive and memory functions, and also participates in processing sensorial

information (as evidenced by its involvement in Alzheimer's disease)(66).

There is clear evidence that immune cells can establish intimate contact with nerve endings inside of lymphoid organs and tissues such as ganglions, the spleen, the amygdalae and thymus, where they recognize antigens, develop the immune response, and stimulate the production of effector cells (67). It is known that some hormones and neurotransmitters share secondary intracellular messengers, transcription factors and post-transcriptional mechanisms, a situation that allows for mutual modulation of intracellular events. On the other hand, diverse immune cells like macrophages and neutrophils express various receptors for a given neuroendocrine agent, and these receptors are modified after activation (68). When there is inflamed tissue, stimulation is directed in an afferent manner from the periphery by means of pro-inflammatory cytokines produced locally and through the vagus nerve. Such a stimulus reaches hypothalamic neurons, which emit a response transmitted through the sympathetic or parasympathetic branch (64).

FIGURE 4. The sympathetic ANS via the β2 receptor activates the macrophage for the production of TGF-β. Adrenaline stimulates the macrophage through the smad 4 pathway which, when translocated to the nucleus, activates another mechanism for the production of the anti-inflammatory cytokine TGF-β



CONCLUSION

Neuroimmunoregulation of the inflammatory process is complex. The neurotransmitters adrenaline, noradrenaline (sympathetic nervous system) and acetylcholine (parasympathetic nervous system) participate in the regulation of the inflammatory process that is triggered by the pathogenesis of amebiasis. Through cholinergic and adrenergic receptors, the inflammatory process induced by *E. histolytica* is modified. Curiously, with a vagotomy of the liver of hamsters inoculated with *E. histolytica*, there is a more abundant formation of collagen, an increase in the levels of IL-10 and INF-γ, and a decrease in macrophages, which impedes the dissemination of trophozoites.

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