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PATHOGENETIC MECHANISMS OF NEUROLOGICAL DAMAGE IN HIV-1 INFECTION

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ABSTRACT

Infection by Human Immunodeficiency Virus-1 (HIV-1) can affect the central nervous system (CNS) by triggering various neurological symptoms. HIV-associated neurocognitive disorders (HAND) is a term that refers to the varying neurological and cognitive impairments that can afflict HIV patients, and HIV-associated dementia (HAD) is one of the most severe forms. HIV-1 causes systemic infection through infected CD4⁺ cells and CD14⁺ monocytes. Entry of the virus into the CNS causes neuroinflammation mediated by CD8⁺ T cells that can act against virus-infected cells. HIV-1 induces a high level of trafficking of immune cells and a strong inflammatory environment in brain tissue, which results in the release of pro-inflammatory cytokines that can increase the inflammatory state and contribute to CNS disorders.

KEYWORDS: *AIDS, HIV, CNS, neurological symptoms, infection, HIV-associated neurocognitive disorders, HIV-associated dementia*

INTRODUCTION

The central nervous system (CNS) is often affected by human immunodeficiency virus-1 (HIV-1) (1). The varying neurological and cognitive impairments in HIV-1 patients are collectively referred to as HIV-associated neurocognitive disorders (HAND), which range from asymptomatic neurocognitive impairment to severe HIV-associated dementia (HAD). The new therapies to treat AIDS have reduced not only the pathogenesis of the disease, but also the neurological and neurocognitive disorders caused by HIV-1 (2). Commonly used diagnostic tests such as neuropsychological tests, magnetic resonance spectroscopy, and neuroimaging have made it possible to better study the pathogenesis of HAND. Numerous experimental and clinical evidence have highlighted the presence of neurological symptoms in over 40% of AIDS patients, in different stages (3). However, in the last 10 years, greater clarity has been gained on pathogenesis, diagnosis, and therapy, which has extended the life span of patients infected with HIV-1.

DISCUSSION

HAND includes a varied range of cognitive, behavioral, and motor impairments which can afflict HIV-1 infected patients. Neurological involvement is expressed by various pathologies such as HIV-induced encephalopathy, progressive multifocal leukoencephalopathy, vacuole myelopathy, and necrotizing myelitis (4). Among them, the most specific and frequent clinical syndrome is HAD, recurring in over a third of patients with neurological symptoms (5).

HAD is the expression of a complex neurological, behavioral, and psychiatric symptomatology in which the pathogenetic mechanisms are not yet completely clear. HAD can be related to a series of mechanisms in which the priority

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participation of monocyte/macrophage isotype cells of both peripheral origin and neuro resident immune cells such as microglia is likely (6). They would have the dual function of spreading the infection and producing toxic immune substances, such as cytokines and other mediators, directed against neurons and oligodendrocytes (7).

According to the accumulated experimental evidence, it is possible that in immunopathological determinism, a singular mechanism is created according to which the virus would have the function of catalyzing a series of interdependent events tending to damage neurons through the mediation of substances produced remotely by other cell types (paracrine effect). These mechanisms would determine a variety of histopathological expressions such as reactive gliosis, focal necrosis, nuclear atypia of oligodendrocytes, and dimerization, to which is added a typical hallmark such as the presence of giant multinucleated cells composed of macrophage antigens and antigens of the HIV-1 virus itself (8).

The precise mechanisms by which HIV-1 enters the CNS are not fully understood, although several hypotheses have been proposed. However, the virus is certainly present in the CNS already at the time of seroconversion (9). Simian immunodeficiency virus (SIV) inoculation experiments in rhesus macaques revealed that infected cells invade brain tissue within two weeks of primary infection at rates ranging from 20 to 65% (10). Among the hypotheses, it has been suggested that macrophages coming from the peripheral blood would transport HIV-1, and the virus could penetrate through anatomical damage to the blood-brain barrier (BBB) in the form of a virion or transported by T lymphocytes. Furthermore, *in vitro* studies have shown that the cells of the choroid plexus and the endothelial cells of the CNS are susceptible to direct HIV-1 infections (11).

Other studies have underlined that HIV-1, similarly to other lentiviruses, requires macrophage strains endowed with neurotropism (12). This neurotrophic macrophage would be determined by the V3 domain (V3 region) of the gp 120 glycoprotein, but only some viral subsets are endowed with these properties and the ability to invade the CNS. Viruses with this important mutated determinant would be different from those that infect T lymphocyte lines (13). In this context, however, much still needs to be clarified, and above all, it is necessary to clone and study the amino acid sequences of many viral strains isolated from the CNS to confirm this possibility.

During the early stages of HIV-1 infection, CD4⁺ T cells that have bound HIV-1 transport it into the brain tissue (14). In healthy individuals, CD4⁺ T cells are present in the cerebrospinal fluid (CSF) where they represent approximately 300,000 cells per 150 ml of CSF and are very vulnerable cells to HIV-1 infection (15). The cerebral lymphatic vessels drain the CSF transporting CD4⁺ T cells and, in smaller quantities, CD8⁺ cells (16).

Numerous studies have identified the brain as a reservoir of large quantities of HIV-1 provirus and non-integrated DNA, even in the presence of minimal brain damage (17). Post-mortem neuropathological studies also have highlighted a selective localization of the HIV-1 virus in macrophages and microglia, while cells such as neurons, oligodendrocytes, and astrocytes were spared (18).

However, the same number of affected macrophages and microglial cells does not appear to be correlated with the extent of neurological damage. Such evidence would suggest that brain damage should be caused by indirect mechanisms (19). In this context, it is also necessary to clarify the role of microglia.

Microglia share a series of antigenic markers and other properties with the macrophage cells of the phagocytic system and secrete a series of substances that have the role of determining the development, differentiation, inflammation, and immunization of the CNS. Some proteases, human leukocyte antigens (HLAs), and cytokines such as TNF and IL-1 β fall into this list (20). This secretory ability has been recognized in the culture of both rodent and human cells. During various pathologies or infections of the CNS, microglial cells undergoing activation present a series of phenotypic expressions that are not entirely known.

A powerful marker of microglial activation is represented by HLA class II antigens (DR) which are also found in AIDS (21). Furthermore, this marker can also be induced by some cytokines and by gamma interferon (IFN- γ) (22).

During HIV infection, microglia appear to be more particularly infected in some areas that present some common characteristics such as a high iron content and a high content of neurotransmitter peptides (23). Ultimately, the population of macrophages and their brain equivalents, i.e. microglia, of the CNS is mostly, although not uniformly, affected by HIV-1 infection. Monocytes are generally infected via the CD4 receptor, not only by the virus but also by contact with the gp120 glycoprotein (24). A severe infection drastically reduces the presence of CD4⁺ T lymphocytes with much higher risks of developing neurological disorders. However, in HIV-positive individuals, antiretroviral therapy (ART) treatments at the beginning of the infection induce a benefit after 6 months by reducing the levels of inflammatory markers in the brain, including CD163 (25).

In AIDS, CD14⁺ monocytes represent a reservoir of HIV-1. They accumulate in the CNS and infect brain tissue, causing neuronal damage and mediating viral neuro-invasion (26). Monocytes in the peripheral blood of healthy individuals constitute 6-10% of all white cells, but these percentages can increase up to 40% in individuals suffering from chronic AIDS (27). Monocytes have the chemokine receptors CXCR5, CX3CR1, CXCR7, and CCR2 on their surface,

which helps them cross the BBB and transport viruses into the brain (28). Treatment with ART inhibits viral replication in AIDS and reduces the pathological effects exerted by HIV-1.

CONCLUSIONS

HIV-1 causes systemic infection, including brain invasion, via infected CD4⁺ cells and CD14⁺ monocytes. Entry of the virus into the CNS causes neuroinflammation mediated by CD8⁺ T cells that can act against virus-infected cells. In addition, the high trafficking of immune cells and the inflammatory environment in brain tissue induced by HIV-1 infection, leads to the release of pro-inflammatory cytokines which can increase the inflammatory state leading to CNS disorders.

Conflict of interest

The author declares that they have no conflict of interest.

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ROLE OF TOLL-LIKE RECEPTORS IN ALZHEIMER'S DISEASE

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ABSTRACT

Toll-like receptors (TLRs) are a group of pattern recognition receptors (PRRs) that play a key role in both infections and innate immunity. To date, 11 TLRs have been described that recognize pathogen-associated molecular patterns (PAMPs) expressed on infectious agents. In Alzheimer's disease (AD), TLRs modulate cytokine-mediated inflammation and participate in the innate immune response by mediating neuroinflammation. TLRs modulate the immune system and participate in the clearance of amyloid-beta (A β) in AD. A β molecules activate the immune system and TLRs can interact with NOD-like receptors (NLRs) to activate inflammasomes. IL-1 is generated by microglia in response to A β plaques and plays a crucial role in AD when it is overproduced by causing inflammation and fever. TLR activation in AD leads to the production of pro-inflammatory cytokines such as IL-1 that induce neuroinflammation and worsen AD.

KEYWORDS: *Alzheimer's Disease, neurodegeneration, Toll-like receptor, pattern recognition receptor, inflammation*

INTRODUCTION

Toll-like receptor (TLR) family proteins are a group of pattern recognition receptors (PRRs), which play a fundamental role in pathogen recognition and activation of innate immunity (1). In the innate immune response, PRRs play a critical role system by recognizing pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) (2). There are 11 TLRs, numbered TLR1 through TLR11 (Table I).

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Table I. *The biological effects of TLRs.*

<i>TLR1/TLR2 (Heterodimer):</i>	Recognizes lipoproteins and lipopeptides from bacteria, as well as some fungal components.
<i>TLR2:</i>	Detects lipoteichoic acid from Gram-positive bacteria and lipopeptides.
<i>TLR3:</i>	Recognizes double-stranded RNA (dsRNA) from viruses.
<i>TLR4:</i>	Recognizes lipopolysaccharides (LPS) from Gram-negative bacteria.
<i>TLR5:</i>	Recognizes bacterial flagellin.
<i>TLR6/(TLR2) (Heterodimer):</i>	Detects lipoteichoic acid from Gram-positive bacteria and lipopeptides.
<i>TLR7:</i>	Recognizes single-stranded RNA (ssRNA), particularly from viruses.
<i>TLR8:</i>	Also recognizes ssRNA, similar to TLR7.
<i>TLR9:</i>	Recognizes unmethylated CpG DNA motifs commonly found in bacterial and viral DNA.
<i>TLR10:</i>	The specific ligand is not fully understood, but it may have regulatory roles in the immune response.
<i>TLR11:</i>	In mice, plays a role in recognizing pathogens such as <i>Toxoplasma gondii</i> .

TLRs are highly conserved from *Drosophila* to humans and share structural and functional similarities. They recognize PAMPs that are expressed on infectious agents and mediate the production of cytokines necessary for the development of effective immunity (3). PRRs play a key role in the innate immune system by recognizing PAMPs and damage-associated molecular patterns (DAMPs). In Alzheimer's disease (AD), TLRs have a dual role: They modulate cytokine-mediated inflammation, and they intervene in the immune response “*in toto*”. TLRs participate in neuroinflammation in AD and TLR2, TLR4 and TLR9, are activated by amyloid-beta (A β) plaques (4).

DISCUSSION

A β functions as a DAMP, triggering TLR-mediated inflammatory pathways (5). TLRs are expressed by microglia cells that inhabit the brain and mediate their activation (6). A β plaques are capable of activating microglia, causing a neuroinflammatory cascade with cytokine production.

Microglia cells are similar to macrophages and when they come into contact with A β plaques, they phagocytose them, releasing inflammatory compounds that exacerbate AD pathology (7). The production of cytokines through TLR activation leads to the activation of NF- κ B, which leads to the transcription and translation of inflammatory cytokines such as IL-1, TNF, IL-6, and IL-18. At the same time, chemokines are also generated and released which contributes to the neuroinflammation (8).

It is possible that anti-inflammatory cytokines, such as IL-10, IL-37, and IL-38, are also released, but probably in insufficient amounts to inhibit inflammation in AD (9). Therefore, cytokine dysregulation is one of the important features in this neurodegenerative disease. In AD, TLRs not only modulate the immune system, but also participate in A β clearance. In fact, TLR4 promotes microglia phagocytosis to promote A β clearance (10). The effect of TLR4 also improves astrocyte degradation (11). Regulating TLR could improve the immune system with positive effects on both A β clearance and local and systemic inflammation. Activation of TLR9 has neuroprotective effects and can also have a positive effect on inflammation, as has been demonstrated in experimental models (12).

TLRs are dysregulated in AD and do not permit the correct immune response. A β molecules continuously activate the immune system to overreact. TLRs can interact with NOD-like receptors (NLRs) to activate inflammasomes, such as NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3), exacerbating inflammation through caspase-1 activation and the release of cytokines such as IL-1 β . It is known that some TLRs, such as TLR2, TLR4, and TLR9, specifically participate in the pathological effect that occurs in AD (13) (Fig.1).

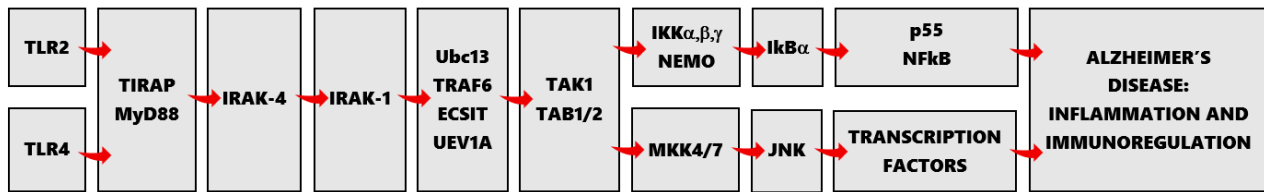


Fig. 1. Toll-like receptors (TLRs)-2 and 4 start a cascade that leads to inflammation and immunoregulation in Alzheimer's disease (AD) (arrows mean activation).

TLR2 recognizes A β oligomers, contributes to the production of pro-inflammatory cytokines, and is linked to cognitive decline in AD, while TLR4 promotes A β clearance. TLR9 has been shown to be neuroprotective and interacts with mitochondrial DNA released from damaged neurons (14). These effects suggest a role for TLR9 in AD therapy. Recently, it has been seen that rat TLR1 (or CD281) polyclonal antibody (concentration: 0.25 mg/ml purified IgG) work with the selective affinity and could be used to treat AD (15). Targeting and modulating TLR could be an important new therapeutic strategy, as currently AD drugs are limited and nonspecific (16). One of the interesting strategies would be to stimulate the neuroprotective TLR9 with the hope of increasing the clearance of A β (17). The specific inhibition of TLR2 and 4 would reduce the production of pro-inflammatory cytokines improving the health status in AD (18). In addition, the therapeutic use of inhibitory cytokines such as IL-37 and IL-38 that significantly reduce IL-1 β could be another therapeutic option (19).

IL-1 and Alzheimer's disease (AD)

IL-1 is an important cytokine of the immune system that plays a crucial role in AD (20). In addition to being an immune molecule, when it is overproduced, IL-1 causes inflammation and fever (21). It is produced in the brain mostly by microglia in response to A β plaques. This cytokine can aggregate A β plaques and cause hyperphosphorylation of *tau* protein, worsening neuronal dysfunction and synaptic efficiency (22).

Targeting IL-1 can improve neuroinflammation in AD. IL-1 and TLR have similar pathways and interact to increase the inflammatory response (23,24). In fact, TLR activation in microglia leads to increased signaling of MyD88, the precursor of IL-1, which in turn re-stimulates IL-1. This creates a vicious cycle where IL-1 induces IL-1 to create the chronic and self-sustaining inflammatory state observed in AD (25). NLRP3 is a multiprotein complex that is part of the innate immune system and acts as an intracellular sensor that detects a broad range of microorganisms (26). When activated, it leads to the cleavage of pro-caspase-1 into its active form, caspase-1, triggering an inflammatory response with the release of the pro-inflammatory cytokine IL-1 (27,28).

Activation of NLRP3 in microglia plays a significant neuroinflammatory role in the pathogenesis of AD and potential therapies have now been shown to target the NLRP3 inflammasome (26). Microglial cells recognize A β and activate the NLRP3 inflammasome, an effect which is also exerted by hyperphosphorylated *tau* aggregates. In AD, excessive production of IL-1 β contributes to neuronal damage, and chronic activation of NLRP3 impairs phagocytosis of microglial cells (29).

CONCLUSIONS

In conclusion, TLR activation in AD leads to the production of pro-inflammatory cytokines and results in neuroinflammation. Targeting TLRs with different specific strategies or inhibiting pro-inflammatory cytokines could be used for new therapies that are currently needed due to the lack of pharmacological tools. AD is increasing in the population, especially in the elderly, and continued research is vital for creating new therapies. In AD, TLRs play an important role in cytokine-mediated neuroinflammation and also in the clearance of A β . Targeting TLRs represents a promising therapeutic option in this severe debilitating disease.

Conflict of interest

The authors declare that they have no conflict of interest.

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WEST NILE VIRUS DISEASE CAN BE NEUROINVASIVE

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ABSTRACT

West Nile virus (WNV) is a single-stranded, positive-sense RNA virus (ssRNA+) transmitted by mosquitoes of the *Culex* genus. WNV enters the host cell by endocytosis and replicates via the E protein, interacting with specific cellular receptors. Eighty percent of infected people show no symptoms, but 20% may experience a mild form with fever, headache, fatigue, and mild nausea, or a neuroinvasive form that can affect the elderly or immunocompromised, which can cause fever and encephalitis, manifesting with inflammation. WNV infects the central nervous system (CNS) by increasing the permeability of the blood-brain barrier (BBB). Brain infection affects microglia, which are activated to produce proinflammatory cytokines, causing neuropathy with activation of endothelial cells, neurons, and astrocytes.

KEYWORDS: *West Nile virus, mosquito, central nervous system, brain, neuroinvasive disease*

INTRODUCTION

West Nile virus (WNV) is transmitted by mosquitoes of the *Culex* genus (1). The RNA virus belongs to the Flaviviridae family, which also includes the virus that causes dengue, yellow fever and Zika (2). WNV is classified as Baltimore Group IV, a single-stranded, positive-sense RNA virus (ssRNA+). There are two main seropositive strains, lineage 1 and lineage 2, both of which are pathogenic to humans and animals (3).

WNV is not transmitted by direct contact between people, although it can be transmitted from mother to fetus or by blood transfusion (4). The virus's final hosts are horses and humans (5). Risk factors include immunosuppression and chronic diseases such as diabetes, heart and kidney failure, and highly invasive viral strains (6). The incubation period for WNV in humans ranges from approximately 2 to 14 days, although it can sometimes reach 21 days (7). Diagnosis is made in serum and cerebrospinal fluid (CSF) by detecting specific anti-WNV IgM immunoglobulins (8). The methods used for detection are ELISA and Northern blot analysis. RNA can be identified with polymerase chain reaction (PCR) (9).

WNV measures 40–60 nm in diameter, has icosanoidal symmetry, and is surrounded by an envelope containing a lipid peri-capsid derived from the host membrane. The single-stranded RNA is positive-sense, approximately 11 Kb in length, and encodes a single multiplex protein, which is subsequently cleaved into 10 proteins: 3 structural proteins, 1 C capsid, which forms the internal core of the virion, 2 membrane-bound prM/M proteins, which protect the E protein during assembly, and 3 E envelope proteins, which mediate attachment and fusion with the host cell (10). The other proteins are non-structural (NS1–NS5) and are involved in RNA replication, immune evasion, and viral assembly.

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WNV replicates by attaching to the host cell via the E protein and interacting with specific cellular receptors (11). The viral receptor mediates endocytosis through fusion of the envelope with the endosomal membrane and release of the RNA into the cytoplasm (12). Viral replication occurs in the endoplasmic reticulum through a replication complex composed of NS proteins and the assembly of new virions in the endoplasmic reticulum, with maturation in the Golgi apparatus (13). Virions are released by exocytosis and can infect birds and *Culex* mosquitoes.

DISCUSSION

WNV disease is not very common, but it can be severe in the neuroinvasive form, which is characterized by three main types: meningitis, encephalitis (with death), and flaccid muscle paralysis similar to polio (14). Approximately 80% of infected people infected with WNV have no symptoms, but around 20% may experience a mild form with fever, headache, fatigue, and mild nausea. The most severe form is neuroinvasive with higher risk for the elderly or immunocompromised. This neuroinvasive form of WNV is characterized by viral invasion of the central nervous system (CNS) (15).

When WNV becomes neuroinvasive, it can affect the meninges and cause meningitis, producing brain inflammation with fever, photophobia, and nausea. WNV can also cause encephalitis, leading to inflammation, mental changes, convulsions, confusion, and disorientation (16). Additionally, WNV may cause acute flaccid paralysis resembling polio, with asymmetric weakness and paralysis, reduced reflexes, and impaired sensation (14).

Inflammatory damage to the CNS is highlighted with neuroimaging using magnetic resonance imaging (MRI) (17). As is usually the case with viruses, there are no specific treatments, but supportive care is used, such as the use of antipyretics and anti-inflammatories, as well as anticonvulsants, respiratory support, and hydration (18).

WNV reaches the CNS through increased blood-brain barrier (BBB) permeability (19). In the meninges, particularly in the microglia, the virus induces inflammatory cytokines such as IL-1, TNF, and IL-6, which cause endothelial cell dysregulation (20). The dysregulated BBB allows peripheral blood monocytes to pass through, which reach the CNS and contribute to the inflammatory process mediated by inflammatory mediators, including cytokines (21). Additionally, macrophages activated by phagocytosis act as reservoirs for the virus, which is subsequently transported to the brain (22). WNV invades peripheral nerve endings and microglia, where it also replicates in endothelial cells, exacerbating the disease (23). Neurons are the virus's primary target cells, particularly those in the brainstem, cerebellum, hippocampus, and spinal cord (24). WNV-induced damage manifests as an inflammatory neuropathy with activation of astrocytes (25).

Prevention is achieved with mosquito-repellent insecticides and body protection. Careful monitoring of endemic areas could drastically reduce transmission of the virus through its vector (26). WNV is sensitive to lipid solvents (such as ether and chloroform), heat, and acidic pH, but is resistant to low temperatures and can survive prolonged freezing (27).

CONCLUSIONS

WNV transmitted by the *Culex* mosquito can affect humans and cause systemic infection. The virus is not transmitted from human to human but only through the bite of an infected mosquito. The most severe form of WNV disease is neuroinvasive and, when infected, the CNS produces inflammatory proteins, including cytokines that aggravate the disease.

Conflict of interest

The authors declare that they have no conflict of interest.

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THE IMPACT OF IL-1 IN NEUROLOGICAL FUNCTIONING

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KEYWORDS: *IL-1, interleukin, cytokine, inflammation, neuroinflammation, CNS, neurological*

INTRODUCTION

IL-1 is a regulator of both physiological and pathological processes, and its dysregulation can cause neuroinflammation and neurodegeneration. The interleukin-1 (IL-1) family primarily includes IL-1 α , IL-1 β and IL-1 receptor antagonist (IL-1Ra), an endogenous inhibitor. In general, IL-1 is involved in inflammatory reactions, infections, and neurological disorders (1,2). IL-1 is a pro-inflammatory cytokine that plays a key role in the immune response and has significant effects on the brain. It has multiple effects on the central nervous system (CNS) and can be inhibited by specific antagonists of the IL-1 receptor (3). IL-1 is primarily produced by activated macrophages, microglia, and astrocytes in the CNS and can exert various effects on brain physiology and pathology.

DISCUSSION

The cytokine IL-1 plays different roles in the brain, where it mediates inflammatory responses and modulates neuronal function. IL-1 is involved in slow-wave sleep, neuroendocrine responses, appetite suppression, fever, and neuroinflammation (4). This cytokine also affects memory and neuroplasticity and has been associated with neurodegenerative disorders such as Alzheimer's and Parkinson's diseases (5).

In vivo studies in mice have shown that IL-1 can interact with GABA receptors to induce sleep and depression (6). IL-1 binds to the IL-1 receptor type 1 (IL-1R1) on the surface of target cells and interacts with the IL-1 receptor accessory protein (IL-1RAcP) to form a signaling complex. At the transductional level, IL-1 recruits myeloid differentiation primary response 88 (MyD88) as an adaptor protein. IL-1 activates kinases including IL-1 receptor-associated kinase (IRAK) and TNF receptor-associated factor 6 (TRF-6).

IL-1 stimulates the NF- κ B and mitogen activated protein kinase (MAPK) signaling pathways and activates the inflammasome (7). The NLRP3 inflammasome is important for the processing of pro-IL-1 β into its mature and active form via caspase-1. IL-1 is regulated by IL-1Ra which competitively inhibits the binding of IL-1 to IL-1R1 while the IL-1 receptor type 2 (IL-1R2) acts as a decoy receptor, controlling the effect of IL-1.

IL-1 is involved in brain pathophysiology, including neuroinflammation. It mediates infectious and neurodegenerative responses by recruiting immune cells to the site and amplifying the inflammatory reaction. It has been reported that IL-1 can increase the vascular permeability of the blood-brain barrier (BBB) to allow the passage of immune cells into brain tissue and contribute to neurodegeneration (8). Among the effects of IL-1 on the brain, it is important to highlight its action on the hypothalamus with the induction of fever by mediating effects such as increased body temperature with

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systemic inflammation, anorexia, and lethargy. At low levels, IL-1 helps maintain normal synaptic plasticity and regulates cognitive function, while its excessive increase causes neurodegeneration. In fact, by stimulating the production of amyloid- β and phosphorylation of tau, IL-1 participates in neurodegenerative diseases such as Alzheimer's and Parkinson's disease. It activates microglia, causing damage and neuronal disorders (9). IL-1 can influence neurogenesis in the hippocampus, altering the mood of the individual. Its inflammatory effect on the brain can cause depression, anxiety and other mental disorders. It has been seen that IL-1 also plays a role in the development of the embryo, interrupting normal brain maturation, which could be linked to diseases such as autism in which the cause is still unknown. Thus, it could be proposed that inhibiting IL-1 with specific cytokines could improve its pathological effects. IL-1 inhibition may be an important therapeutic strategy for neurodegenerative diseases and other brain pathologies.

CONCLUSIONS

IL-1 is a cytokine that, when elevated above physiological limits, is highly inflammatory. This cytokine is produced by macrophages and by microglia in the brain. IL-1 binds to IL-1R1, can interact with GABA receptors to induce sleep and depression, and is implicated in Alzheimer's disease and Parkinson's disease. Inhibiting IL-1 with IL-1 receptor antagonists or anti-inflammatory cytokines may be a valid and novel therapy for neurodegenerative diseases.

Conflict of interest

The author declares that they have no conflict of interest.

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CROSSTALK AT THE LIVER-CNS AXIS

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KEYWORDS: *CNS, liver, liver-brain axis, neuroendocrine pathway, brain*

INTRODUCTION

It is known that the central nervous system (CNS) communicates bidirectionally with the liver, influencing various biological reactions such as cognitive and behavioral functions, cellular metabolism, regulation of hormones and the immune system, and the inflammatory response (1). The liver-brain axis is a set of physiological processes that connect liver metabolism to brain function without affecting individual chemical reactions (2). The main reactions described concern the regulation of energy and metabolism, such as glycogen synthesis and glycogenolysis, which control blood sugar levels. The liver is an immunological organ: it produces cytokines and acute-phase reactants. It also regulates glucose, lipids, and amino acids, and produces ketone bodies (3). Alterations such as steatosis and insulin resistance modify the brain's energy supply.

DISCUSSION

Gluconeogenesis is a reaction by which the liver synthesizes glucose from non-carbohydrate precursors. The main substrates for these reactions are lactate, alanine, glycerol, and glucogenic amino acids, which are involved in the Krebs cycle. The sites where these reactions occur are mitochondria, the cytosol, and the endoplasmic reticulum. The important reactions of glycolysis involve pyruvate, which is converted to oxaloacetate through the reaction: $\text{pyruvate} + \text{CO}_2 + \text{ATP} = \text{oxaloacetate}$, which is a fundamental metabolic intermediate in cellular metabolism, especially in the Krebs cycle (4). Insulin and glucagon affect hunger, satiety, and energy expenditure. The liver regulates the availability of tryptophan, (a precursor to serotonin), dopamine, and norepinephrine (a precursor to tyrosine), and GABA and glutamate, which affect mood, attention, and behavior (5).

The liver is also involved in detoxifying urea by eliminating ammonia (6). If this organ is malfunctioning, ammonia accumulation can occur, leading to encephalopathy and other symptoms. The activation of neuroinflammation is due to the production of inflammatory cytokines that are implicated in stress, mental fatigue, and cognitive decline, such as IL-1, TNF, and IL-6 (7). The liver-CNS axis influences the neuroendocrine metabolism of thyroid hormones, modulating the hypothalamic-pituitary-adrenal (HPA) axis, which has effects on stress and the sleep-wake cycle.

The liver-brain interaction regulates lipid metabolism and myelin. The synthesis of cholesterol and lipoproteins is important for the formation and maintenance of neuronal membranes and myelin. Additionally, the liver influences processes of the CNS such as learning and memory, alertness, and appetite control, and dysregulation can cause confusion, apathy, and irritability. Liver inflammation can become systemic and cross or modulate the blood-brain barrier (BBB), affecting mood and cognition. In these cases, the HPA axis is involved and could implicate immune cells and mediators

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such as inflammatory cytokines, prostaglandins, and chemokines (8). The mechanism driving these effects is linked to the release of corticotropin-releasing hormone (CRH) generated by mast cells and other cells, adrenocorticotropic hormone (ACTH) from the pituitary gland, and cortisol from the adrenal glands. Gut microbiota produce metabolites such as ammonia, short-chain fatty acids, and endotoxins that pass from the liver to the brain (8).

CONCLUSIONS

There is interesting bidirectional communication between the CNS and the liver. This crosstalk influences metabolism, cognitive and behavioral systems, hormone production, immune responses, and inflammation. Dysbiosis induces liver inflammation with neurological effects such as hepatic encephalopathy, where ammonia and neurotoxin accumulation occurs, leading to confusion, cognitive impairment, depression, sleep disturbances, and impaired consciousness. Ultimately, the liver communicates with the CNS through metabolic, immune, and inflammatory signals, and when this communication is disrupted, both neurological and psychological effects can occur.

Conflict of interest

The author declares that they have no conflict of interest.

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INDUSTRIAL TRANS-FATTY ACIDS INCREASE THE RISK OF BRAIN DISEASE

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ABSTRACT

Trans-fatty acids (TFAs) consumed through diet are very dangerous for public health. TFAs should constitute less than 1% of the diet, as they bind to membrane phospholipids and alter the natural *cis* conformation. TFAs cause dysfunction of receptors and ion channels, signal transduction, endothelial function, and can clog arteries, resulting in ischemic stroke or cerebral ischemia. TFAs increase the risk vascular damage and attract immune cells, promoting inflammation. TFA-induced plaques contain cellular and noncellular components, such as free cholesterol, cholesterol esters, phospholipids, and cellular debris. Additionally, TFAs mediate oxidative stress, with damaging systemic effects that also affect the brain. Neuroinflammation and neuronal damage caused by TFAs are implicated in neurodegenerative diseases such as Alzheimer's Disease and Parkinson's Disease.

KEYWORDS: *Trans-fatty acid, vascular damage, inflammation, neurodegeneration, unsaturated fat*

INTRODUCTION

Trans-fatty acids (TFAs) from the diet are mainly produced industrially and are very harmful for public health and for the health of the brain (1). The World Health Organization (WHO) recommends completely eliminating TFAs from the diet, or at least they should represent less than 1% of daily energy intake (2). Omega-3 fatty acids are brain-protective fats and therefore have an opposite effect to TFAs. Damage from TFAs is a key issue in cardiovascular pathophysiology (3). In many European countries, the use of industrial TFAs has been severely limited since 2021 (<2 g per 100 g of total fat) (4).

TFAs are unsaturated fats derived from the partial hydrogenation of vegetable oils with at least one double bond in the *trans* configuration, which alters the natural *cis* conformation and causes cellular and molecular effects on blood circulation (5). They are found in small amounts in processed foods, as well as in milk and meat. TFAs bind to membrane phospholipids, endothelial cells, platelets, erythrocytes, macrophages, and other cells, subsequently altering the cell membrane to become more rigid (6). This effect alters receptors and ion channels, signal transduction, and endothelial function (7).

Eliminating as much saturated and trans fats as possible from the diet improves the physiology of the body and brain. TFAs can cause clogged arteries that increases the risk of heart attacks and blocks cerebral blood flow, which could result in ischemic stroke or cerebral ischemia (8).

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DISCUSSION

Diets high in industrial TFAs, such as those found in some industrially produced hydrogenated foods, promote arterial clogging and increase the risk of cardiovascular disease and brain damage (9). TFAs increase LDL cholesterol and decrease HDL, which can cause vascular disease that can be fatal (10).

TFAs promote vascular inflammation, promoting the formation of atherosclerotic plaques, chronic lesions in the arterial wall that form during atherosclerosis (11). Atherosclerotic plaques are composed of various cellular and noncellular components, which together determine their appearance and degree of risk for the body. The main composition of an atherosclerotic plaque is damaged endothelial cells that promote the adhesion of lipids and inflammatory cells (6). The cellular components of the plaque include smooth muscle cells that produce extracellular matrix such as collagen, elastin, and proteoglycans, and the inflammatory cells of the atherosclerotic plaque are primarily macrophages that phagocytose lipids and become foam cells (12,13).

Other immune cells found in atherosclerotic plaques include lymphocytes, neutrophils, and mast cells (MCs) (14). Lymphocytes modulate the immune and inflammatory response, neutrophils are activators and amplifiers of inflammation in the plaque, while MCs release chemokines, such as CXCL1, and other inflammatory compounds that drive neutrophil recruitment in atherosclerotic lesions (6).

MCs have been identified in the arterial wall, both in the intima and in the adventitia, and in regions of the atherosclerotic plaque. Their activation occurs through various stimuli: neuropeptide factors, complement system (C5a), IgE, and immune complexes (15). They release biochemical mediators including proteases such as trypsin and chymase, which activate metalloproteinases (MMPs) that degrade the extracellular matrix. Furthermore, MCs generate prostaglandins (PGD₂), leukotrienes, and pro-inflammatory cytokines that amplify local inflammation (16).

Plaques also contain noncellular components, such as the lipid core that consists of free cholesterol, cholesterol esters, phospholipids, and cellular debris (17). The extracellular matrix is composed of structural proteins that hold the plaque together. Calcium deposits accumulate as the plaque persists and calcifies (18). All of this increases the risk not only of cardiovascular disease, but also of stroke and other brain diseases.

In addition to the cardiovascular system, there is evidence that TFAs may also have negative effects on the brain (19). Inflammation and oxidative stress can be caused by industrial TFAs which can act systemically (20). These effects can extend to the brain, contributing to neuroinflammation and oxidative stress, two factors implicated in neurodegenerative diseases such as Alzheimer's Disease and Parkinson's Disease (21).

TFAs can cause neuronal and cell membrane damage due to inflammation. They insert themselves into cell membranes, altering their fluidity and functionality. Neuronal membranes are very rich in lipids and TFAs can cause them to be less efficient in synaptic transmission, reducing cognitive function (22). Excessive TFA consumption can affect memory and learning, increasing the risk of cognitive decline (23). These symptoms can also be accompanied by mood changes and an elevated risk of depression (24). Elevated plasma levels of TFA can increase the risk of neurodegenerative diseases (25). In addition to chronic inflammation due to TFAs, there may be impairment of the blood-brain barrier, which could contribute to brain damage (26).

CONCLUSIONS

TFAs are primarily produced industrially and when they are consumed through the diet for an extended period of time, they become harmful for the brain. They can cause clogged arteries to increase the risk of heart attacks and block cerebral blood flow, which can cause ischemic stroke or cerebral ischemia. Furthermore, TFAs can stimulate immune cells and induce local and systemic inflammation. The most common industrial trans fats consumed by humans are margarines and hydrogenated vegetable fats, packaged snacks, fast foods, and repeatedly used frying oils. The use of unsaturated fats such as omega-3, which have a protective effect on the brain, can be a healthy alternative (27).

Conflict of interest

The authors declare that they have no conflict of interest.

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