ETHANOL CONSUMPTION AND INNATE NEUROIMMUNITY

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ABSTRACT

Emerging researches from human and animal models have shown the role of ethanol in innate immune system modulation, particularly in the central nervous system. The activation of receptors of the innate immunity, Toll-like receptors and nucleotide-binding oligomerization domain-like (NOD-like) receptors, triggers the signaling pathways that bring to the production of pro-inflammatory cytokines and chemokines, which, in turn, provokes neuroinflammation and neural damage. The neuroimmune system response to ethanol intake, in specific brain regions such as amygdala, hippocampus and frontal cortex, is involved in addiction and in behavioural deficits observed in alcoholism. In marine models, the knockout for Toll-like or NOD-like receptors abolishes most of the effects of ethanol on the immune system and preserves these mice from neural damage, neuroinflammation and alcohol dependence. Molecular targeting of immune system pathways is a new and promising area of research for the discovery of new biomarkers for neuroinflammation and for the development of novel pharmacotherapies in order to treat neurological and behavioural consequences of ethanol addiction. Biomed Rev 2017; 28: 49-61.

Keywords: ethanol addiction, neuroinflammation, neuroimmunity, Toll-like receptors, NOD-like receptors, inflammasomes

INTRODUCTION

Ethanol modifies the immune inflammatory signals in the central nervous system (CNS) as well as in the rest of the body, so the immune system is strongly modulated by alcohol intake (1, 2). Alcohol consumption may disrupt tight junctions in gut epithelium, allowing the bacterial lipopolysaccharides (LPS), part of the external membrane of the Gram-negative bacteria, to leak from the gut, where they are usually confined, and pass into the bloodstream (3, 4). Lipopolysaccharides (also termed endotoxin) activates the immune receptor 4 in liver Kupffer cells promoting an alcohol-induced liver inflammation enhanced by immune cells; monocytes, macrophages, T lymphocytes and dendritic cells are stimulated to secrete pro-inflammatory cytokines such as interleukins (IL), IL-1b, IL-6 and tumor necrosis factor-alpha (TNF-α) (1). Indeed, this pro-inflammatory cascade (5), induced by alcohol in the periphery, stimulates both the adaptive and the innate immune system (3, 6). Lymphocytic cells that specifically recognize and memorize invading pathogens, producing antibodies, constitute the adaptive immune system that creates the immunological memory to defend the organism from future infections. Instead, in innate immunity, pathogens trigger a non-specific immune response that, secreting

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pro-inflammatory cytokines and chemokines stimulate CNS neuroimmune cells (microglia and astrocytes) to further produce cytokines (7).

Pro-inflammatory cytokines may use different routes to access the brain: via afferent vagal fibres (8), through leaky regions of the blood-brain barrier (area postrema), by active cytokine-specific transporter or through second messenger molecules of CNS endothelia (9, 10).

THE ACTIVE IMMUNE DEFENCE IN THE CNS: MICROGLIA AND ASTROCYTOS

Microglia, a type of glial cells in the CNS and spinal cord, actively manages immune defence in CNS; along with the resident macrophages and astrocytes, microglia recognizes and destroys infectious agents and prevents the damage to the neural tissue (11–13). Microglia cells also control the overall brain homeostasis, as they continuously scavenge the CNS looking for damaged neuron cells and pathogens (12). The multiplicity of microglia functions are made possible by their exceptional plasticity, these cells can change their morphology and phenotype to respond to local chemical signals (14, 15). In absence of pathogens or dying cells microglia adopt the “resting form” that consists in a small cellular body with long branching processes, that constantly scan the surrounding area to sense even small changes in physiological conditions (16, 17).

When microglia detects an endogenous or exogenous insult, it becomes activated and undergoes changes in morphology and gene expression through a response gradient that goes from a ramified form to a totally active phagocytic form (18, 19). In this state, microglia quickly uptakes the major histocompatibility complex (MHC) class I/II proteins and becomes an efficient antigen presenter for T-cell activation. Also in this form these cells can destroy foreign materials and interact with astrocytes, other components of neuroimmune system able to secrete cytokines after activation (20,21).

THE TOLL-LIKE RECEPTOR SYSTEM

Lipopolysaccharides as well as other microbe-derived evolutionarily conserved molecules are recognized by the innate immune Toll-like receptors (TLR; from 1995 Nobel Prize winner Christiane Nüsslein-Volhard’s 1985 exclamation Das ist ja Toll - that’s great/amazing). The TLRs belong to an evolutionary conserved family of receptors involved in the protection against microbial infections (22). The family of these receptors includes 11 members (TLR1-11) in humans, the most studied of which is TLR4. This kind of receptors are pattern recognition receptors (PRRs) that identify the pathogen-associated molecular pattern (PAMPs) and molecular signatures of different classes of bacteria (23). The cytoplasmic nucleotide binding domain leucine-rich repeat containing receptors (known as NLRs or nucleotide-binding oligomerization domain-like receptors, in brief NOD-like receptors) can also activate an innate immune response, recognizing circulating pathogens. Both, cytoplasmic NLRs and membrane TLRs react not only to pathogens but also to host-cell derived molecules, called damage-associated molecular patterns (DAMPs, danger signals, or alarmins), which are generic markers for damage (24). Among them, there are the IL-33 and the High-Mobility Group Box 1 (HMGB1) proteins, which, when activated, become hyperacetylated on lysine residues, translocate from nucleus to cytosol where bind to different receptors and finally activate the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) (25, 26). The role of alarmins in eliciting the “sterile inflammation” without the presence of pathogens is crucial in the CNS neurodegenerative diseases (27).

INTERACTION BETWEEN ETHANOL AND THE IMMUNE RESPONSE

The first demonstration that ethanol can activate the immune signalling pathway and the synthesis of pro-inflammatory cytokines in the brain was obtained by experimental studies of Valles (28). The up-regulation of NF-kB and the expression of pro-inflammatory proteins induced by ethanol was observed in vitro in rat brain slices (29) and in primary cultured astroglial and microglial cells (30, 31). Ethanol can modulate the signalling of different immunoreceptors, the most studied are TLR4 and NLRP3 (NACHT, LRR and PYD domains-containing protein 3). The link between them is the activation of NF-kB (32). The receptor signalling associates with its internalization and trafficking (33) and through the activation of MAPK and transcription factors such as NF-kB or AP-1. The subsequent production of cytokines such as pro-IL-1β, IL-6, IL-8 and TNF-α, chemokines, like the monocyte chemoattractant protein-1 (MCP-1), and inflammatory mediators such as inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), leads, finally, to neuroinflammation (30, 31, 34).

The activation of receptor signalling starts with a “priming signal” of TLR4 that generates, via induction of NF-kB, the synthesis of pro-IL-1β. This signal, along with reactive
ethanol on mitochondria, generates a second signal that activates the formation of a big multiprotein complex called inflammasomes that mediates the activation of caspase-1 that, in turn, produces and releases the mature form of IL-1β (35). The crucial role of TLR4 in inflammatory response and glial activation induced by ethanol was confirmed in vitro using siRNA. Interference against TLR4 abolished inflammatory response in vivo, in mice models of chronic ethanol intake, and in vitro, in cultured glial cells or in glial cells from TLR4 knockout mice (34, 35). In these models, TLR4 knockout mice resulted to be protected from neuroinflammation, myelin disruption and apoptosis in cerebral cortex, mediated by induction of MAPK and NF-kB (36–40).

Alcohol also impairs the pathways of ubiquitin-proteasome and autophagy-lysosome: ubiquitinated proteins accumulate contributing to brain damage and neurodegeneration (41). The activation of TLR4/NLRP3 inflammasomes promotes leukocyte infiltration, compromises the blood-brain barrier integrity (40) and inhibits hippocampal neurogenesis (42). The high levels of cytokines induced by ethanol remain in the brain for a long period after alcohol exposure whereas in periphery cytokines return more rapidly to normal levels (29). This long-term effect of ethanol in the neuroimmune system was also observed in animals exposed to alcohol in adolescence (43, 44) and in postmortem alcoholic brain (45, 46), where, in addition, blood-brain-barrier integrity alterations have been found (47). Moreover, ethanol induces activation (through acetylation) and extracellular release of HMGB1, its pro-inflammatory action is mediated by the activation of TLR4. Ethanol promotes also the expression of NLRP3 in neurons and in astrocytes; the increased expression in these cells was also observed in post-mortem alcoholic brains.

**ACUTE AND CHRONIC ETHANOL CONSUMPTION EFFECTS**

The immunomodulatory regulation of ethanol produces opposite effects depending on acute or chronic alcohol drinking (5), but the exact molecular mechanism behind this effect is still unclear. In animal models exposed to a pathogen, acute alcohol administration decreases the levels of IL-6, TNF-α and IL-1β (48). LPS stimulated human monocytes or binge drinking animal models have shown that acute alcohol administration induces TLR4/LPS tolerance, which develops through the up-regulation of the nuclear protein Bcl-3 that binds to the p50 subunit of the nuclear factor NF-kB (32A). This binding blocks the transcription of NF-kB regulated genes, that include pro-inflammatory cytokines (49), while stimulates the transcription (50) of apoptotic genes (51). In contrast, chronic ethanol exposure converts the anti-inflammatory response to pro-inflammatory through NF-kB activation and TNF-α induction (50,52,53).

While the immune response to ethanol is a sex-independent event, the extent of neuroinflammation, the levels of inflammatory markers such as iNOS and COX-2, the neuronal loss and the activation of caspase-1 are much more pronounced in females (38).

**HYPOTHALAMIC-PITUITARY-ADRENAL-AXIS (HPA)**

Dysregulation of HPA and imbalance of glucocorticoid receptor are commonly observed during alcohol administration; the severity of these effects depends on the stage of alcoholism and on the ethanol dose (54). In chronic ethanol intake, basal adrenocorticotropic hormone (ACTH) levels are elevated and the stress-induced release of cortisol and corticotrophins is inhibited (55). During withdrawal, the negative behavioural effects and the dysphoric symptoms such as tremor, anxiety and agitation arise from an immune-mediated activation of brain stress circuitry, because of the inflammatory cytokines that are strong inducers of the hypothalamic corticotrophin-releasing factor (CRF) (56, 57).

Glucocorticoids produced by inflammatory cytokines dysregulate the catabolic pathway of tryptophan, the serotonin precursor, activating two different enzymes: the hepatic tryptophan 2,3-dioxygenase (TDO) (58, 59) and indolamine 2,3 dioxygenase (IDO) in the brain. Both of them degrade tryptophan along the neurotoxic kynurenine pathway (60, 61). The activation of this metabolic pathway causes a depletion of serotonin, while the production of metabolites of kynurenine such as anthranilic and quinolinic acid by brain microglia, that acts as NMDA receptor agonists, causes neurotoxic effects (62). Dysregulation of tryptophan metabolism lasts for a long period during abstinence and induces physiological responses with mood disorders and emotional and behavioural lability, traits in common with depressive disorders (63–65).

**NEUROIMMUNE SIGNALLING IN ADDICTION AND ALCOHOL DRINKING**

Many pieces of evidence have shown that ethanol-induced neuroimmune signalling is involved in the progression of addiction (66). The alcohol-dependent alteration of the limbic system and frontal cortex imbalances long-term po-
tentiation and long-term depression and reduces neuronal plasticity; particularly, binge drinking is followed by a long term default in learning, (67, 68) emotive response and memory, typical of alcoholism (7, 67–70) (Fig. 1).

Zou and Crews, using an ex vivo model of organotypic hippocampal-entorhinal cortex brain slice culture, showed that 4 days of treatment with 100mM ethanol decreased neurogenesis, cellular proliferation (73) and caused an imbalance of neuroimmune/neurotrophic factors. Augmented pro-inflammatory cytokine IL-1β increased the expression of cAMP response element binding protein (CREB), involved in the activation of many different transcription factors, while brain-derived neurotrophic factor (BDNF) levels were reduced. The blocking of IL-1β with a neutralizing antibody or administration of inhibitors of NF-kB reversed the ethanol-induced inhibition of neurogenesis. Neurogen-

**Figure 1. Neuroimmune molecular pathway in addiction.**
The alcohol–mediated stimulation of microglia and astrocytes in the central nervous system activates the neuroimmune receptors TLRs and RAGE and the alarmin HMGB1. This alcohol–mediated stimulation of microglia and astrocytes downregulates CREB and increases the expression of NF-kB that in turn activates the transcription of innate immune genes. This pathway produces multiple cycles of neuroimmune gene activation which lead to amplification and spreading of neuroinflammation causing neuronal cell death and up-regulation of the limbic system circuitry. This neuroimmune gene activation elicits also negative effects on anxiety and craving, frontal cortex down-regulation with changes in impulsivity, progressive loss of attention and reduced decision making. All these behavioural modifications culminate in addiction (adapted from 45, 66).
esis and hippocampal stem cells proliferation were also impaired in vivo models of chronic binge drinking (74). Anti-depressive treatment reversed the depression-like behaviour and the inhibition of neurogenesis (71, 73).

Chronic alcohol intake determines a permanent activation of microglia and astrocytes (74) that, at the end, results in neuronal damage and cell death (28). Interestingly, in a murine model, administration of prednisone, a synthetic glucocorticoid, was found to increase anxiety-like behaviour and to induce microglial proliferation in frontal cortex and hippocampus (77). These evidences that represent a link between neuroimmune signalling, endocrine system and behavioural alterations, can be at the basis of novel strategies for the treatment of addictions. Moreover, knockout mice models demonstrated that modulation of alcohol intake relies on TLRs/NLRs signalling. TLR4 knockout mice are preserved from up-regulation of brain cytokines and chemokines, do not show cognitive dysfunction or anxiety during withdrawal (after chronic ethanol administration) and manifest a less marked preference for alcohol intake (33, 78–81). Similar results were obtained in knockout mice models for immunorelated genes coding for proteins produced by microglia and astrocytes (82). Recent studies in murine models, employing the infusion in vivo of siRNA vectors targeting TLR4/MCP-1 in specific brain regions such as central nucleus of the amygdala or ventral tegmental area, demonstrated that the block of this signalling blunted binge drinking (79). Moreover, a protein crosstalk between TLR4 and CRF was described: alcohol drinking increases the expression of CRF that, in turn, exert a feedback regulation on TLR4/MCP-1 signalling, this mechanism can potentially contribute to the switch to alcohol dependence (79).

**CYTOKINES AS BIOMARKERS**

The clinical diagnosis of alcoholism needs the development of reliable biomarkers that can be indicators of alcohol use and abuse. An emerging research area concerns the use of plasma or serum cytokine levels as potential biomarkers of alcoholism and alcohol-induced tissue damage (83). To increase sensibility and specificity, serum and plasma levels of cytokines may be tested together with other markers already in use: ethyl glucuronide (EtG) (84,85), gamma-glutamyltransferase (GGT) (86), alanine aminotransferase (ALT), aspartate aminotransferase (AST) (87), mean corpuscular volume (MCV) (88), carbohydrate-deficient transferrin (CDT) (89), 5-hydroxytryptophol (5HTOL) (90), phosphatidylethanol (PEth) (89).

In neurological diseases like Alzheimer’s (AD) and Parkinson’s diseases high levels of inflammatory cytokines were observed. Björkqvist and colleagues identified a panel of plasma proteins, including cytokines, which enabled the accurate diagnosis of AD with an accuracy of 90% (92). The development of biomarkers panels (cytokines) as a signature of neurological disease may provide a strong rationale to extend this strategy to alcohol abuse, considering that alcoholism also causes neuroinflammation and neurodegeneration (75). Indeed, TNF-α IL-1 and IL-6 were found to be elevated in both chronic and acute alcohol-induced liver disease (93) and TNF-α levels were higher in hospitalized alcoholics than in general population (94, 95). These higher levels of circulating cytokines, which correlate with liver dysfunction, were also present in alcoholics without liver disease. A biomarker panel, comprehensive of other circulating proteins such as growth factors, could improve sensibility of alcohol abuse testing (96–107). Studies on pregnant women consuming alcohol have shown a profound effect of ethanol intake on the concentration of circulating epidermal growth factor and placental growth factor (108). Recent studies have also shown the role of small non coding RNAs as modulators of neuroinflammation and as potential bio-markers in addiction and neurological diseases (109, 110): miR-155 in cerebellum, that is TLR4-dependent and up-regulates TNF-α and MCP-1 levels, is modified by chronic alcohol abuse (111); miR339-5p inhibits neuroinflammation and regulates NF-kB signalling (112).

**NEUROIMMUNE SYSTEM AND BINGE DRINKING**

Studies in animal models confirm that occasional and repeated episodes of binge drinking, a common way of drinking alcohol in adolescence, induce modifications in the hippocampus and brain cortex (113, 114), dysfunction of neurogenesis (45) and disorganization in synapses and myelin (80). During adolescence, the still growing brain performs structural and functional remodelling of neural pathway in regions such as cortex, amygdala, hippocampus and nucleus accumbens (115, 116). These regions are crucial for a normal brain maturation from childhood to adulthood (117). The synaptic remodelling during adolescence, coupled to an increased sensitivity to alcohol toxicity, impairs self-control and goal setting behaviours and can bring to cognitive and behavioural deficits (43, 44, 80, 119) and to a later
development of alcohol dependence (118).

Binge drinking activates the neuroimmune system cells microglia and astrocytes. The release of pro-inflammatory cytokines, chemokines and ROS causes neuroinflammation and neuronal death (120-122). Binge-like ethanol administration in adolescent rats up-regulates TLRs, receptor for advanced glycation end products (RAGE), HMGB1, TNF-α and IL-1β mRNA in the prefrontal cortex and activates microglia; this activation lasts for a long period after alcohol consumption (6, 33, 123). Damaged neurons release HMGB1 that activates TLR4, RAGE and the signaling pathway that produces cytokines (124). Interestingly, chronic ethanol exposure has been proven to promote the neuronal release of HMGB1, presumably through a decrease in HDAC activity, mediating this way the pro-inflammatory effects of ethanol (124). Other works have shown that mitochondrial ROS produced by ethanol activates TLR4/NLRs response in microglia stimulating HMGB1 release (35, 40). The stability and persistence of HMGB1 secretion define its role of an enduring activator of inflammation damage (113).

In a rat model, maternal binge drinking during gestation and lactation caused motor coordination impairments during the rotarod test and Y maze performance disruptions in adult male offspring (125), supposedly linked to up-regulation of pro-inflammatory signalling (TLR4, NF-kB p65, NLR protein3, caspase 1, and IL-1β). Moreover, neuronal loss and down-regulation of structural myelin proteins in prefrontal cortex and hippocampus (125) were also observed. The consequent neuroinflammation might be responsible for the worsening of behavioural deficits observed in fetal alcohol spectrum disorders (FASD). In a rat model of adolescent mice wild-type and knockout for TLR4, Montesinos and colleagues showed that binge-like ethanol drinking promoted the up-regulation of BDNF and FosB genes (through epigenetic changes in the promoter regions) in the medial prefrontal cortex. In these young animals, long-term rewarding and anxiogenic effects that increase alcohol preference were observed, while TLR4-knockout mice were protected from these alterations (43).

PHARMACOLOGICAL APPROACHES MODULATING NEUROIMMUNE SYSTEM ACTIVATION

The involvement of neuroimmune system in alcohol consumption and dependence and its role in neurological damage associated with ethanol abuse have encouraged the development of pharmacological treatments in an attempt to normal-ize the immune signalling. The aims are to control the short and long-terms’ effects of ethanol intake in adulthood and in adolescence and to fine-tune a more effective immune-based pharmacotherapy. Many anti-inflammatory compounds that treat the neural damage induced by alcohol and reduce microglia activation are under observation. Minocyclines, for example, inhibit microglia activation and reduce ethanol intake in a 2-bottle choice voluntary drinking model (126). Anakinra, an antagonist of IL-1 receptor, blocks the activation of NLRP3 and reduces alcohol-induced sedation in mice models (111, 127). Nonsteroidal anti-inflammatory substances, such as indomethacin, an inhibitor of COX-2, reduces neuroinflammation and behavioural deficits in a binge drinking model of rats receiving alcohol in adolescence (121). Antagonists that blocks the over-expression of HMGB1, such as glycyrhizin or ethyl pyruvate, avoid the brain damage induced by chronic alcohol consumption (128). Recently, it was shown that oleylethanolamide, a compound with anti-inflammatory and neuroprotective properties, was able to stop the neuroimmune signalling in the rat frontal cortex and to improve the behavioural deficits induced by ethanol binge administration (129).

CONCLUSIONS AND PERSPECTIVES

The complex pathology of alcoholism strongly depends on genetic, epigenetic and environmental factors. A deeper knowledge is needed to understand the global pattern of cellular and molecular mechanisms related to alcoholism and to unravel the role of other proteins such as growth factors and adipokines (adipose tissue-derived signaling proteins). In addition, the influence of other components such as lifestyle, nutrition, aging and gender differences need to be further investigated. Polyphenols are a family of compounds consistently present in the human diet. There are different types of polyphenols like tannins, flavonoids and resveratrol. Polyphenols can counteract inflammation because of their action on transcription factors and their inhibitory effect on NF-kB signalling. Many polyphenols have been studied for their anti-inflammatory and/or antioxidant properties and for their role in regulating neurotrophins levels (130). Their potential therapeutic application against inflammation and oxidative imbalance extends to a large number of conditions affecting different organs, brain included (131). A better comprehension of the protective effect provided by polyphenols might be of primary interest for drug discovery and diet-based prevention of the neuroimmune insults associated with
chronic alcohol abuse.

CONFLICT OF INTEREST STATEMENT

The authors certify that they have no affiliations with or involvement in any organization with any financial interest in the subject matter discussed in the present review.

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**ABBREVIATIONS**

| 5HTOL | 5-hydroxytryptophol |
| ACTH | Adrenocorticotropic hormone |
| AD | Alzheimer's disease |
| ALT | Alanine aminotransferase |
| AP-1 | Activator protein 1 |
| AST | Aspartate aminotransferase |
| BBB | Blood–brain barrier |
| BDNF | Brain-derived neurotrophic factor |
| CDT | Carbohydrate-deficient trasferrin |
| CeA | Central nucleus of the amygdala |
| CNS | Central nervous system |
| COX2 | Cytochrome c oxidase subunit 2 |
| CREB | cAMP response element-binding protein |
| CRF | Corticotropin-releasing factor |
| DAMPs | Damage-associated molecular patterns |
| EGF | Epidermal growth factor |
| ETH | Ethylglucuronide |
| FASD | Fetal alcohol spectrum disorders |
| FosB | FBJ murine osteosarcoma viral oncogene homolog B |
| GGT | Gamma-glutamyltransferase |
| HMGB1 | High mobility group box 1 |
| HPA | Hypothalamic–pituitary–adrenal axis |
| IDO | Indoleamine-pyrolole 2,3-dioxygenase |
| IL | Interleukins |
| iNOS | Inducible Nitric oxide synthases |
| LPS | Lipopolysaccharide endotoxin |
| LTP | Long-term potentiation |
| MAPK | Mitogen-activated protein kinase |
| MCP-1 | Monocyte chemoattractant protein 1 |
| MCV | Mean corpuscular volume |
| MHC | Major histocompatibility complex |
| miR | microRNA |
| mPFC | Medial prefrontal cortex medial prefrontal cortex |
| mROS | Mitochondrial Reactive oxygen species |
| NAc | Nucleus accumbens |
| NF-kB | Nuclear factor kappa-light-chain-enhancer of activated B cells |
| NLR | Nucleotide-binding oligomerization domain-like receptors |
| NLRP | NLR family pyrin domain containing 1 |
| NMDA | N-Methyl-D-aspartic acid |
| PAMPs | Pathogen-associated molecular patterns |
| PD | Parkinson's disease |
| PEth | Phosphatidylethanol |
| PGF | Placental growth factor |
| Pro-IL | Interleukin precursor |
| PRRs | Pattern recognition receptors |
| RAGE | Receptor for advanced glycation endproduct |
| siRNA | Small interfering RNA |
| TDO | Tryptophan 2,3-dioxygenase |
| TLR | Toll-like receptors |
| TNF-a | Tumor necrosis factor alpha |
| VTA | Ventral tegmental area |

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