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Cytokines in the CNS

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Abstract

The innate immune system plays a critical role in the ethanol-induced neuroimmune response in the brain. Ethanol initiates the innate immune response via activation of the innate immune receptors Toll-like receptors (TLRs; e.g., TLR4, TLR3, TLR7) and NOD-like receptors (inflammasome NLRs) leading to a release of a plethora of chemokines and cytokines and development of the innate immune response. Cytokines and chemokines can have pro- or anti-inflammatory properties through which they regulate the immune response. In this chapter, we will focus on key cytokines (e.g., IL-1, IL-6, TNF-α) and chemokines (e.g., MCP-1/CCL2) that mediate the ethanol-induced neuroimmune responses. In this regard, we will use IL-1β, as an example cytokine, to discuss the neuromodulatory properties of cytokines on cellular properties and synaptic transmission. We will discuss their involvement through the set of evidence: 1) changes in gene and protein expression following ethanol exposure, 2) association of gene polymorphism (humans) and alterations in gene expression (animal models) with increased alcohol intake, and 3) modulation of alcohol-related behaviors by transgenic or pharmacological manipulations of the chemokine and cytokine systems. Over the last years, our understanding of the molecular mechanisms mediating cytokine- and chemokine-dependent regulation of immune responses has advanced tremendously, and we review evidence pointing to cytokines and chemokines serving as neuromodulators and regulators of neurotransmission.

Introduction

Innate immunity is the first line of defense against an immune challenge (e.g. infection, toxin and trauma), and the response is characterized by limited specificity and a lack of memory. Regardless of the type of stimulus, the neuroimmune response involves activation of receptors of the innate immune system and release of inflammatory mediators. Inflammatory mediators comprise a heterogeneous group of factors, including cytokines, prostaglandins, free radicals, complement system, acute phase proteins, and neurotransmitters. These mediators regulate diverse aspects of the immune response including its intensity and duration. In general, the immune response/inflammation encompasses innate and adaptive immune responses that work together through direct cell contacts and through interactions involving chemical mediators (e.g. cytokines, antibodies). Contrary to the innate immunity, the adaptive immune response is very specific, develops slowly, and shows a memory (repeated challenge with the same microbe induces a faster and

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stronger response) [1, 2]. This chapter focuses on a group of inflammatory mediators – cytokines and chemokines, and their role in the ethanol-induced neuroimmune response and adaptive changes in the brain.

Cytokines

Cytokines are a group of more than 300 soluble glycoproteins that are produced by cells in response to immunological stimuli (microbes, toxins, tissue damage, etc.). Cytokines are characterized by pleiotropic, redundant, synergistic and antagonistic effects, and play a crucial role in regulation of the innate and adaptive immune response. The term ‘cytokine’ encompasses several classes of proteins including: interleukins, chemokines, tumor necrosis factor, interferons, and growth factors [1, 2]. Members from each of these cytokine subgroups are involved in ethanol-induced pathology in the central nervous system (CNS) [3, 4].

Interleukins (ILs) mediate signaling between cells of the immune system. ILs are produced by a variety of cells and are involved in regulation of cell growth, differentiation, and motility of immune cells [5]. Chemokines, such as MCP-1/CCL2 (Monocyte chemotactic protein 1/Chemokine ligand 2) are involved in leukocyte trafficking under both homeostatic and inflammatory conditions [6]. The tumor necrosis factor (TNF) family are characterized by their critical role in the inflammatory responses as well as in homeostatic processes [7, 8]. Interferons (IFNs) are pro-inflammatory molecules that are essential for innate and adaptive immunity and provide critical protection during early stages of viral, bacterial, or pathogen infections [9]. Growth factors include members of colony stimulating factors (CSF) which mediate development, differentiation, and expansion of cells of the myeloid series, and transforming growth factor β (TGFβ) which inhibits activation of macrophages, growth of B and T cells, and is cytotoxic [1, 2].

The diversity of cytokine molecules reflects their broad functional roles in regulation of the immune responses and homeostatic processes in the peripheral organs as well as in the CNS. During the immune response, cytokines act in concert via complex interactions to regulate gene expression, cytokine release, induction and termination of cytokine activity. While these interactions are fine-tuned under physiological conditions, their imbalance often leads to the development of pathological immune responses that are associated with numerous disorders.

Cytokines in the CNS

In the CNS, cytokines are produced locally, primarily by glial cells, but all CNS cell types are capable of synthesizing cytokines [10]. Under physiological conditions, some cytokines are produced constitutively at relatively low levels. However, cytokine levels are significantly increased after various CNS and PNS (peripheral nervous system) injuries, seizures or infections [11]. While activation of cytokine signaling in glial cells is crucial for the immune response [12, 13], cytokine signaling in neurons induces rapid and often persistent changes in excitability and/or presynaptic neurotransmitter release [11]. In addition to the local production of cytokines, cytokines are also transported across the blood-

brain barrier (BBB) from the periphery via active and passive transporter systems [14–16] and are produced by CNS-invading leukocytes [17]. Activation of cytokine signaling in endothelial cells of the BBB mediate the recruitment of circulating leukocytes and in some cases induces breakdown of tight junctions resulting in a leaky, permeable BBB [18–23]. Additionally, peripheral cytokines can communicate with the CNS by acting on vagal afferent inputs, which modulate cholinergic signaling in the brain [24, 25].

Beyond regulating the immune response, cytokines in the CNS are also involved in regulation of homeostasis of the nervous system [10]. Cytokines play a critical role in synaptic pruning during development, synapse removal, neurogenesis, and modulation of synaptic transmission in the brain [11, 26–31]. Thus, dysregulation of cytokines, for instance by ethanol exposure, has a complex impact on brain physiology and can cause long-lasting neuroadaptive changes [4]. The overall effect of cytokines on neurons and glia is dependent on several factors including interaction with other cytokines, age, sex/gender, brain region, type of stimulus, and previous history of immune challenges [32–39].

Neuroimmune system and Alcohol Used Disorders

The neuroimmune system and ethanol have a complex reciprocal interaction, wherein the neuroimmune system modulates the effects of ethanol on synaptic transmission, ethanol drinking, and alcohol-related behaviors, and ethanol modulates the activity of the neuroimmune system. There are several lines of evidence supporting this bidirectional interaction. Genetic predisposition to increased ethanol/alcohol drinking is associated with polymorphisms in neuroimmune genes and altered gene expression of cytokines in humans [40–42] and rodents [43, 44]. Moreover, transgenic and pharmacological manipulation of cytokine signaling alters ethanol drinking, ethanol-related behaviors, and the molecular and cellular effects of ethanol in the CNS [44–53]. Reciprocally, ethanol exposure induces acute and chronic changes in brain cytokine production, making these interactions very complex. The severity and duration of the neuroimmune response represented by a particular cytokine profile vary with the type of ethanol exposure/drinking (e.g., binge consumption). Table 1 summarizes the acute and chronic ethanol-induced dysregulation of the cytokine production in the animal models and humans. Alcohol use disorder (AUD) is associated with a chronic neuroimmune response and persistently altered neuroimmune gene expression [54]. Human and animal studies suggest that key mediators of the ethanol-induced neuroimmune response and neuroadaptive changes in the CNS include interleukins IL-1β, IL-6, IL-10, chemokine MCP-1/CCL2, and TNF-α. This chapter will highlight our current understanding of the role of these cytokines in AUDs.

The interleukin 1 family

The interleukin 1 (IL-1) family is a group of 11 cytokines that initiate and regulate inflammatory responses [55]. IL-1α/β and its cognate IL-1 receptor type 1 (IL-1R1) are expressed throughout the brain [56–67] and are synthesized in both neurons [12] and glial cells [68, 69]. Specifically, IL-1R1 is enriched in post-synaptic compartments in rat hippocampus and cortex [70, 71]. In general, IL-1α is produced constitutively, whereas IL-1β synthesis is induced and requires activation of the inflammasome pathway. The

inflammasome is a multiprotein complex mainly functioning as a platform for the activation of inflammatory caspases to produce pro-inflammatory cytokines (IL-1β and IL-18) and as a trigger for the release of proteins involved in coordination of cell proliferation and tissue repair. First, an initial immune stimulus induces gene expression and protein synthesis of the inactive proIL-1β. The release of an active IL-1β requires a second stimulus that activates the inflammasome, which leads to cleavage of the proIL-1β by caspase 1 [72, 73]. Notably, activation of the inflammasome pathway, particularly NLRP3/ASC inflammasome, plays a critical role in regulation of the alcohol-induced neuroimmune response [53, 74–77].

The pro-inflammatory activity of IL-1α and IL-1β are mediated by downstream signaling of IL-1R1. IL-1α/β binds to the extracellular domain of IL-1R1 leading to the recruitment of accessory proteins (e.g. the co-receptor IL-1R1 accessory protein (IL-1RAcP)), formation of a receptor heterodimeric complex (comprised of IL-1α/β, IL-1R1, and IL-1RAcP), and assemblage with the intracellular adaptor protein MyD88. Downstream of IL-1R1, many intracellular signaling pathways are activated such as: NF-κB, c-Jun N-terminal kinase, and p38 MAPK. Additionally, transcription factors, which induce gene expression of the inflammatory mediators including IL-1α/β, are also activated [78]. Importantly, IL-1α/β-IL-1R1 signaling is regulated by an endogenous antagonist (IL-1Ra) and a decoy receptor (IL-1R2). IL-1Ra (IL-1 receptor antagonist) competes with IL-1α/β for binding sites on IL-1R1, and IL-1α/β binds to the decoy receptor IL-1R2, which does not assemble into the IL-1R1/IL-1RAcp/MyD88 complex [79, 80]. In both cases, the inhibition of IL-1α/β-mediated response is carried out by preventing the activation of downstream IL-1R1 signaling [79].

Based on the available literature, ethanol does not induces changes in the IL-1α levels in the brain [53]. While this does not exclude the possibility of IL-1α playing a role in the ethanol induced neuroimmune response, IL-1α does not appear to play a critical role in ethanol effects in the CNS [45, 81]. Here, we will focus on IL-1β which play a critical role in the ethanol-induced neuroimmune response in the CNS [82].

The mechanisms by which IL-1β exerts its effects can be broadly categorized into two branches: 1) primarily immune cell mediated effects and 2) direct neuronal effects. The first branch of the IL-1β mechanisms encompasses various processes of the neuroimmune response (e.g., free radical generation, activation of glial cells) in which the IL-1β serves as a key regulator. The second branch includes the direct regulation of homeostasis in the CNS by IL-1β and IL-1β−dependent modulation of synaptic transmission. Importantly, the individual mechanisms from both branches do not act independently, but rather work in parallel, influencing the actions of each other.

The IL-1β system modulates the functional activity of neurons in a cell- and brain region-specific manner including: excitability, neurotransmitter receptors, neurotransmitter release, and synaptic plasticity. For example, IL-1β directly modulates voltage-gated ion channels [11]; it increases firing in Purkinje cells [83], decreases firing in dorsal raphe nucleus serotonergic neurons [84, 85], and has dual effects in orbitofrontal cortex neurons [86]. In the hippocampus (including hippocampal neuronal cell cultures), IL-1β increases the membrane expression of GABA (γ-Aminobutyric acid) receptors [87, 88] and IL-1R1 at

synaptic sites, where IL-1R1 colocalizes and binds to the GluR2B subunit of NMDA (N-methyl D-aspartic acid) receptors [70]. IL-1β-IL-1R can increase NMDA receptor phosphorylation (e.g., GLuR2B subunit) leading to an increase in NMDA mediated calcium (Ca^{2+}) flux, excitability and excitotoxicity [89]. The dual effects of IL-1β on presynaptic GABA and glutamate release as well as postsynaptic inhibitory and excitatory activity are specific to neuronal type and brain region [81, 90–97]. Moreover, IL-1β inhibits synaptic plasticity in CA1 and dentate gyrus neurons of the hippocampus [97–101].

IL-1β and Alcohol

There are several lines of evidence supporting the critical role of IL-1β in the neuropathogenesis and behavioral changes associated with alcohol dependence. In humans, polymorphisms in *Il1rn* and *Il1b*, the genes encoding IL-1Ra and IL-1β, respectively, are associated with a susceptibility to alcoholism in Spanish men [40]. Similarly, mice with a genetic predisposition to high alcohol consumption show altered expression of several genes of the IL-1/IL-1R system, including *Ilf5, Ilf6, Ilf8, Irak4*, and *Il1rn*. All of these genes, except *Irak4*, are also located within QTLs (quantitative trait locus) for human alcoholism susceptibility and are considered as candidate genes for alcohol drinking [43]. ILf5, ILf6 and ILf8 are ligands for IL-1R2 [102]. *Irak4* encodes the protein IRAK4 (IL-1 receptor-associated kinase 4), which plays a key role in the activation of NF-κB signaling [103]. Interestingly, high alcohol preferring (HAP) mice have altered levels of several genes involved in the NF-κB pathway (*Casp8, Fadd, Ikbkb, Ikbkg, Map3k1, Map3k7, Tradd*), through which IL-1α/β -IL-1R1 mediate its biological action [43]. Follow-up behavioral studies show the involvement of some of these genes in alcohol drinking and preference. *Il1rn* encodes the IL-1Ra protein that is an endogenous competitive antagonist of IL-1R1. *Il1rn* knockout mice exhibit a reduction in alcohol drinking and preference [49], increased ethanol clearance and decreased ethanol-induced conditioned taste aversion, increased sensitivity to the sedative/hypnotic effects of ethanol and flurazepam, and reduced severity of acute ethanol withdrawal. Pretreatment with exogenous IL-1Ra (Kineret) reverses some of the behavioral phenotypes of *Il1rn* KO mice, specifically it reduces the ethanol- and flurazepam-induced sedation and restores the severity of acute ethanol withdrawal [47]. Mice lacking the *Il1r1* gene, encoding IL-1R1, exhibit the opposite phenotype of *Il1rn* KO mice – decreased ethanol-induced sedation and increased severity of ethanol withdrawal, indicating that IL-1R1 signaling plays a crucial role in these behaviors. However, the findings that ethanol intake and preference are not altered in *Il1r1* KO mice and recovery from ethanol-induced motor incoordination is only altered in female *Il1r1* KO mice suggests that these alcohol-related behaviors are not solely regulated by the IL-1β system [47]. Moreover, systemic administration of IL-1Ra reduces alcohol-induced sedation and motor impairment recovery time in mice [51] and also prevents alcohol-induced neuroinflammation [53].

Pharmacological manipulation of the IL-1 system selectively in the CNS provides further evidence for a critical role of the brain IL-1 system in several alcohol-related behaviors. Intracerebroventricular administration of IL-1β increases alcohol withdrawal-induced anxiety [104], while bilateral infusion of IL-1Ra into the basolateral amygdala (BLA), but not the central nucleus of the amygdala (CeA), reduces ethanol consumption with no impact

on either sucrose drinking or open-field locomotor activity, a behavioral measure of anxiety [105]. Overall, these evidences indicate that IL-1β plays a critical role in activation of the ethanol-induced immune response in the brain and is involved in the regulation of critical neurocircuitries mediating the alcohol-related behaviors.

IL-1β mechanisms of action

Evidence for the involvement of IL-1β and its signaling pathways in alcohol-related behaviors are compelling. Indeed, ethanol increases IL-1β levels in neuronal and glial cell cultures [74, 106–108], and in specific brain regions in animal models of AUDs as well as in humans (see Table 1). In this regard, the hippocampus, PFC, and cerebellum seems to be the most sensitive to ethanol-induced dysregulation of IL-1 - IL-1R1 signaling [53, 109–111]. However, the mechanisms through which IL-1β modulates alcohol-related behaviors are still not fully understood. Therefore, the focus of current research has extended to the other brain regions such as the amygdala, which plays a critical role in alcohol dependence and withdrawal [112]. Thus, here, we will summarize our current understanding of the mechanisms of action of the IL-1β and the IL-1β-ethanol interactions at the cellular and behavioral levels in the CeA, BLA and hippocampus.

IL-1β in the CeA

The CeA, a major component of the extended amygdala, is a primarily GABAergic nucleus involved in stress-, fear- and anxiety-like behavior [113] and excessive drinking [112, 114]. The GABAergic system tightly controls neuronal excitability [115, 116], and it is critical in the development of alcohol dependence [117, 118].

Modulation of GABA-A receptors alters many ethanol behaviors [119–121]. Specifically, muscimol, a GABA-A receptor agonist, injection into the CeA greatly reduces ethanol self-administration, but only in dependent rats [122], and a GABA-A antagonist reduces ethanol self-administration [123] in non-dependent rats. The CeA has abundant corticotrophin releasing factor (CRF)-containing fibers and CRF receptors [124], and is thought to be a target of the peripheral neuroimmune system [125]. CRF1 receptors play an essential role in ethanol's effects on GABA release in the CeA and in ethanol dependence [114, 126–128]. Interestingly, facilitation of ethanol withdrawal-induced anxiety by TNFα or MCP-1/CCL2 microinjection into the CeA is dependent on CRF [129], and CRF-amplified neuronal TLR4/MCP-1 signaling in the CeA regulates alcohol self-administration [44]. Moreover, IL-1β and IL-1Ra regulate GABAergic transmission in the CeA [45, 81]. Under basal conditions IL-1R is detected in the amygdala [130], but expression of IL-1β and IL-1Ra are not detectable but rather appears to be inducible in the CeA [125, 131], suggesting that modulation of basal GABAergic transmission with acute application IL-1Ra is likely through IL-1α. Systemic IL-1β and LPS administration activates the CeA, as indicated by an increase in gene expression of the immediate early gene product cFos [125, 130, 132]. At the cellular level, IL-1β significantly decreases amplitudes of evoked inhibitory GABA-A mediated postsynaptic potentials (eIPSP), without affecting paired-pulse facilitation (PPF), a paradigm to assess pre- and postsynaptic mechanisms for evoked responses. Interestingly, IL-1β has dual effects on action potential independent miniature inhibitory postsynaptic currents (mIPSCs) in CeA neurons: in the majority of the cells, IL-1β increases mIPSC frequency

suggesting an increase in presynaptic vesicular GABA release. However, in some CeA neurons, IL-1β decreases vesicular GABA release as well as postsynaptic GABA-A receptor function represented by a decrease in mIPSC amplitude. Consistent with the IL-1β effects, IL-1Ra alone had dual effects on mIPSCs, and it also blocks the effects of IL-1β on CeA GABA transmission [45, 81].

Further, acute ethanol facilitates GABA transmission in the CeA [128]. IL-1β interacts with the effects of acute ethanol on GABA transmission in the CeA. Although IL-1β pretreatment does not block the ethanol-induced facilitation of evoked responses, IL-1β occludes ethanol's effects on presynaptic vesicular GABA release in CeA neurons responding to IL-1β. Overall, these findings indicate that the IL-1 system is involved in tonic regulation of GABA transmission and that IL-1β interacts with the ethanol-induced enhancement of the GABAergic transmission in the CeA [81].

The endogenous IL-1Ra is an anti-inflammatory element that may play a critical role in the development of alcohol dependence [43, 49, 51, 53]. Transgenic mice lacking endogenous IL-1Ra (*Il1rn* KO) exhibit reduced alcohol intake [49], prolonged loss of the righting reflex (LORR) induced by ethanol or by the GABA-A receptor positive allosteric modulator flurazepam [47]. Also, GABAergic neurotransmission in the CeA of *Il1rn* KO mice is disrupted. Notably, both baseline evoked GABA responses and baseline frequency of action potential dependent spontaneous inhibitory postsynaptic currents (sIPSCs), but not mIPSCs, are significantly increased in these KO mice compared to wildtype (WT) mice, indicating increased GABA release in the CeA of KO mice. Acute application of ethanol increases the frequency of sIPSCs and mIPSCs in a vast majority of the WT CeA neurons, but these effects are observed only in about half of the KO CeA neurons. Pretreatment with exogenous IL-1Ra (Kineret) reverses this increase in KO mice without altering the frequency in WT mice. Kineret is also capable of restoring the ethanol-induced increase in GABA release in KO mice, indicating that some of the cellular phenotypes in *Il1rn* KO mice are rescued by application of exogenous IL-1Ra [45]. This suggests that IL-1R1 antagonism regulates basal GABA release and plays a key role in the effects of ethanol at inhibitory synapses in the CeA

IL-1β in the BLA

Acute application of IL-1β hyperpolarizes the membrane and decreases input resistance in most BLA neurons. The hyperpolarization induced by IL-1β is dose-dependent, reversible, action potential independent, and blocked with a GABA-A antagonist. IL-1β inhibits excitatory and inhibitory responses evoked by stimulating either the bed nucleus of stria terminalis or the lateral amygdala via presynaptic mechanisms. Thus, IL-1β hyperpolarizes the membrane through indirect mechanisms, possibly by enhancing the action of endogenous GABA in the BLA and inhibits excitatory and inhibitory transmission at presynaptic sites [133].

Binge-like ethanol drinking induces a significant increase in IL-1β mRNA and protein expression within the amygdala, but not CeA. Interestingly, bilateral infusions of IL-1Ra into the BLA, but not the CeA, reduces ethanol drinking without affecting sucrose drinking or open-field locomotor activity [105]. These results highlight a specific role for IL-1

receptor signaling in the BLA in modulating binge-like ethanol consumption and indicate that pro-inflammatory cytokines can be induced prior to progression into alcohol dependence.

IL-1β in the hippocampus

The hippocampus expresses a high density of IL-1β receptors presumably on dendrites of granule cells [134]. Exogenously applied IL-1β enhances neuronal excitability and increases NMDA receptor function. Indeed, data from primary rat hippocampal neuron cultures suggests that IL-1β increases NMDA receptor function through activation of tyrosine kinases and subsequent NR2A/B subunit phosphorylation [89]. IL-1β reduces seizure thresholds and inhibition of IL-1R1 by its antagonist limits seizures [135]. Moreover, convulsant and/or excitotoxic stimuli increases the production of IL-1β in microglia-like cells in the hippocampus [135]. A later study, clarified the mechanism of IL-1β-associated seizures and the interaction between IL-1β and Ca2+ mobilization on glutamate and GABA releases using mice hippocampal mini-slice [136]. Both basal and K^+-evoked GABA releases are regulated by Ca^{2+} influx and Ca^{2+}-induced Ca^{2+} releasing system (CICR). Similarly, the K^+-evoked glutamate release is also regulated by Ca^{2+} influx and CICR, but basal glutamate release is not. IL-1β increased basal releases of glutamate and GABA depending on the activation of Ca^{2+} influx and ryanodine receptor (RyR)-sensitive CICR. During neuronal hyperexcitability, the effect of IL-1β on GABA release is more predominantly modulated by Ca^{2+} influx and RyR-sensitive CICR than that on glutamate [136].

IL-1β can also impact neuronal plasticity. Low, physiological levels of IL-1β play a role in long-term potentiation (LTP), an important cellular correlate of learning and memory, while high, pathological levels can disrupt this process. Blockade of IL-1β signaling by its antagonist, IL-1Ra, impairs memory. However, addition of excessive IL-1β also impairs memory [137]. Therefore, immune signaling impacts plasticity through finely tuned changes in cytokine levels that alter neuronal activity, neural circuitry and consequently behavioral phenotypes [4].

IL-1β can also affect neurogenesis, the process of generating functional neurons from neural precursors, in the hippocampus. Inflammation [138] and chronic stress [139] reduce neurogenesis and cause depression-like behavior. In particular, stress induces IL-1β expression in the hippocampus, which decreases neurogenesis and contributes to depression. Blockade of IL-1β signaling inhibits stress-induced decreases in neurogenesis and depression-like behavior [140]. The increased gene expression and protein levels of IL-1β in the hippocampus following prolonged/binge and chronic ethanol exposure, found in animal models as well as in human alcoholics (Table 1), indicate that IL-1β may play a critical role in the ethanol-reduced hippocampal neurogenesis [141]. Indeed, blocking IL-1β or inflammasome signaling reverses the ethanol effects on the neurogenesis [141]. These findings indicate that inflammasome and IL-1β mediate the ethanol-induced inhibition of the hippocampal neurogenesis [74].

Thus, it is clear that the IL-1β system plays a neuromodulatory role and interacts with ethanol in CeA/BLA/hippocampus neurons. At the same time, there are still many

unanswered questions regarding the mechanisms mediating brain region differences in the IL-1β effects and neuroadaptive changes of the IL-1β system induced by chronic ethanol exposure and withdrawal.

Interleukin-6

Interleukin-6 (IL-6) is a prototypical pro-inflammatory cytokine involved in the transition from innate to adaptive immunity. IL-6 plays a major role in the neuroimmune response to brain injury and is associated with multiple neurobiological (e.g., multiple sclerosis, Parkinson's disease, Alzheimer's disease) and psychiatric (major depression, post-traumatic stress disorder, substance use disorders) disorders [142]. In addition to mediating the neuroimmune response, IL-6 is critical in neurogenesis and the regulation of various physiological processes (e.g., food intake, body weight, body temperature, stress, sleep-awake behavior, etc.) [143–148]. Neurons, astrocytes, microglia and endothelial cells are the essential sources of IL-6, but astrocytes are the primary source of the IL-6 under physiological conditions and during alcohol exposure in the CNS [149–152]. Production of IL-6 in brain cells is regulated by other cytokines and inflammatory factors (e.g., IL-1β and TNF-α) as well as by neurotransmitters and neuropeptides (e.g., norepinephrine, serotonin, substance P) [142, 153–156]. IL-6 signaling is initiated by binding of IL-6 to the IL-6 receptor (IL-6R) and recruitment of additional accessory proteins including gp130, which leads to the activation of major signaling pathways including JAK2/ STAT3, p44/42 MAPK, and PI3-K [157]. IL-6 modulates gene expression of many inflammatory mediators and proteins involved in apoptosis and other processes [142]. At the cellular level, IL-6 has an inhibitory effect on sodium (Na^+) and Ca^{2+} voltage-gated ion channels that may serve as a neuroprotective mechanism in the CNS [11, 158]. Moreover, IL-6 modulates glutamate receptor (mGluR2/3) expression and glutamate-mediated excitotoxicity [159–161]. IL-6 also reversibly decreases GABA-A mediated currents, likely via modulation of GABA-A receptor compartmentalization and PI3-K-Akt pathway [162]. The direct effects of IL-6 on cellular physiology and synaptic transmission indicate that a dysregulation of the IL-6 signaling may lead to a significant disturbance in network activity in a brain region-specific manner.

IL-6 and Alcohol.

A polymorphism in the *Il6*, the gene encoding IL-6, is associated with alcoholism in humans [41, 42], and genomic studies show modifications in *Il6* gene expression in alcohol-preferring rodents [43]. Transgenic mice with a null mutant *Il6* have lower ethanol intake and ethanol preference compared to WT mice [49]. On the other hand, transgenic mice with elevated astrocyte production of IL-6 in the CNS (IL-6tg mice) show increased susceptibility to acute alcohol withdrawal hyperexcitability [163].

While ethanol has mixed effects on the IL-6 levels in neuronal and glial cell cultures [107, 108, 164–166], both acute and chronic ethanol exposures primarily increase IL-6 levels in a brain-region and ethanol-exposure (time and dose) specific manner (see Table 1.). In addition to the direct effects of ethanol on IL-6 levels in the brain, ethanol's effects on IL-6 levels might also be under conditioned control. Repeated pairings between distinctive odor

cues (conditional stimulus) and ethanol can result in elevation of IL-6 levels in the hippocampus and amygdala upon presentation of the odor cues alone [167]. At the synaptic level, IL-6tg mice exhibit an altered response in hippocampal LTP to acute ethanol. While acute ethanol depresses fEPSPs (field excitatory postsynaptic potentials), PTP (post-tetanic potentiation) and LTP, and does not affect sPS (secondary population spikes) in WT (non-tg) mice, acute ethanol increases fEPSPs and sPS and does not affect the PTP and LTP in Il-6tg mice [163, 168]. These studies on IL-6tg mice suggest possible mechanisms mediating IL-6 and ethanol interactions, particularly following the ethanol-induced increase in IL-6 levels in the brain.

Interleukin 10

Interleukin-10 (IL-10) is an anti-inflammatory cytokine that negatively regulates inflammation. IL-10 is expressed in the brain; specifically, it is produced by microglia, astrocytes, and neurons [169]. IL-10 binds to its cognate cell surface receptor, a heterotetrameric complex consisting of two ligand binding IL-10 receptor 1 (IL-10R1) chains and two accessory IL-10 receptor 2 (IL-10R2) chains [169, 170] also expressed in glia and neurons. This interaction leads to the activation of downstream signaling cascades including the JAK/STAT3 and PI3-K/AKT pathways [169–172] and ultimately results in diverse biological effects in the brain such as: limiting the synthesis of pro-inflammatory mediators and reducing cytokine receptor expression and activation [173], neuroprotection [171, 174], and modulation of synaptic structure and activity [175, 176]. At the cellular level, IL-10 regulates GABAergic transmission in the hippocampal (dentate gyrus) neurons via both pre- and postsynaptic mechanisms; IL-10 decreases mIPSCs and tonic GABA currents, and its postsynaptic mechanisms of actions are mediated by PI3K pathways [176].

IL-10 and Alcohol.

IL-10 is implicated in alcoholism in humans. Human genetic studies show that a −592C>A polymorphism in the IL-10 gene is associated with alcoholism [41]. Further, IL-10R2 levels are decreased in the CeA and cortex of alcoholics [177]. Notably, IL-10 regulates SOCS (suppressor of cytokine signaling), and SOCS mRNA levels are also decreased in the CeA and cortex of alcoholics [177].

IL-10 expression and signaling are altered in several CNS pathologies [169]. Expression studies show that a single intoxicating dose of ethanol increases IL-10 content in rat hippocampus and primary cultured cortical neurons [176], 24-hour ethanol exposure increases IL-10 production by human monocytes [172], 4-day binge ethanol exposure results in protracted increases in IL-10 levels in the rat hippocampus [178], and 12-day withdrawal after chronic ethanol exposure increases IL-10 content in the rat hippocampus, prefrontal cortex, and brainstem [179]. In contrast, 4-day binge drinking in the dark paradigm decreases IL-10 levels in the mouse BLA, but not in the CeA, and IL-10 infusion into the BLA, but not the CeA, decreases binge-like drinking [52]. A 10-day binge ethanol exposure decreases mouse brain IL-10 levels [110]. The differential effects on IL-10 expression are likely due to differences between species, animal models, and examination of region-specific versus whole brain changes. Despite the growing body of evidence on an important role of

IL-10 in regulation of the alcohol-related behavior, particularly binge drinking, the mechanistic and functional aspects of IL-10 and ethanol interactions are very limited.

Tumor Necrosis Factor-alpha

Tumor necrosis factor-alpha (TNF-α) is a member of the TNF superfamily and is central to the innate immune response and maintenance of homeostasis at the cellular, tissue and organism levels. In the CNS, TNF-α displays pro-inflammatory effects and is considered a major mediator of the secondary CNS damage following acute injury and during chronic inflammation. However, TNF-α also exerts essential beneficial functions in the CNS. Its potent pro-inflammatory effects require very tight temporal and spatial control, as dysregulation of TNF-α production and activity can trigger cell death and tissue degeneration [8]. TNF-α is produced in two bioactive forms transmembrane (tmTNF) and soluble (solTNF), that differ in their biological activity and intracellular signaling [180]. In general, solTNF has systemic inflammatory effects and is necessary for optimization of the immune response, whereas tmTNF mediates a subset of beneficial TNF-α activities and only basic immune responses [8]. The TNF-α system has two receptors – TNFR1 and TNFR2. While both TNF-α forms bind to TNFR1, tmTNF is the sole ligand for TNFR2 [181]. TNFR1 is ubiquitously and constitutively expressed, and its activation induces pro-inflammatory signaling through the NF-kB and AP1 transcription factors [182]. TNFR2 expression is restricted to immune cells, endothelial cells, and CNS cells – including neurons, astrocytes, and oligodendrocytes. Activation of TNFR2 leads mainly to induction of pro-survival signals mediated by AKT and NF-kB signaling pathways [183, 184]. Under physiological conditions, TNF-α plays an important role in the regulation of homeostatic processes such as synaptic scaling and plasticity [185–187] and regulation of inhibitory and excitatory neurotransmission [11]. Under pathological conditions in the CNS, TNF-α has both protective and pro-inflammatory effects [8]. For example, a mechanism by which TNF-α mediates neurotoxicity is by inhibiting glutamate uptake causing glutamate excitotoxicity [188].

Similar to IL-1β and IL-6, TNF-α has neuromodulatory effects in the CNS. TNF-α enhances Na^+ channels and has mixed effects on voltage-gated Ca^{2+} channels (solTNF-α decreasing and mTNF-α increasing Ca^{2+} currents) [11]. Presynaptically, TNF-α increases action potential dependent spontaneous excitatory postsynaptic currents (sEPSCs) in corticostriatal projections, through AMPA receptors [189]. Also, TNF-α can modify extracellular glutamate levels indirectly by inducing glutamate release from microglia [190] and astrocytes [191] and by inhibiting glutamate uptake by astrocytes [188]. TNF-α-TNF-R1 signaling preferentially affects AMPARs in a brain region-specific manner. TNF-α facilitates AMPAR-mediated glutamatergic transmission and enhances neuronal excitability in the hippocampus, cortex, amygdala and spinal cord [192–194]. Notably, activation of the CB_1 cannabinoid receptor reverses TNF-α effects on AMPAR [195]. In the striatum, however, TNF-α induces the internalization of GluR1-GluR2 AMPAR subunits leading to a decrease in the excitatory drive on inhibitory GABA neurons. Also, TNF-α promotes the endocytosis of GABA-A receptors (subunits b2/3) [192]. Thus, TNF-α effects on glutamate and GABA receptors lead to enhanced neuronal excitability and in some instances to excitotoxicity [185, 192, 196, 197]. In the CeA, TNF-α increases the amplitude of mEPSCs

via the PI3-K signaling pathway but does not affect mEPSC frequencies, suggesting a predominantly postsynaptic mechanism of action. Further, TNF-α increases the firing of CeA neurons through its action on glutamate receptors [129, 198]. Finally, TNF-α increases the frequency of mIPSC, indicating an increase in presynaptic GABA release, and this effect is blocked by a CRF_1 antagonist and minocycline, which is an inhibitor of glial activation [198]. These findings indicate that TNF-α interacts and modulates key neurotransmitters (GABA and glutamate) and neuropeptide (CRF) systems involved in alcohol-related behaviors [199].

TNF-α and Alcohol.

Elevated plasma levels of TNF-α in alcoholics is associated with increased craving and relapse to drinking [200]. In contrast to IL-1β and IL-6 cytokines, genomic studies in rodents did not find alterations in TNF-α gene expression in alcohol-preferring mice [43]. In general, TNF-α levels are predominantly decreased following acute ethanol treatment and increased after chronic ethanol exposure. Intracerebroventricular (i.c.v.) and intra-CeA administration of TNF-α before a single chronic ethanol exposure and ethanol withdrawal sensitizes ethanol withdrawal-induced anxiety-like behavior [104, 129], and this effect is mediated by CRF_1, as a CRF_1 antagonist reduces the TNF-α induced elevation of withdrawal-induced anxiety [129]. The interactions of TNF-α and the CRF system particularly in the CeA, where CRF_1 is known to mediate ethanol effects on GABAergic transmission, may represent one of the mechanisms involved in TNF-α -induced modulation of the synaptic transmission. However, the mechanisms and functional consequences of TNF-α and its interaction with ethanol on neuromodulation are not known.

Chemokine ligand 2

The chemokine ligand 2 (CCL2), also known as monocyte chemotactic protein 1 (MCP-1), is a member of the monocyte chemo-attractant protein (MCP) family. CCL2 is a vital chemokine that controls the migration and infiltration of monocytes/macrophages [201]. In the brain, CCL2 is produced mainly by astrocytes and microglia and to a lesser extent by endothelial cells [202]. The neuronal expression of CCL2 is present in several brain regions including the cortex, hippocampus, hypothalamus, substantia nigra, and cerebellum [203]. Importantly, the expression of CCL2 colocalizes with classical neurotransmitters, particularly acetylcholine and dopamine [203], and cell depolarization can induce Ca^{2+}-dependent CCL2 release [204, 205]. Compared to CCL2, its receptor CCR2 is expressed by resident immune cells, such as microglia [206, 207]. Moreover, CCR2 production is also found in cultured rat microglia [208], human fetal astrocytes [209], and in neurons of the adult rat brain [210], mainly from the cortex, hippocampus, hypothalamus, amygdala, substantia nigra, ventral tegmental area (VTA) and cerebellum [211]. There are two splice variants of CCR2 - CCR2A and CCR2B. The splice variants are expressed in different immune cells, and they activate different signaling pathways and exert distinct actions. CCR2, as a Gαi class G-protein coupled receptor [212], signals through inhibition of adenylate cyclase, and PI3-K, MAPK and protein kinase C pathways [213–215]. CCL2 enhances neuronal excitability and excitatory synaptic transmission in CA1 hippocampal neurons via presynaptic mechanisms [216]. Importantly, CCR2 has both pro-inflammatory

and anti-inflammatory actions [201], and CCL2-CCR2 are involved in some physiological processes and the pathogenesis of neurodegenerative disorders and AUD.

CCL2 and Alcohol

CCL2 levels are elevated in several brain regions (e.g. hippocampus and cortex) in postmortem tissue of human alcoholics [217, 218] and the cerebrospinal fluid (CF) of alcohol-dependent human subjects [219]. Similarly, ethanol exposure and withdrawal increases levels of CCL2 in several brain regions [36, 110, 129, 220–226]. Indeed, alterations in the CCL2 system affect ethanol intake and motivation as mice deficient in Ccl2 or Cclr2, the genes encoding CCL2 and its receptor CCLR2, drink less ethanol and show reduced ethanol-induced aversion [50]. There is no significant difference in ethanol intake between ethanol non-dependent CCL2-tg (mice overexpressing CCL2 in astrocytes) and their control WT (non-tg) mice, whereas ethanol-dependent CCL2-tg mice drink less than the dependent non-tg mice [227]. Notably, chronic infusions of CCL2 results in long-lasting heightened ethanol intake in rats suggesting that persistent exposure to CCL2 may be required for CCL2/alcohol interactions [228]. Interestingly, CCL2-tg mice did not show acute alcohol-induced impairments in contextual learning that are observed in non-tg mice[168]. However, ethanol induced a spatial learning impairment in non-dependent CCL2-tg mice but not in non-dependent non-tg mice. Overexpression of CCL2 has a protective effect against alcohol-induced impairments in associative learning [227]. Like IL-1β and TNF-a, intracerebral injection of CCL2 before ethanol exposure and withdrawal elevates ethanol withdrawal-induced anxiety-like behavior [104]. At the cellular level, CCL2-tg mice are resistant to the depressing effects of acute alcohol (20–60 mM) on hippocampal LTP in non-tg mice. CCL2 can enhance neuronal excitability and excitatory synaptic transmission in CA1 hippocampal neurons via presynaptic mechanisms [168]. These studies on transgenic animals targeting CCL2 have significantly advanced our understanding of the potential role of CCL2 in the neuropathology of AUD.

Mechanistically, CCL2/CCR2 system involvement in the neurobiology of AUD includes interactions with other neurotransmitter and neuropeptide systems, particularly CRF and the orexigenic peptide MCH (melanin-concentrating hormone). CCL2 is expressed in cholinergic and dopaminergic neurons [203], and it modulates neuronal activity and synaptic transmission [229, 230]. CCL2 levels in the CeA and VTA are increased in alcohol-preferring P rats compared to non-preferring NP rats, and CCL2 in these brain regions, but not in ventral pallidum, mediates binge drinking in P rats. Importantly, CRF mediates feedback regulation of TLR4 (toll-like receptor 4) and CCL2 signaling in the CeA and VTA during ethanol consumption [44] suggesting that CRF, TLR4 and CCL2 in these regions regulate the initiation of excessive drinking [44]. Moreover, prenatal exposure to ethanol increases later adolescent ethanol drinking which is associated with increased CCR2 levels and increased density of neurons co-expressing CCR2 and MCH in the lateral hypothalamus [224]. As both CCR2 and MCH are believed to promote ethanol intake, these findings suggest that these systems may work together to promote ethanol drinking. Although our understanding of mechanisms mediating CCL2's contribution to the AUD has advanced, there is still a lot of unknowns regarding CCL2 regulation of the synaptic transmission in other alcohol-related brain regions.

Conclusion

The role of the neuroimmune system and cytokines in the neurobiology of AUDs is supported by several lines of evidence. Ethanol-induced cytokine responses in the CNS are dynamic and depend on multiple factors including the duration and amount of ethanol exposure, sex, brain region, cellular specificity, and history of previous immune challenges (e.g. infection, trauma, stress, etc). Cytokines contribute to the neuroadaptive changes in the CNS induced by ethanol exposure through their direct and indirect effects on all CNS cell types, which lead to the modulation of neuronal activity, glia cells, neurogenesis, and potentially neurodegeneration.

Although our understanding of the role of key cytokines in the ethanol-induced immune response has advanced, there are still many unanswered questions especially regarding the therapeutic implications of targeting cytokines and their downstream signaling pathways. The critical role of the neuroimmune system in the neuropathology of AUD suggests its potential to be targeted for the development of new treatments for AUDs. Currently, the focus of preclinical research is on inhibiting the alcohol-induced neuroimmune response and associated alcohol-related behaviors, particularly alcohol drinking. The strategies involve targeting individual components of the neuroimmune system (e.g. TLR4 [231], IL-1R1 [51], or IL-10 [52]) or to use drugs that simultaneously target several inflammatory pathways as well as other brain signaling systems (e.g. peroxisome proliferator-activated receptor agonists (fenofibrate, pioglitazone, tesaglitazar, bezafibrate) [232–234], phosphodiesterase inhibitors (e.g. ibudilast, rolipram) [235, 236], and naloxone/naltrexone [237, 238]. Regarding cytokines, preclinical studies suggest that activation or increased expression of anti-inflammatory cytokines such as IL-1Ra and IL-10 might have therapeutic value. There are, however, several challenges in targeting the neuroimmune system for the development of therapeutic strategies for alcoholism: 1) different inflammatory pathways seem to be critical for different stages of alcohol addiction and alcohol-related behaviors [239], 2) the peripheral immune system is compromised in human alcoholics [240], and 3) the neuroimmune response has both neurotoxic as well as neuroprotective roles and thus, strategies based solely on blocking the neuroimmune system may be counterproductive [241]. Understanding the role and mechanisms of action of individual components of the neuroimmune systems in the development and maintenance of alcohol addiction and relapse will be crucial for identification of new, more target specific and efficacious therapies for AUD.

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Table 1.

Ethanol-induced changes in the brain cytokine gene expression and protein levels in the animal models and humans.

Animal models (rodents)				
Cytokine	**Ethanol Treatment**	**Brain region**	**Δ mRNA levels**	**Δ Protein levels**
IL-1β	Acute	Whole brain	= [106, 110, 242] ↓ [242]	↑ [106] = [110] ↓ [242]
		Cortex	↑ [243] = [35, 243–245]	= [244, 246]
		Hypothalamus (PVN)	↑ [242] = [167, 242, 247] ↓ [247]	= [246]
		Hippocampus	↑ [242] = [167, 242, 247] ↓ [247]	= [246]
		Cerebellum	= [242]	
		Amygdala	= [167, 247]	
	Prolonged/Binge	Whole brain	= [248] [110]	= [110, 248]
		Cortex	↑ [35] = [225]	↑ [249–251]
		Hippocampus	↑ [225]	↑ [251]
		Cerebellum	↑ [39, 225]	
		Striatum/NAc		↑ [249]
	Chronic	Cortex	↑ [244, 252] = [244] ↓ [223]	↑ [252–254] = [244, 252]
		Hypothalamus (PVN)	↓ [242]	
		Hippocampus	= [242]	↑ [254, 255]
		Cerebellum	↑ [53]	↑ [53]
		Amygdala	↓ [242]	
		Striatum/NAc		↑ [226]
IL-6	Acute	Cortex	= [245]	= [245]
		Hypothalamus (PVN)	↑ [242, 247] = [167, 242]	
		Hippocampus	↑ [242, 247] = [167, 242, 247]	
		Cerebellum	↑ [242] = [242] ↓ [242]	
		Amygdala	↑ [247] = [167]	
	Prolonged/Binge	Whole brain	↑ [248]	↑ [248]
		Cortex	= [221, 222]	↑ [178] = [178]

		Hypothalamus (PVN)		↑ [255]
		Hippocampus	= [221, 222]	= [178]
		Cerebellum	= [222]	
	Chronic	Cortex		↑ [253]
		Hypothalamus (PVN)	= [242]	↑ [256]
		Hippocampus	= [242]	↑ [253]
		Amygdala	↑ [242]	
IL-10	Acute	Whole brain	= [110]	
		Hippocampus		↑ [176]
	Prolonged/Binge	Whole brain	= [110]	↓ [110]
		Cortex		= [38, 178]
		Hippocampus		↑ [178] = [38, 178]
		Cerebellum	= [39]	
	Chronic	Cortex		↓ [253]
		Hippocampus		↓ [253]
IL-1Ra	Chronic	Cerebellum		↑ [53]
TNF-α	Acute	Whole brain	↑ [106, 110]	↑ [106] = [110]
		Cortex	↑ [243, 245] = [243–245]	↑ [244, 257] = [246]
		Hypothalamus (PVN)	↑ [242] = [167, 242] ↓ [242, 247]	
		Hippocampus	↑ [242] = [167, 242] ↓ [242, 247]	= [246]
		Cerebellum	= [242] ↓ [242]	
		Amygdala	= [167, 247] ↓ [247]	
	Prolonged/Binge	Whole brain	↑ [110, 248] = [110]	↑ [110, 248] = [110]
		Cortex	↑ = [221, 222, 225]	↑ [35, 250, 251] = [38, 178]
		Hypothalamus (PVN)		↑ [255] = [258]
		Hippocampus	↑ [225] = [221, 222]	↑ [38, 250, 251] = [38, 178, 259]
		Cerebellum	↑ [39, 225] = [39, 222]	
		Striatum/NAc		↑ [35]
	Chronic	Cortex	↑ [223, 244, 252] = [244]	↑ [252–254] = [244]

		Hypothalamus (PVN)	= [242]	↑ [256]
		Hippocampus	↓ [242]	↑ [253, 254]
		Cerebellum	↑ [53]	↑ [53]↓
		Amygdala	= [242]	
		Striatum/NAc		↑ [226] = [226]
MCP-1/CCL2	Acute	Whole brain	↑ [110]	↑ [260] = [110, 260]
		Cortex	↑ [245] =[35] [222, 244, 245]	↑ [249] = [244]
		Hippocampus	↑ [222]	
		Cerebellum	↑[222]	
	Prolonged/Binge	Whole brain	↑ [110, 248]	↑ [110, 248] = [110]
		Cortex	↑ [35, 221, 225] = [221]	↑ [221]
		Hippocampus	↑ [221, 225] = [221] ↓	↑ [221]
		Cerebellum	↑ [225]	
		Striatum/NAc		↑ [249]
	Chronic	Cortex	↑ [223, 244] = [244] ↓	↑ = [244] ↓
		Cerebellum	↑ [53]	↑ [53]
		Striatum/NAc		↑ [226]
Humans				
Cytokine	**Ethanol Anamnesis**	**Brain region**	**Δ mRNA levels**	**Δ Protein levels**
IL-1β	Alcoholics –acutely exposed to EtOH	CF		= [219]
	Alcoholics (postmortem)	Hippocampus		↑ [74]
IL-6	Alcoholics + hepatic encephalopathy	Superior frontal gyrus		=[261]
		Precentral gyrus		= [261]
IL-10	Alcoholics + hepatic encephalopathy	Superior frontal gyrus		=[261]
		Precentral gyrus		= [261]
TNF-α	Alcoholics –acutely exposed to EtOH	CF		= [219] ↓ [219]
MCP-1/CCL2	Alcoholics (postmortem)	VTA		↑ [218]
		Substantia nigra		↑ [218]
		Hippocampus		↑ [218]
		Amygdala		↑ [218]
	Alcoholics –acutely exposed to EtOH	CF		↑ [219]

Table 1. We define “Acute treatment” as a single administration or continuous application for less than 24 hrs. The “Prolonged/Binge treatment” includes several binge models and repeated ethanol exposure for less than 2 weeks, and “Chronic treatment” corresponds to ethanol treatments exceeding 2 weeks. The primary reasons for the discrepancies in the direction of the ethanol effects on a particular cytokine among and within the studies include age (e.g. adolescent vs adult), sex, ethanol treatment/administration (e.g. intraperitoneal vs intragastric application, or continuous vs intermittent treatment), and posttreatment time of the tissue collection (e.g. 1 day vs 28 days). The references in red correspond to the mouse studies and references in black to the studies in rats. The term “Cortex” encompasses findings from the studies on the neocortex, frontal cortex, mPFC, entorhinal and temporal cortex. We mark the direction of the ethanol effects on the cytokines (Δ mRNA/protein levels) as ↑ - increase, = - no change, and ↓ - decrease in the mRNA or protein levels. Abbreviations: CF – cerebrospinal fluid, VTA – ventral tegmental area, PVN – Paraventricular nucleus of the hypothalamus, NAc – Nucleus accumbens.