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INFLAMMATION AND PAIN IN TRIGEMINAL NEURALGIA: ROLE OF SOME PRO-INFLAMMATORY CYTOKINES

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ABSTRACT

The trigeminal ganglion transmits all the sensory information of the skull and face to the brain through afferent pathways. Afferent fibres are divided into nociceptive and non-nociceptive fibres. Primary afferent pathways express receptors for cold, heat, mechanical damage, and more. Inflammation in the head and neck can cause pain that can become neuropathic with nerve damage. An alteration of cytokine production, which may be activated by numerous potentially damaging stimuli, is involved in hyperalgesic states of several neurological diseases. In nerve injury, inflammation initiates pain, a process that is mediated by certain cytokines such as IL-1, TNF and IL-6, which cause neuropathic pain. TNF is mostly produced by mast cells and macrophages and is involved in arthritis, graft versus host disease, and other disorders, mediating inflammatory diseases and playing a key role in the neuropathic pain processes. TNF can activate other cytokines (such as IL-1) and after neurological injury it is expressed by macrophages, fibroblasts, neutrophils, and Schwann cells. In trigeminal neuralgia, TNF is linked to hyperalgesia and neuropathic pain. This shows that the inflammatory mechanisms are overlapping with the those of pain. In pain and inflammatory conditions, IL-1 is produced by many cell types, mediates hyperalgesia and neuropathy, and is involved in trigeminal neuralgia, and this effect is down-regulated by IL-1 inhibitors. IL-6 has also been reported to play a major role in the induction of neuropathic pain. In fact, in neuropathies, such as damaged nerves, IL-6 levels are increased, demonstrating that major pro-inflammatory cytokines participate in pain and inflammation. However, the pathophysiological mechanisms involved in pain and inflammation of the trigeminal nerve still need to be elucidated, as there is insufficient research on this topic. Here, in this article, we report the relationship between trigeminal neuralgia, inflammation, and pain that is mediated by pro-inflammatory cytokines.

KEYWORDS: *trigeminal neuralgia, inflammation, pain, cytokines, IL-1, IL-6, TNF, neuropathic pain*

INTRODUCTION

Trigeminal neuralgia (TN) (tic douloureux) is a specific orofacial neuropathic pain manifested by a sudden paroxysmal event on one side of the face affected by the trigeminal nerve and hyperesthesia, and most frequently affects the second and third divisions of the trigeminal nerve (1). TN is a neurovascular disease affecting the root of the trigeminal nerve, is the most common pain pathology due to compression of the cranial nerves, and is characterized by severe episodic, paroxysmal pain which is similar to an electric shock. The intensity of the pain that comes from a trigger area

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can be of different degrees or even absent. Often, the pain is very strong, excruciating and constant, and can last for long periods. The cause of trigeminal neuralgia, which is usually idiopathic or from vascular compression, is due to damage to the nerve and pressure against it which causes some ischemic and mechanical damage including structural changes of neurons. In fact, in TN, there may be a defect in the axons and their myelin sheaths and therefore, the myelin may also be absent or deficient. It can be idiopathic or associated with compression of the trigeminal nerve (3).

Various stimuli, including tactical, sometimes harmless ones, can trigger a pain attack in the trigeminal nerve that usually affects only one side of the face. The sudden pain, which affects females more often than males, worsens rapidly and lasts for seconds to a few minutes and may involve the facial muscles (4). The right facial side seems to be the most affected and the course of the disease can be spontaneous and occurs after several months. Diagnosis with brain magnetic resonance imaging (MRI) can help identify demyelinated areas, and vascular compression at the root of the trigeminal nerve (ganglion of Gasser) which represents the entry area (5). In TN, sodium channel dysfunction along trigeminal nociceptive axons, myelin impairment, and structural changes in the trigeminal nerve with idiopathic pain may occur (6). In these altered areas, the neurons can excite the nearby axons, which when demyelinated, can generate anomalous electrical impulses, increasing the pain effect. Therefore, in trigeminal neuralgia there is a repetitive, high frequency hyperexcitability of sensory neurons with sharp pain (7).

DISCUSSION

In the interesting article by Kashiba H, et al. (8), it was reported that crush injury of small diameter neurons leads to an upregulation of histamine receptor mRNA. Also, other authors confirmed the inflammatory effect of histamine in neuralgia (9), an effect that can be inhibited by blocking the histamine receptors. Histamine exerts its pro-inflammatory effect by acting on endothelial cells, mediating vascular permeability and promoting platelet adhesion, an effect mediated by the adhesion molecule P-selectin. This shows that in addition to the various immune cells that participate in neuroinflammatory process, there are also mast cells (MCs) (10). In fact, MCs are ubiquitous cells that derive from pluripotent stem cells that mature in tissues and can be activated through the FcεRI receptor. The activation of MCs leads to the rapid release of inflammatory mediators residing within their granules, such as histamine, serotonin (in mouse cells), proteoglycans, TNF, and tryptase, a serine proteinase, etc (11). Furthermore, the activation of these cells can occur without degranulation by producing, through mRNA, pro-inflammatory cytokines, such as IL-1, TNF, IL-33, which play an important role in neuroinflammation (12) (Table I, II).

Table I. *Some compounds that activate MCs*

Bacteria	**Fungi**	**LPS**
Mercury	**SCF**	**PTH**
Venoms	**Parasites**	**Substance P**
IL-4	**IL-6**	**IL-1**
IL-33	**Adenosine**	**Oestradiol**
NSAIDs	**CRH**	**NGF**
Neurotensin	**Thrombin**	**Endorphin**
Endothelin	**Morphine**	**Viruses**

Table II. *Some compounds released by Mast Cells.*

Histamine	**IL-6**
IL-8	**IL-33**
LCT4	**PAF**
PGD2	**CRH**
NT	**TNF**
tryptase	**RANKL**
serotonin	**VIP**
Chymase	**renin**

TNF, which acts on the two receptors p55 and p75, can also be released from MCs granules immediately (after a few seconds) as this cytokine is the only one that can be stored by MCs. IL-1 induces IL-6 and TNF released and other pro-inflammatory cytokines, increasing the inflammation at the site. In addition, IL-33 is a potent activator of MCs and stimulates the production of cytokines including TNF, IL-1, and IL-13 (13). Chemokines can also be produced by MCs, such as CXCL8 secreted by PMNs and fibroblasts which recruits inflammatory cells and cooperates with the CCL2 / MCP-1 chemokine which mainly attracts monocytes. The activation and release of arachidonic acid compounds by MCs leads to the release of PGD2 and leukotrienes LTC4, D4, E4, which collaborate to increase pain and the inflammatory process (14). Therefore, in neuralgia, damaged nerves are infiltrated not only by MCs, but also by neutrophilic granulocytes that mediate neuropathic pain, especially in the early stages. In addition, macrophages are also found in damaged nerves which produce pro-inflammatory cytokines that contribute to inflammation and neuropathic pain (15).

Therapy

The basic therapy for TN utilizes anticonvulsant drugs such as carbamazepine and oxcarbazepine which are the most common drugs (16). In the case of no pharmacological effect or drug intolerance, microvascular decompression can be used, as vascular compression occurs in TN. The mechanism of action of these drugs is based on the inhibition of voltage-gated sodium channels which have a crucial role with regard to neuronal function, since the control of the sodium exchange between the extracellular and intracellular spaces is essential for the initiation and firing of action potentials (17). These treatments increase the excitability threshold of neurons, reducing both the frequency of attacks and pain. Moreover, when pharmacological treatment is ineffective in idiopathic pain, the "nerve combing" method can be implemented, which consists in splitting the trigeminal root for pain relief (18).

CONCLUSIONS

From the concepts described above, we can conclude that in TN the inflammatory process mediated by cytokines, chemical mediators (produced by MCs), and compounds of the arachidonic acid cascade (PGE2 and leukotrienes) are very important, both for the generation of pain and for the induction of inflammation (19).

Conflict of interest

The author declares that they have no conflict of interest.

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THE FEBRILE RESPONSE TO INFECTIOUS MICROORGANISMS AND NEUROLOGICAL DISORDERS

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ABSTRACT

Interleukin-1 (IL-1) is a potent pro-inflammatory cytokine which mediates cells, and organ and tissue dysfunctions. IL-1 is generated and released during infection by microorganisms, causing fever and neurological disorders. Here we report that there is a relation between the fever induced by IL-1 after infection and brain disease.

KEYWORDS: *IL-1; febrile response; fever; infection; neurological disorders; brain*

INTRODUCTION

Microbial infections can be located ubiquitously in all body tissues and are life-threatening. They cause acute-phase defensive responses that can affect homeostatic, metabolic, and immunological processes (1). Microorganisms such as bacteria are a common cause of infections that can affect all or parts of the body. The bacteria can affect the lungs, for example, in respiratory disease, but infections outside the lungs can also be present. The central nervous system (CNS) and one site may be involved with fever and systemic inflammation (2). It is known that the hypothalamus in the brain mediates the febrile phenomenon and is involved in host defense by modulating the immune system (3). Therefore, host immunity against pathogenic infections causes neuroinflammatory responses and can give rise to feverish phenomena.

Interleukin-1 induces fever and affects the CNS

Interleukin-1 (IL-1) is a very important inflammatory cytokine that mediates the acute response after microbial invasion, with biological effects on all organs and tissues (4). It is mainly responsible for fever and is mostly synthesized by macrophage cells stimulated by microorganisms and parts of them (5). IL-1 affects RNA transcription and acute phase protein synthesis by inducing C-reactive protein, serum amyloid A (SAA), complement components, and other inflammatory mediators, with decreased albumin (6). IL-1 stimulates endothelial cells in the brain, promoting angiogenesis and microorganisms cause these cells to release IL-1 and mediate inflammation (7). IL-1 produced by endothelial cells causes various pathological effects including vasculitis. Furthermore, IL-1 activates the endothelial cells

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to produce adhesion molecules, prostaglandin PGE2, and prostacyclin PGI2, the latter both involved in vasodilation and favoring edema and leakage of blood cells from the vessels (8).

IL-1 also affects fibroblasts where it stimulates mitosis and the production of PGE2 and granulocyte-monocyte colony-stimulating factor (GM-CSF), mediating fibrosis (9). IL-1 induces fever in rodents that is similar to bacterial endotoxin, with increases in adrenocorticotropic Hormone (ACTH) and various acute phase proteins with decreases in neutrophil counts and many other biological effects (5). IL-1 also acts on the mesangial cells of the kidney and on the glial cells which, together with the neurons, make up the nervous system (10).

IL-1 induces fever by involving the hypothalamus, where the body's temperature regulation center resides, and where pro-inflammatory cytokines, such as IL-1, are released (11). There are many cytokines that act at the hypothalamic level as an endogenous pyrogen, for example IL-1a, IL-b, tumor necrosis factor (TNF), Interferon-α, Interferon-β, Interferon-γ and others, although the exact mechanism of action has not yet been clarified (12).

Microbes and their products, such as endotoxin, and IL-1 induce fever with activation of hypothalamic endothelial cells and PGE2 synthesis (8). The release of neurotransmitters activates the cerebral vasomotor center, generating vasoconstriction which retains heat with an increase in the febrile temperature (13). Microorganisms cause brain infection by activating glial and neuronal cells with the production of pro-inflammatory cytokines, including IL-1, IL-6, and TNF, that produce fever when injected intravenously or into the third ventricle in rats (14). At the therapeutic level, blocking IL-1 with IL-1 receptor antagonist (IL-1Ra) or IL-37 is known to reduce fever (15) and since IL-1 induces PGE2, non-steroidal anti-inflammatory drugs blocking cyclooxygenase-2 inhibit fever (16). Therefore, IL-1 is a major pro-inflammatory molecule and is related to TNF, which has different receptors than IL-1. It is expressed by almost all human cells and organs, in the brain, and physiologically participates in the regulation of cell growth and reparative processes. This cytokine mediates a large number of pathological effects, including inflammation of organs and tissues, and plays a crucial role in the pathogenesis of disease (17). In fact, blocking this cytokine improves the pathological state of disease (18).

CONCLUSION

In the last twenty years, new members of the cytokine family have been discovered and the IL-1 genes have been found to be located on chromosome-2 (19). In the CNS, IL-1 is produced by both immune cells and non-immunocompetent cells (20). The synthesis of IL-1 in the brain leads to a series of pathology with inflammation and neurological defects. IL-1 produced by microorganisms after an infection reaches the brain through disruption or impaired permeability of the blood brain barrier (BBB). IL-1 passes the BBB through the alteration of endothelial cells and can be generated or reach the CNS via the vagus nerve, other nerve fibers, or via microglia which produce it locally upon activation. In the acute phase of ischemic stroke with cerebral hemorrhage, there is strong IL-6-mediated inflammation that can be reduced with the IL-1Ra, since IL-1 induces IL-6. In fact, stroke severity correlates with high IL-1 levels.

These results demonstrate a close relation between IL-1 secreted during microorganism infection, the brain and brain disease, stroke, and fever.

Conflict of interest

The author declares that they have no conflict of interest.

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IL-1 ACTIVATES MAST CELLS IN RHEUMATIC INFLAMMATORY DISEASE: POSSIBLE INHIBITORY EFFECT OF IL-37

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic inflammatory disease which can be mediated by mast cell (MC) products. Activated MCs secrete pro-inflammatory cytokines such as IL-1, IL-6, and tumor necrosis factor (TNF) and several chemokines including CC5, CCL2, MCP-1 and CXCL8. The activation of MCs in the synovium of RA contributes to inflammation and tissue destruction. In addition, this chronic disease can affect the central nervous system (CNS), causing neuropsychiatric disorders such as depression and anxiety. However, more studies are needed to clarify the complex mechanism/s involved.

KEYWORDS: *Rheumatoid arthritis, IL-1, IL-37, mast cells, inflammation, immune, central nervous system*

INTRODUCTION

IL-1 is a pleiotropic cytokine that functions at very low concentrations on both in vitro cells and brain tissue. IL-1 was discovered over 35 years ago and the pro-inflammatory cytokines of the IL-1 family orchestrate acute and chronic inflammatory diseases, including autoimmune disorders, with a broad-spectrum of action (1). IL-1 is a pro-inflammatory cytokine that stimulates genes for chronic inflammatory diseases. It activates inflammatory molecules such as cyclooxygenase type 2 (COX-2) (an inducible molecule), type 2 phospholipase A, and nitric oxide synthase (iNOS) (2). IL-18 also belongs to the IL-1 family, which is involved in autoimmune diseases and can increase the levels of adhesion molecules such as ICAM-1 and vascular VCAM-1 (3). Rheumatoid arthritis (RA) is a debilitating inflammatory autoimmune disease where IL-1 plays a crucial role (4-6). In experimental models of RA, when the serum of RA mice containing IL-1 is transferred to healthy animals it can cause them to develop joint inflammation (7). RA is often associated with type 2 diabetes (8) and cardiovascular events (9) mediated by IL-1. IL-1 orchestrates leukocyte communication and stimulates the generation of other pro-inflammatory cytokines. Therefore, the inhibition of this cytokine certainly leads to an improvement in the pathological state of the disease. In addition, several lines of evidence support the importance of IL-1 in RA (10), but less is known about the populations of innate immune cells that contribute

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to the production of IL-1 in this disorder. Certainly, the cells of innate immunity such as macrophages and mast cells (MCs) intervene in a decisive manner. MCs emerge as important elements of innate immunity against invading pathogens, producing stored products such as histamine and tryptase, but also pro-inflammatory cytokines such as IL-1 (11). In RA, MCs contribute to acute arthritis especially in the early stages. It has been reported that tyrosine kinase inhibitors have shown therapeutic benefits in RA experimental models and in human *in vivo* (12).

Inflammation is mediated by inflammatory cytokines, particularly by IL-1 and tumor necrosis factor (TNF), and other MC products. In addition, other pro-inflammatory elements can intervene, such as complement, intracellular molecules including protein kinases (PK) and NF-kB. In both innate and adaptive immunity and in rheumatic inflammation, different types of immune cells are present, producing pathophysiological substances such as cytokines and chemokines. In models of rheumatic inflammation, the production of anti-inflammatory cytokines such as IL-10 produced by MCs, and IL-37 generated by macrophages, can reduce many features of inflammation in the affected sites (13,14).

Monocytes /macrophages express high levels of the FcγR activation receptor, can respond to various stimuli and play an important role in rheumatic inflammation, even though the compounds generated by these cells still play an unclear role.

Mast cells (MCs)

MCs are produced from bone marrow, mature in tissues, and are classic cells of allergic inflammation, but they also help to defend the organism against bacterial and helminthic infection. MCs can also be activated in many inflammatory disorders such as atopic dermatitis, asthma, psoriasis, multiple sclerosis, anaphylaxis, asthma, and inflammatory arthritis. The proliferation, differentiation, and activation of MCs is regulated by the stem cell factor (SCF) which binds receptor kit and also by IL-3, but other cytokines intervene to a lesser extent (15). MCs are stimulated by IgE but can also be activated by neuropeptides, bacterial products, chemical agents, and cytokines (16). The classic role of MCs is performed in IgE-dependent allergies and in anaphylaxis, where the MCs express a high number of high-affinity receptors for IgE immunoglobulins. The molecular mechanism of IgE has been extensively revised.

Here we briefly report that the cross-linking of antigen-specific IgE bound to the receptor FcεRI causes receptor aggregation with cellular activation. These reactions are mediated by a series of biochemical events that lead to the production of chemical mediators that are immediately released and to pro-inflammatory proteins such as cytokines and chemokines that are belatedly released. Therefore, there is much evidence showing that MCs are involved in inflammatory rheumatic disorders. Histamine as well as tryptases are stored and released by the MCs granules, contributing to allergic reactions (17). The tryptases secreted constitutively by MCs are derived from α- and β-pro-tryptases and are more stable than histamine (18). They are considered to be potentially important mediators of acute inflammation and promote osteoarthritis-associated pathology, where the levels of tryptase are very high in the synovial fluids (19).

In the innate immune system, MCs are real sentinels of the human body, ready to react immediately with external pathogens that can cause damage. In fact, these cells release IL-33 which is considered an alarm cytokine for the body and called "alarmin". Furthermore, MCs can release other pro-inflammatory cytokines and neuropeptides with appropriate stimuli. Thus, MCs participate in osteoarthritis, a disease characterized by progressive degeneration of joint cartilage and low-grade synovial inflammation due to dysregulated innate immunity which is mainly mediated mainly by IL-1 (20). MCs express interleukin-1 receptor 1 protein (IL-1RL1) which binds the IL-33 expressed in many inflammatory diseases including RA (21).

The chemokines RANTES and MCP-1, and other cytokines, are produced by the rheumatoid synovium and are potent proteins with the power to recruit inflammatory immune cells and thus contribute to the immunopathogenesis of RA (22). Therefore, in synovial inflammation, both the cytokines as well as the chemokines that cause the recruitment of inflammatory cells are produced. Over 20 years ago, we reported that when the chemokines Rantes and MCP-1 were injected under rat skin, they recruited inflammatory MCs and stimulated the levels of histidine decarboxylase (HDC) in vivo in the rat. This effect highlighted the role of chemokines in inflammation with activation of leukocytes and tissue MCs (23)

After activation, MCs release preformed mediators such as histamine and tryptases from their granules but can also produce synthesized cytokines such as IL-6, IL-1, IL-31, IL-33 and TNF (which can be stored also in the granules) and several chemokines such as CC5, CCL2, MCP-1, and CXCL8. MCs produce high amounts of TNF, both intra and extra-cellularly. This cytokine helps the body fight bacterial infections, but it is also a highly inflammatory protein. TNF proteolytically cleaves intracellular caspase-1 and stimulates IL-1 production with a self-inflammatory mechanism (24). Caspase-1 needs a complex intracellular protein called inflammasome to be activated. TNF-induced inflammation inhibitors such as IL-37 can be very effective whereas other compounds such as steroids or anti-TNF may be refractory and unsuccessful. In addition, IL-37 blocking IL-1 can reduce the severity of inflammation, joint damage, and pain in patients with RA (25).

MCs are known to play an important role in the pathogenesis of RA, as these cells are activated in the synovium and contribute to inflammation and tissue destruction. At the inflamed site, there is a high number of MCs, a characteristic phenomenon of autoimmune diseases. The presence of activated MCs leads to the secretion of cytokines that mediate the inflammatory phenomenon. Therefore, MCs not only mediate IgE-dependent immune responses, but may also intervene

in non-IgE-mediated immune diseases. In RA, the cleavage of complement C5a and autoantibodies can activate MCs which participate in the pathogenesis of the disease (26).

It is well known that chronic peripheral inflammation can affect the central nervous system (CNS) (27). Individuals with RA may also have neuropsychiatric disorders including depression, anxiety related to neurodegenerative disease, and age-related problems (28,29). Autoimmune diseases, including RA, present with a dysfunction of the immune system involving the CNS and mediates neurodegenerative and psychiatric diseases. It seems that these relationships are due to genetic problems involving the human leukocyte antigen (HLA) site on chromosome 6 (30). But regarding these last observations more studies are needed to clarify the relationship between RA and the CNS.

Conflict of interest

The author declares that they have no conflict of interest.

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IL-1 AND NEUROINFLAMMATION

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ABSTRACT

Inflammation is involved in many neurological diseases, which are mediated by IL-1 and other inflammatory cytokines. Microglia are brain macrophages responsible for innate immunity of the central nervous system (CNS) and can generate IL-1 when activated. In addition, microglia can phagocytize microorganisms and activate inflammasomes, and cellular sensors sensitive to pathogens such as infectious agents, excesses of neurotransmitters, and abnormal host proteins. For example, the NLRP3 inflammasome activates pro-caspase-1 and subsequently caspase-1, causing IL-1 to mature. IL-1 can be blocked by IL-1Ra, leading to therapeutic effects for limiting inflammation, including neuroinflammation. Here, we report evidence for the first time that dumping IL-1 by IL-1Ra can have therapeutic effects.

KEYWORDS: *Neuroinflammation; brain damage; cytokines; IL-1; microglia*

INTRODUCTION

There is considerable scientific evidence indicating that inflammation contributes significantly to many neurological diseases (1-5). Inflammatory cytokines are responsible for many brain pathologies, altering the synthesis of proteins and the physiology of brain functioning. Brain pathologies such as stroke, Alzheimer's Disease, Parkinson's, trauma, haemorrhages, and others, present an inflammatory response that plays an important role in the pathological state of the disease.

Inflammation in degenerative states of the brain is largely mediated by IL-1 (6, 7). Infections and brain tissue lesions can activate microglia, causing the generation of pro-inflammatory cytokines such as IL-1, IL-6, and TNF. The release of these cytokines occurs in defence against external insults, but they can cause inflammation and damage brain tissue, including neurons and cells.

After brain damage, microglia, a defensive cellular system in the brain, secrete IL-1, which feeds the inflammatory network. Neuroinflammation activates inflammasomes, which are cellular sensors sensitive to pathogens such as infectious agents, excesses of neurotransmitters, and abnormal host proteins. This process activates innate immunity by producing inflammatory proteins, including cytokines and chemokines released by microglia, the main innate immune cells of the brain.

Therefore, inflammasomes are mainly activated by brain microglia, but other types of CNS cells, such as astrocytes and neurons, can also activate inflammasomes and generate IL-1. In addition, inflammasomes participate in degenerative brain diseases by activating the inflammatory network.

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IL-1 induces brain inflammation

The cytokine IL-1 is a key protein in *in situ* and systemic inflammation (8). The innate or adaptive immune response in the CNS can lead to neuroinflammation, which can be acute or chronic. IL-1 mediates a large number of inflammatory diseases and, when administered *in vivo*, is highly toxic, causing fever, arthralgia, myalgia, anorexia, gastrointestinal disturbances, and other serious pathologies (9).

IL-1 acts through the binding with its receptor IL-1R1, which exists on all cells and is increasingly expressed in inflammatory pathologies. The blockade of this receptor with IL-1Ra, an IL-1 receptor antagonist, exhibits therapeutic effects (10). It has been seen that IL-1Ra deficient mice show severe arthritic inflammation that can even lead the rodent to death (11). In experimental mouse models presenting a pathology similar to multiple sclerosis, a significant improvement in the disease was noted by inhibiting IL-1 with IL-1Ra, partly because IL-1Ra induces IFNβ, a therapeutic cytokine for multiple sclerosis (12). In addition, IL-1 is elevated in amyotrophic lateral sclerosis (ALS), a disease caused by the destruction of neurons due to a mutation of superoxide dismutase-1 (SOD1). There is strong evidence of inflammation in this disease, as seen by the lack of IL-1Ra (13).

Therefore, biological brain insults or traumatic injuries can lead to cerebral and systemic inflammation. Systemic inflammation can spread to brain tissue resulting in destruction, and this is an IL-1-mediated effect that can be targeted for therapeutic action. IL-1 can cause permeabilization of the blood-brain barrier (BBB) and can cross the BBB and reach the brain resulting in stimulation of adrenocorticotropic hormone (ACTH) with increased blood pressure (14) and worsening of the inflammatory process. The addition of IL-1 to cultured microglia activates the TLR, an important receptor that mediates the induction of the inflammatory response (15). IL-1 activates MAPK by upregulating other pro-inflammatory cytokines, such as TNF and IL-6, while also stimulating cyclooxygenase-2 (COX-2) with the formation of prostaglandin E2 synthesis (PGE2) (16).

The NLRP3 cellular protein complex can activate caspase-1 with the release of IL-1β and IL-18, cytokines that mediate the innate response in many inflammatory diseases, an effect that can potentially lead to patient death. The NLRP3 inflammasome activates pro-caspase-1 and subsequently caspase-1, causing IL-1 to mature. Inflammasome activation is crucial for host defense against pathogens, but it is correlated with cell death and inflammation when it increases dramatically. Therefore, the activation of caspase-1 leads to the formation of pro-IL-1, and subsequent mature IL-1, a phenomenon that occurs in the cytosol dependent on activating the P2X7 receptor (17).

Microglia are yolk sac-derived tissue-resident immune cells of the brain that are similar to macrophages and are responsible for the innate immunity of the CNS, where they control changes and antigen presentation. Microglia respond to antigens with or without phagocytosis by generating pro-inflammatory molecules, such as cytokines, that promote neuroinflammation.

Inflammation without infection, such as cancer, stroke, atherosclerosis, diabetes, myocardial infarction, etc., is termed “sterile inflammation”, but, as in infectious inflammation, sterile inflammation is mediated by cytokines of the IL-1 family (18). Generally, the most important mediator in sterile inflammation is IL-1α (or IL-1F1), which is implicated in brain injury (19). Sterile inflammation initiates associated molecular damage models (DAMPs) produced by dead or transformed cells following a disease. These molecules are recognized by pattern recognition receptors (PRRs) located on immune cells that mediate inflammation and cytokine release, including those of the IL-1 family (19). Therefore, the mechanisms involved in inhibiting IL-1α and IL-1β lead to a great therapeutic relevance for neuroinflammation.

Conflict of interest

The author declares that they have no conflict of interest.

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EFFECT OF 6-HYDROXYDOPAMINE ON BLOOD VESSEL REACTIVITY IN THE ISOLATED PERFUSED HIND LEG OF RAT WITH ADJUVANT ARTHRITIS

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ABSTRACT

Catecholamines, essential in stress responses, also modulate inflammatory processes. The synthetic organic compound 6-hydroxydopamine (6-OHDA) can modify the time course of swelling and the exudate volume for carrageenan paw oedema and adjuvant arthritis in rat models. In this study, the effects of 6-OHDA treatment on the vasoreactivity to noradrenaline were investigated using standard and adjuvant arthritic rat models of acute and chronic inflammation. Blood vessel reactivity was tested at different time frames following 6-OHDA and adjuvant injections, with differences seen in vasoreactivity in the isolated perfused hind leg of rats with adjuvant arthritis compared with normal rats, with the maximum vasopressor response to noradrenaline, EAm, successively becoming reduced after the acute phase in the days following injection. The simultaneous injection of 6-OHDA with Freund's complete adjuvant (FCA) caused increased paw swelling in the primary phase of arthritis. An injection of 6-OHDA in the paw of normal non-arthritic rats was associated to a decrease in EAm and an increase in pD2 for noradrenaline, up to day 5 following the 6-OHDA injection; EAm slightly increased, and pD2 decreased in the days leading to day 12 after the 6-OHDA injection. It was also observed that a 6-OHDA injection into the same rat paw 5 days before the FCA injection resulted in increased EAm in the isolated perfused hind leg from days 3 to 5 of arthritis. Arthritis strength significantly increased on days 3 and 5 of arthritis when 6-OHDA had simultaneously been injected with FCA, and on day 7, this effect disappeared. In this paper, we report that 6-OHDA injection increases paw swelling in a time-dependent manner and that adjuvant arthritis changes vasoreactivity compared to normal non-arthritic rats.

KEYWORDS: *6-OHDA, arthritis, catecholamines, inflammation, vasoreactivity*

INTRODUCTION

It has been shown that catecholamines play an important role in the modulation of inflammatory processes (1-2) and that 6-hydroxydopamine (6-OHDA) can modify the time course of swelling of both the carrageenin paw oedema and the effect of adjuvant arthritis, as well as of the exudate volume. Furthermore, both local and systemic vasoreactivity

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to noradrenaline has been proven to be reduced in anaphylactic (3), dextran, and carrageenin paw edema, as well as in adjuvant arthritic rats (4).
In this paper, we investigate the influence of 6-OHDA treatment on the vasoreactivity to noradrenaline in normal and adjuvant arthritic rats to elucidate the role of catecholamines in inflammation.

MATERIALS AND METHODS

In this study, male rats (140-180g) of an outbred Wistar strain were used, and arthritis was induced by subplantar injection of 0.1 ml of Freund's complete adjuvant (FCA) into the right hind paw. The strength of arthritis was recorded by a plethysmometer and a sliding calliper and was recorded visually by a score using strength and frequency of paw swelling and visible secondary lesions as the parameters. In addition, blood vessel reactivity to noradrenaline was tested at different times after adjuvant and 6-OHDA injection, respectively, in the isolated perfused hind leg and paw diameter was measured.

RESULTS

According to Fig. 1, arthritis strength was significantly increased on days 3 and 5 of arthritis when 6-OHDA (60μg per paw) had simultaneously been injected with FCA; this could mean that catecholamines normally act as inflammatory inhibitors after FCA injection at the beginning of arthritis. These effects were not seen after the 6-OHDA sympathectomy, resulting in increased paw volume.

On day 7, the 6-OHDA effect disappeared (Fig. 1); however, in some experiments, increases of the secondary phase of arthritis were also seen (4).

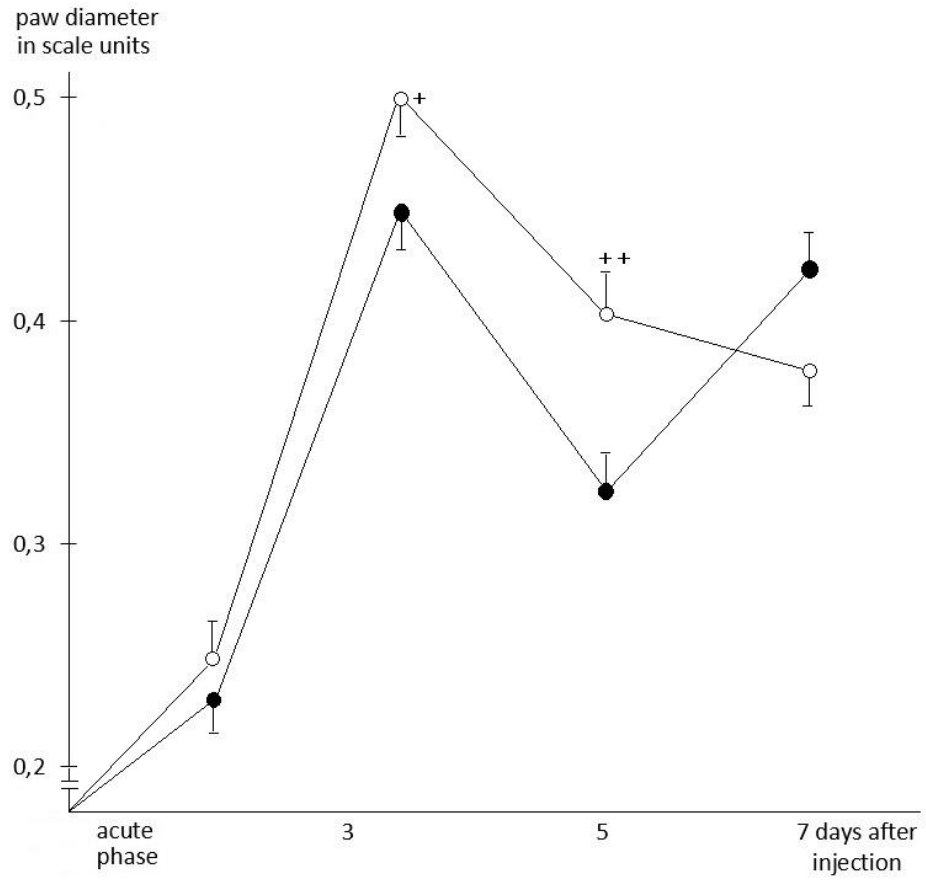

Fig. 1. *The paw diameter was calculated in scale units starting from day 1 at intervals of 3, 5, and 7. The maximum diameters for both adjuvant arthritis rats without and after administration of 6-OHDA at 60 μg /0.1ml were found at day 3. Mean paw swelling of adjuvant arthritic rats without (-●-) and after (-o-) simultaneous administration of 6-OHDA (60 μg/0.1 ml FCA). +, ++ means with p≤ 0.05 and 0.01 statistically different from arthritic controls; n=9-14.*

Blood vessel reactivity in adjuvant arthritis is characterized by a practically unchanged (Table 1), or even slightly increased, resting perfusion pressure, by a decrease of maximum vasopressor effect, E_{Am}, to noradrenaline, and by an increase of the pD_2 value (5).

When 6-OHDA had simultaneously been injected with FCA, resting perfusion pressure remained widely unchanged, whereas E_{Am} was further decreased compared with arthritic rats (Table I).

Table I. *Resting perfusion pressure p_1 (mm Hg, or torr, which is 1 torr=mm Hg, pressure unit) as well as E_{Am} (mm Hg) and pD_2 value of noradrenaline in the isolated perfused hind leg of arthritic rats without and with simultaneous administration of 6-OHDA at different times. +,++ means p= 0.05 and 0.01, respectively, statistically different from arthritic controls; data is given as x ± SD.*

parameter	normal animals	arthritic animals without 6-OHDA			with 6-OHDA		
	n= 34	0.-3. d n= 9	5.-7. d n= 12	14.-16. d n=9	0.-3. d n= 14	5.-7. d n=13	14.-16. d n= 9
P_1	51± 15	42± 8	42± 13	46± 9	53± 15	57± 13	37± 10
E_{Am}	174± 27	167± 54	151± 21	114± 41	120± 32	138± 32	108± 33
pD_2	3.82± 0.55	3.77± 0.16	4.09± 0.30	4.41± 0.26	4.11± 0.31	4.05± 0.26	4.41± 0.39

It seems that vasoreactivity is impaired by mediators of the inflammatory process. After 6-OHDA injection, impairment of vasoreactivity intensifies and, thus, the E_{Am} of noradrenaline further decreases. The pD_2 value is increased after 6-OHDA treatment but only in the early phase of arthritis (Table I); this could be connected with the intensification of the paw swelling in the early phase after simultaneous injection of FCA and 6-OHDA (Fig. 1).

In normal non-arthritic rats, 6-OHDA treatment likewise resulted in an increase of pD_2 up to day 5 after 6-OHDA injection, but then pD_2 was decreased (Fig. 2).

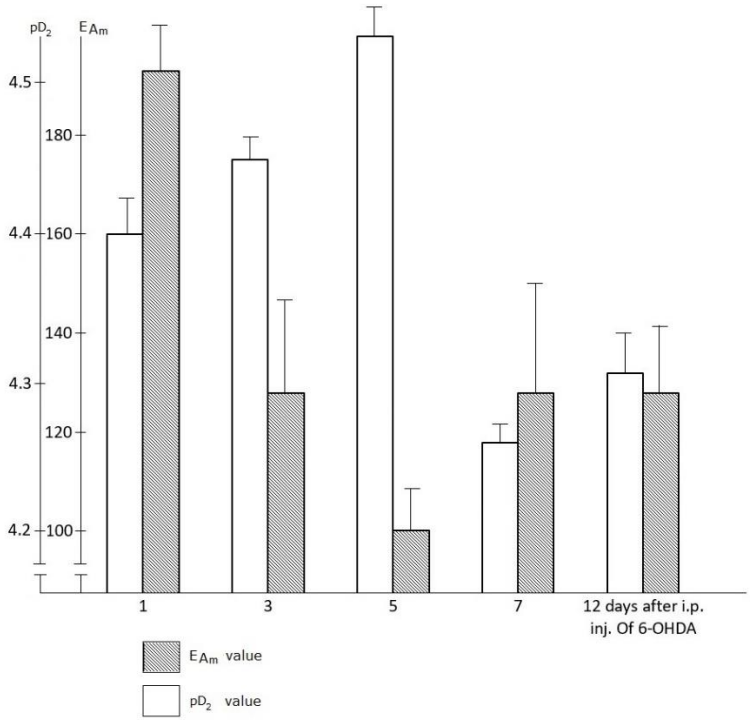

Fig. 2. *E_{Am} (mm Hg) and pD_2 value of noradrenaline in non-arthritic normal rats with 6-OHDA treatment; n=6-7; data is given as x± s.*

On the other hand, E_{Am} successively decreased up to day 5 after 6-OHDA injection and then remained on this low level up to day 12 (Fig. 2). It would be of interest whether an increase of E_{Am} can be expected after this time as a consequence of the sensitization of blood vessel muscles by chemical denervation with 6-OHDA.

Finally, we investigated whether 6-OHDA pretreatment of rats 5 days before FCA injection influences the development of the arthritis and, particularly, the parameters determined in the isolated perfused hind leg. Contrary to the rats with simultaneous 6-OHDA and FCA injection (Table 1), E_{Am} was actually decreased on day 3 of the arthritis (day 8 after 6-OHDA injection) but then was found to be significantly increased on day 5 (Fig. 3).

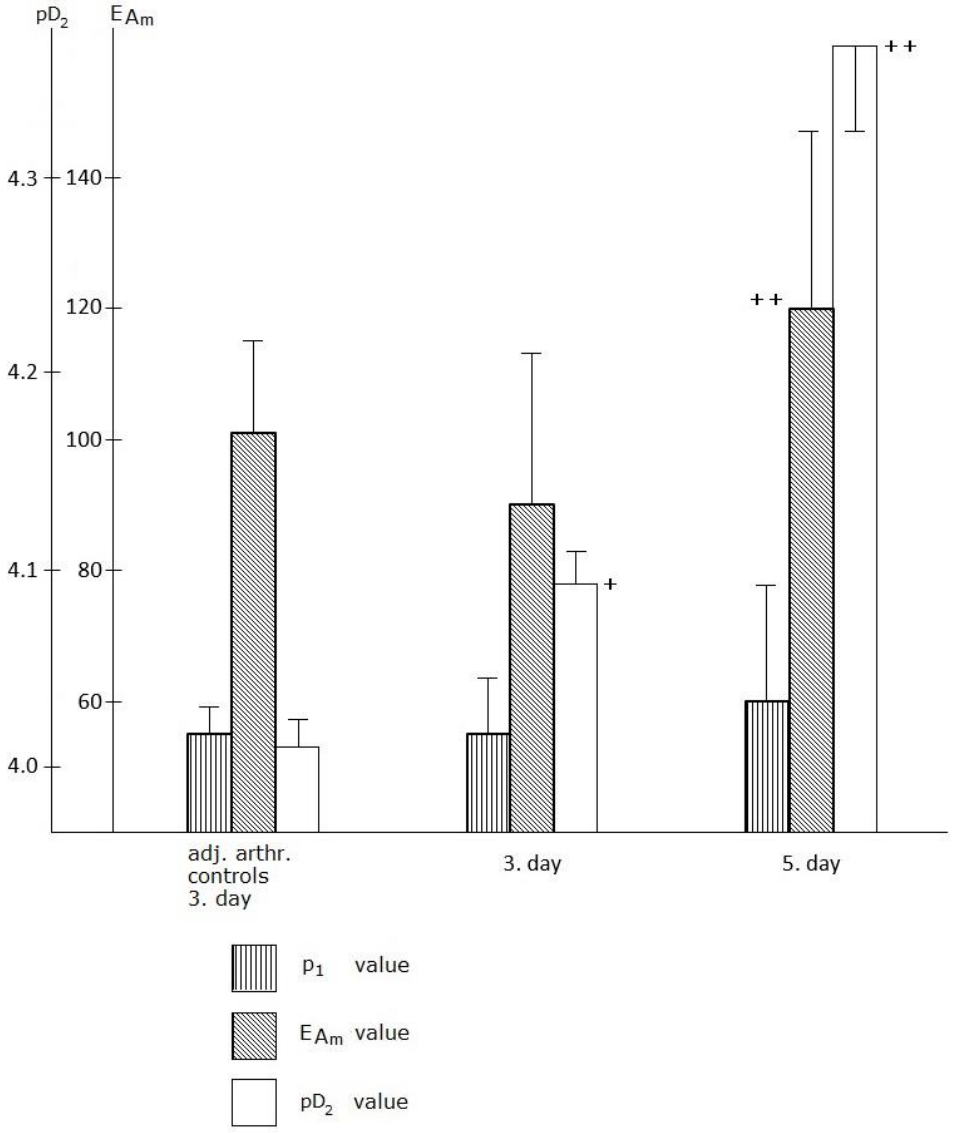

Fig. 3. *Resting perfusion pressure p_1 (mm Hg), E_{Am} (mm Hg), as well as pD_2 value of noradrenaline in arthritic rats (days 3 and 5) after pretreatment with 6-OHDA. +, ++ means with p=0.05 and 0.01 statistically different from arthritic controls; n= 8-16.*

The pD_2 value likewise increased in rats with simultaneous 6-OHDA injection (Table 1) and in normal rats with 6-OHDA injection (Fig. 2) in the early phase. Resting perfusion pressure remained practically unchanged. No explanation can be given for the increase of E_{Am} in arthritic rats given 6-OHDA 5 days before FCA injection.

DISCUSSION

Vasoreactivity was changed in the isolated perfused hind leg of rats with adjuvant arthritis compared to normal rats. The maximum vasopressor response to noradrenaline, E_{Am}, was successively reduced in the inflamed leg from days 0-3 to days 14-16 after injection of FCA into the paw.

Simultaneous injection of 6-OHDA (60μg /per paw) with FCA resulted in increased paw swelling in the primary phase of arthritis, E_{Am} to noradrenaline was further depressed. A slight increase in the pD_2 value of noradrenaline was seen in inflammation, but this increase seems to be of no theoretical and practical significance.

Injection of 6-OHDA (60μg) into the paw of normal non-arthritic rats likewise resulted in a decrease of E_{Am} and an increase of pD_2 of noradrenaline in the isolated perfused hind legs up to day 5 after 6-OHDA injection. Then, E_{Am} slightly increased, but pD_2 decreased until day 12 after the 6-OHDA injection. It would be interesting whether E_{Am} will further increase due to sensitization by 6-OHDA evoked chemical denervation at later times after 6-OHDA injection. In rats injected with 6-OHDA into the same paw 5 days before FCA injection, E_{Am} increased in the isolated perfused hind leg from day 3 to day 5 of arthritis. No explanation can be given for this effect.

CONCLUSIONS

Here, we report that the injection of 6-OHDA increases paw swelling in a time-dependent manner and that adjuvant arthritis changed the vasoreactivity compared to normal non-arthritic rats (control).

Conflict of interest

The author declares that they have no conflict of interest.

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