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Review

Tumour Necrosis Factor in Neuroplasticity, Neurogenesis and Alcohol Use Disorder

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Abstract. Alcohol use disorder is a pervasive and detrimental condition that involves changes in neuroplasticity and neurogenesis. Alcohol activates the neuroimmune system and alters the inflammatory status of the brain. Tumour necrosis factor (TNF) is a well characterised neuroimmune signal but its involvement in alcohol use disorder is unknown. In this review, we discuss the variable findings of TNF's effect on neuroplasticity and neurogenesis. Acute ethanol exposure reduces TNF release while chronic alcohol intake generally increases TNF levels. Evidence suggests TNF potentiates excitatory transmission, promotes anxiety during alcohol withdrawal and is involved in drug use in rodents. An association between craving for alcohol and TNF is apparent during withdrawal in humans. While anti-inflammatory therapies show efficacy in reversing neurogenic deficit after alcohol exposure, there is no evidence for TNF's essential involvement in alcohol's effect on neurogenesis. Overall, defining TNF's role in alcohol use disorder is complicated by poor understanding of its variable effects on synaptic transmission and neurogenesis. While TNF may be of relevance during withdrawal, the neuroimmune system likely acts through a larger group of inflammatory cytokines to alter neuroplasticity and neurogenesis. Understanding the individual relevance of TNF in alcohol use disorder awaits a more comprehensive understanding of TNF's effects within the brain.

Keywords: TNF, tumour necrosis factor, tumour necrosis factor-α, AUD, alcohol use disorder, alcohol associated liver disease, neuroplasticity, neurogenesis, withdrawal, excitotoxicity, neuroinflammation, microglia, astrocytes, cytokines

INTRODUCTION

The ability to learn, remember and adapt after unique experiences is allowed by neuroplasticity. On a cellular level, neuroplasticity is the flexibility of neurons to adjust their synaptic strength and relationships through genetic, neurochemical and structural mechanisms. The best characterised type of neuroplasticity is described by Hebbian theory, which dictates colloquially that "neurons that fire together wire together" [1]. This theory postulates that recurrent postsynaptic activation associated with presynaptic activation increases the strength of a synapse above a certain basal level [2]. Other forces of synaptic plasticity include homeostatic plasticity, whereby the strength of a synapse is shifted back towards its basal homeostatic level [3]. Through the forces of plasticity, the shape of the brain is dynamically changing to integrate, disintegrate and modulate different synapses within circuits. It has been suggested that the modulation of neuroplasticity by various drugs of abuse is an integral component of the progression of addiction [4, 5].

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Alcohol use disorder (AUD) is characterised by behaviours of problematic alcohol use and is a significant burden to individual and public health. It is estimated that AUD affects approximately 12% of the population in the US [6]. Alcohol use is recognised as a leading risk factor for disease burden and has been linked to 60 acute and chronic diseases [7, 8]. Alcohol's promiscuous action on neural function is thought to drive neural plasticity that manifests as the many symptoms of AUD including addiction, dependence and tolerance [4, 5]. Alcohol's activation of the neuroimmune system is a highly relevant component of AUD [9–13]. Indeed, altered neuroimmune function is associated with numerous psychiatric disorders including major depressive disorder, bipolar disorder, schizophrenia and drug addiction [13–16]. Experimentally, it has been shown that activation of the immune system results in increased ethanol self-administration in mice and there is support for the idea that alcohol induced neuroinflammation drives further alcohol consumption in a relentless cycle [17, 18].

Tumour necrosis factor (TNF) is a neuroimmune and inflammatory molecule that was first discovered as a factor in the haemorrhagic necrosis of tumours and has associations with numerous pathological states [19]. Despite its association with pathology, it is now known that TNF has numerous beneficial physiological effects in the CNS which can be altered during inflammation or challenge [20, 21]. The neuroimmune system is involved in neuroplasticity and in AUD and these relationships have been the subject of numerous reviews [22–27]. Given that TNF is an early initiator of inflammation in the CNS, and one of a few cytokines that are involved directly in both synaptic plasticity and neuroimmune signalling, its effect on neurotransmission in AUD deserves discussion. Here, we will provide an overview of TNF's effect on neuroplasticity in normal physiology, followed by its effect on neuroadaptation and neurogenic deficit during AUD.

ETHANOL'S ACTION

Alcohol has many molecular targets that are involved in its rewarding effects. Notably, alcohol's interactions with numerous synaptic ion channels, signalling molecules, neuropeptide mechanisms and enzymes elicit short and long term effects [4, 5, 28]. Upon repeated exposure, alcohol's interactions with these synaptic targets are thought to lead to long term changes in synaptic function [5]. While there is still much unknown about how alcohol interacts with its direct synaptic targets to induce neuroplastic changes, this topic has been the focus of previous reviews [4, 28, 29]. Aside from alcohol's direct targets, alcohol also affects numerous components of the neuroimmune system. The neuroimmune system includes neurons, microglia, astrocytes, oligodendrocytes, peripheral immune cells and vascular and endothelial cells [16, 30]. Signalling between these cells promotes neuroinflammation in response to injury and stress.

Alcohol consumption can increase intestinal permeability to lipopolysaccharide (LPS or endotoxin), which circulates through the blood and stimulates toll like receptor 4 (TLR4) on peripheral immune cells such as resident macrophages [31–33]. TLR4 activation results in the initiation of cellular cascades that activate nuclear transcription factor nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) causing the release of inflammatory cytokines, such as TNF, interleukin 1-β and interleukin 6 (IL-6) [34]. Upon alcohol related cell death within the brain, an array of damage associated molecular patterns (DAMPs) are released and stimulate pattern recognition receptors to further the inflammatory response. Of particular significance is the DAMP high motility group box 1 (HMGB-1). HMGB-1 is released actively from neurons and other glial cells upon alcohol exposure but is also passively released after cell death [32, 35]. HMGB-1 has differential effects depending on the status of certain cysteine residues; oxidation of HMGB-1 appears to attenuate its inflammatory effects, while disulphide and all thiol containing HMGB-1 signal for inflammation through TLR4 and receptor for advanced glycation end products (RAGE) respectively [36].

TNF exists in two forms as transmembrane (tmTNF) and soluble (solTNF) TNF. Upon activation, TNF-α converting enzyme (TACE) cleaves tmTNF into solTNF to be released and have reaching inflammatory effects [21]. The transmembrane form signals through both tumour necrosis factor receptors 1 and 2 (TNFR1 and TNFR2) while solTNF signals solely through TNFR1. Although both receptors are involved in inflammatory responses, TNFR1 activation pathways can lead to cell death while TNFR2 is associated with pro survival responses [21]. Numerous regulatory mechanisms exist to regulate TNF production and curb inflammatory signalling including cyclic AMP, prostaglandins, soluble

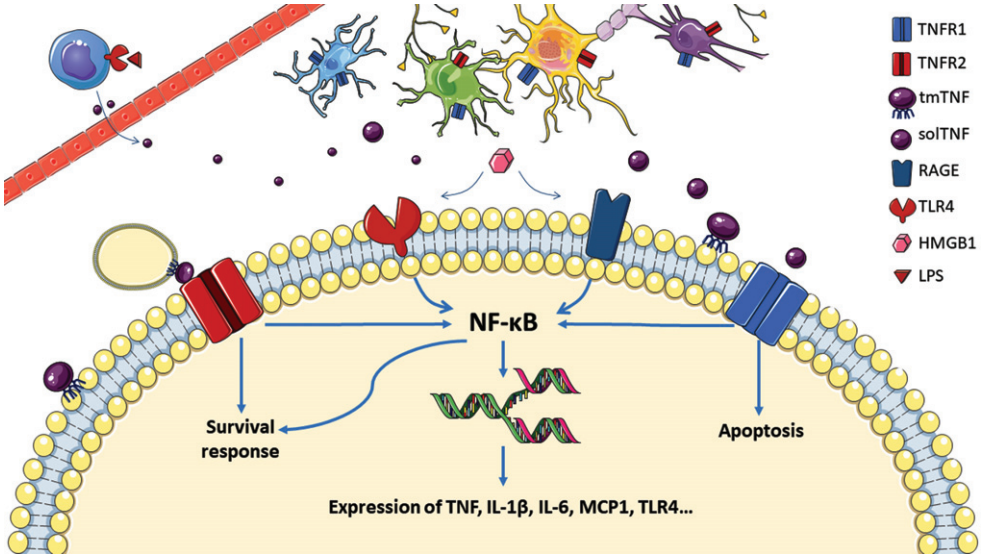

Fig. 1. Overview of TNF signalling after alcohol consumption within a neuron. Peripheral immune cells release TNF following binding of lipopolysaccharide (LPS) through toll like receptor 4 (TLR4), which crosses the blood brain barrier (top left) to stimulate TNFR1 signalling and NF-κB translocation to the nucleus for transcription of TNF and other cytokines. High motility group box 1 (HMGB-1) also activates NF-κB through receptor for advanced glycation end products (RAGE) and toll like receptor 4 (TLR4). Microglia (blue), astrocytes (green), neurons (yellow) and oligodendrocytes (purple) are represented here with their respective TNF receptors.

circulating TNF receptors and anti-inflammatory cytokines [37–40]. Previous reviews provide detailed descriptions of TNFR signalling and regulation [41–43]. During inflammation, released solTNF activates TNFR1 signalling, furthering NF-κB transcription and stimulating activator protein 1 (AP-1) to amplify the inflammatory response in a positive feedback loop [44, 45]. Results in TLR4 knockout mice show that TLR4 signalling is necessary for ethanol induced increases in brain levels of TNF [46]. Despite the importance of TLR4 in ethanol's effect on TNF, in the context of this paper it is important to note that inactivation of TLR4 does not result in reduced levels of ethanol self-administration in multiple rodent models [47, 48]. Inflammatory cytokines induced by ethanol travel throughout the periphery to promote inflammatory responses and some molecules, including TNF, travel across the blood brain barrier (BBB) to participate in neuroinflammation [11, 49]. In addition to chemokines crossing the BBB, circulating monocytes and macrophages are able to infiltrate the BBB during inflammation (Fig. 1).

The neuroimmune system differs between the sexes, and is even involved in the masculinisation of the brain during development [50, 51]. It has been shown in animal models that female and male mice display different drinking patterns [52]. While the general trend of an inflammatory response to ethanol is shared between males and females, there are variations in neuroimmune responses and female mice appear more vulnerable to inflammatory effects following binge drinking [53]. Similar sex associated disparities are seen in many aspects of AUD. Generally, men are more likely to develop AUD and consume larger amounts of alcohol while women are more prone to experience AUD related medical problems [54, 55]. An investigation in rats showed that sex had no effect on TNF mRNA levels following exposure to ethanol vapor; however, this review's bias towards discussing neuroimmune signalling modelled in the male sex remains a shortcoming, which should be kept in mind throughout reading.

TNF IN PHYSIOLOGICAL SYNAPTIC PLASTICITY

TNF is a well known modulator of synaptic plasticity [56–59]. The most popular area of discussion is its ability to potentiate excitatory transmission, which is achieved through numerous mechanisms that will be reviewed throughout this chapter. Firstly, TNF's ability to increase α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) expression has been a dominant subject of research. Seminal

research demonstrated that TNF increases AMPAR surface expression and synaptic strength, with TNF treated slices showing increased frequency of miniature post-synaptic excitatory currents (mEPSCs) [60, 61]. TNF's activity dependent scaling of synaptic strength in these studies indicates its role as a mediator of homeostatic plasticity [62]. Genetic deletion of TNFR1 suppressed synaptic transmission via AMPAR dependent mechanisms in cortical neurons [63]. Importantly, induction of GLuR2-lacking AMPAR trafficking by TNF allows for enhanced calcium influx which has been shown to contribute to excitotoxicity [64, 65]. In contrast to this mechanism in hippocampal neurons, it has been shown in cortical and motor neurons that TNF can preference the expression of GluR2 containing AMPAR expression, thereby protecting against excessive calcium influx [66]. The reasons for this disparity may include differences in neuron type, which underscores the diverse role of TNF in plasticity [66]. Interestingly, TNF can boost glutamate levels by increasing neuronal glutaminase production, which is involved in the conversion of glutamine to glutamate [67].

An effect on N-methyl-D-aspartate receptor (NMDAR) modulation has also been observed. TNF's enhancement of hippocampal mEPSC frequency and amplitude was abolished in TNFR1 knockout mice and mice treated with the NMDAR antagonist ifenprodil, with indications for a role of NR2B subunit containing NMDARs in TNFR1 signalling [68]. The involvement of NMDARs in TNF mediated excitatory transmission has been observed elsewhere, with TNF exposure resulting in a quickly observed change in cellular activity that increased the NR1 subunit of NMDAR surface expression and enhanced EPSCs [69, 70].

To further increase neuronal excitability, TNF can decrease inhibitory signalling. TNF was found to cause $GABA_A$ receptor endocytosis in hippocampal pyramidal neurons, furthering excitatory transmission at these synapses [60]. Later, the intracellular pathway of this $GABA_A$ receptor endocytosis was further characterised in rats and found to be TNFR1 dependent [71]. In contrast, TNF had no effect on reducing the frequency of spontaneous post-synaptic inhibitory currents in rat spinal cord slices [72].

In addition to the neuronal mechanisms discussed above, TNF's recruitment of glia to enhance excitatory signalling is extremely important, if not critical. For example, TNF induced increases in synaptic strength that were abolished in a model of TNFR1 inactivation were returned with the selective activation of TNFR1 in astrocytes [68]. In particular, TNF's ability to affect glial glutamate regulation is an important mechanism of TNF excitation [73]. In rat hippocampal entorhinal cortex slices, TNF was shown to dose-dependently decrease uptake of glutamate [74]. Specifically blocking glial glutamate uptake transporters alone resulted in the same NMDAR dependent neurotoxicity as elicited by TNF [74]. TNF has also been shown to downregulate the expression of the excitatory amino acid transporter gene EAAT2, which regulates neuronal glutamate transporters, and has associations with reducing astroglial glutamate transporter 1 [75, 76]. TNF further potentiates excitatory transmission by inducing glial glutamate release. In microglia, TNF activates TNFR1 in an autocrine manner to induce glutamate release through transporters and through gap junction hemi channels [77]. TNF has also been shown to positively regulate astrocytic glutamate release, with microglial-astrocytic communication amplifying release [78]. Furthermore, microglial TNF release potentiates the intrinsic excitability of Purkinje neurons, as seen in a model of LPS induced cerebellar inflammation [79].

In the hippocampus, astrocytic purinergic receptor activation and subsequent calcium influx can induce mEPSCs in adjacent neurons through glutamate release [80]. It was shown in $Tnf^{-/-}$ mice that this effect is abolished due to alterations in the docking and exocytosis of glutamate vesicles, which affects the balance between astrocytic glutamate uptake and release [80]. Investigators noted that low concentrations of TNF appear to be necessary for this mechanism of gliotransmission and that fluctuations in TNF would have subtle, if not greater, effects on synaptic transmission [80]. However, regulatory feedback systems do exist, with glial release of TNF being regulated by detection of extracellular glutamate. Glutamate treated astrocytes transplanted into neuronal cultures released less TNF and elicited less AMPAR expression in neurons, indicating a role in synaptic scaling to protect against excessive excitation [61].

In contrast to TNF's potentiation of excitatory transmission, studies have demonstrated that TNF application can inhibit components of LTP [81–86]. In the rat hippocampus, it was suggested that TNF's inhibition of LTP is a biphasic mechanism initially involving p38 mitogen-activated protein kinase in the early stage of inhibition while relying on another mechanism in repressing long term LTP [87]. Later,

the same group did similar work and implicated the disruption of intracellular calcium levels related to mGluR5 activation as involved in TNF's LTP inhibition [88]. Another group showed that TNF in low concentrations enhances LTP expression in mouse pyramidal neurons, an effect which was absent when intracellular calcium stores were depleted [89]. Importantly, this study showed that concentration is critical in what effect TNF will have on synaptic plasticity, as low levels of TNF enhance LTP expression while high levels of TNF impair the establishment of LTP but do not affect previously existing LTP. This effect was able to be reversed with neuronal pretreatment with ryanodine, implicating calcium levels in the effect of TNF on both the inhibition and establishment of LTP. Alterations in calcium transport have also been observed in a study involving old age rats where administration of soluble TNF inactivator Xpro1595 was shown to reverse age related hippocampal LTD and behavioural deficits [90]. The importance of TNF in LTD has been shown elsewhere, with TNFR knockout mice showing no LTD establishment in CA1 neurons [91]. Interestingly, another model of transgenic rats with overexpressed TNF showed increased LTP in CA1 neurons and spatial cognition deficits in behavioural tasks [92]. These results indicate TNF's negative effect on cognition through modulation of both LTD and LTP.

Notably, there is evidence that directly conflicts with TNF as a booster of synaptic strength. Research by Lewitus and colleagues demonstrates TNF can downregulate synaptic strength in the striatum under certain conditions [93]. In this study, haloperidol treatment resulted in increased AMPA/NMDA ratios in striatal medium spiny neurons (MSNs) in $Tnf^{-/-}$ but not WT mice. In contrast to previous literature, this work illustrates TNF's ability to dampen synaptic strength rather than increase it under altered function [93, 94]. The authors noted that MSNs are inhibitory cells, and reduced excitatory transmission of these cells would result in reduced overall circuit inhibition [93]. Later, the same group showed that TNF has a protective effect on dopaminergic neurons within the nucleus accumbens in an animal model of cocaine use. It was found that microglial TNF release, regulated by microglia sensing extracellular dopamine through D2 receptors, was able to reduce AMPA/NDMA ratios in D1 expressing MSNs and reduce cocaine sensitisation [95].

Other research using a mouse model of experimental autoimmune encephalomyelitis (EAE) found that microglial TNF was associated with potentiated transmission in the striatum, likely through AMPARs [96]. Anxiety was associated with TNF and altered excitatory transmission in a similar model by the same group [97]. It has been suggested that TNF has region specific effects on AMPAR expression [13]. However, as TNF has displayed opposing effects on synaptic transmission in the same brain region, it is also likely its effect varies based on different conditions, with activity blockade and models of EAE involving the striatum discussed here. As previously mentioned, the concentration of TNF is a critical determinant factor in whether TNF will enhance or inhibit synaptic plasticity; variability in TNF concentration has also been used by others to explain disparate results [89, 98].

Adding to its diverse array of qualifications, TNF has an effect on altering neuronal morphology. Activation of TLR3 signalling following injection of the immunostimulant polyinosinic-polycytidylic acid (poly(I:C)) resulted in TNF dependent remodelling of dendritic spines of pyramidal neurons in the motor cortex [99]. $Tnf^{-/-}$ mice did not show altered dendritic spine dynamics or motor learning deficits following poly (I:C) injection. Interestingly, depletion of microglia did not alter the effects of poly (I:C) administration, indicating that peripheral immune cells are the determinant source of TNF that produce the observed dendritic spine alterations. The importance of peripheral TNF has been demonstrated elsewhere, where increases in peripheral TNF preceded microglial activation and increased dendritic spine turnover in the somatosensory cortex of mice in an EAE model [100]. This is not to discount the importance of microglia in TNF signalling; microglia coordinate numerous TNF effects and have been implicated as important in recruiting peripheral immune cells into the brain in response to peripheral TNF release [101]. Through NF-κB signalling, TNF has also been shown to inhibit neurite outgrowth in mouse neurons *in vitro* [102].

Importantly, the effect of TNF on excitatory/inhibitory receptor regulation, glial cells, glutamate regulation and intrinsic plasticity means TNF can contribute to vulnerability to glutamate induced excitotoxic cell death [65, 103, 104]. Illustrating this point, treatment with soluble TNFR1 was able to protect against cell death in a model of spinal cord injury in rats [64]. However, TNF does have variable and conflicting effects on synaptic strength, which must be considered when discussing the role of TNF in synaptic plasticity during AUD.

ALCOHOL EXPOSURE AND TNF EXPRESSION

Interestingly, early research found that *in vitro* cultures of monocytes or rats injected with alcohol showed an abolished or reduced TNF response following immune challenge [105, 106]. This effect was supported using human blood, with ethanol pretreatment reducing TNF levels in response to LPS *in vitro* [107, 108]. A possible mechanism for alcohol's ability to acutely diminish TNF levels includes an interaction with TACE function to reduce TNF release [109, 110]. More recent research suggests that LPS tolerance following ethanol exposure in human monocytes is due to alterations in heat shock factor 1 and heat shock protein 70 [111]. In support of ethanol working at a post translational level to inhibit TNF release, increases in TNF mRNA expression are seen in animal models after ethanol administration while protein levels in both the brain and serum remain unaffected [112, 113]. Further supporting alcohol's role as an immunosuppressive agent, ethanol pretreatment lowers the release of TNF and other cytokines in the brain following traumatic brain injury; similarly, intragastric administration of alcohol in rats for 3 days prior to physical trauma reduces TNF release [114, 115]. Other short term binge models in rats report no significant increases in TNF protein expression in serum, brain or other tissues compared to controls, although other markers of neuroinflammation can be found [116–118]. It should be noted that TNFR and TLR4 pathways are not the only inducers of TNF expression, and alcohol shows minimal effect on TNF release via TLR2 pathways in human monocytes [119].

In contrast to *in vivo* models and some *in vitro* models, a range of studies show that both acute and chronic ethanol exposure enhance the expression and release of TNF (Table 1) [46, 120–123]. While there may be multiple mechanisms for TNF release after ethanol consumption, one suggestion involves neuroimmune potentiation after drug use, resulting from the 'priming' of microglia which boosts TNF levels following alcohol consumption [10, 13, 123, 124]. It is also likely that the systemic inflammation that can arise in AUD contributes to the enhanced release of TNF after alcohol consumption. This is illustrated in a post-mortem investigation of individuals with AUD, which found the DNA binding patterns of NF-$\kappa\beta$ in the prefrontal cortex were modified resulting in inhibition of $\kappa\beta$ regulated transcription and upregulation of genes usually repressed by p50 homodimers, which includes TNF [125, 126]. It is clear that differential effects on TNF levels have been observed between *in vitro* and *in vivo* results, furthered by disparity between species and brain regions. It is also known that different patterns of alcohol administration can alter neuroimmune gene expression [127]. However, a variable trend of acute alcohol exposure being able to diminish TNF expression with prolonged alcohol exposure increasing TNF expression is observed.

ALCOHOL'S EFFECT ON TNF IN HUMAN MODELS

As shown in Table 1, there is a general consensus in rodent models that acute ethanol decreases TNF while chronic ethanol treatment increases TNF; however, depending on brain region and alcohol exposure model, gene and protein expression of TNF can still vary [128]. Similar disparities are seen in human studies, shown in Table 2.

Investigations in humans have shown significantly elevated plasma levels of TNF and IL-6 in alcohol dependent patients compared to healthy controls [129]. Increased plasma TNF was observed at a relatively constant level throughout 14 days of withdrawal and was not associated with self-reported craving or withdrawal symptoms. Keifer and colleagues corroborated this observation, showing a positive association between duration of alcohol abuse but no direct association with self-rated craving during withdrawal [130]. Another study found plasma TNF that was upregulated in alcohol dependent patients, and was able to find a significant and positive association with alcohol craving both at the start and end of a three week alcohol withdrawal period [33]. Importantly, the individuals in this latter study did not have alcohol associated liver disease (AALD), which would be a confounding source of TNF. Increased TNF levels in those with AUD is also supported by Zahr and colleagues [131]. These results highlight an interesting, albeit variable, effect of TNF on withdrawal during AUD.

In contrast, a study of healthy men without AUD showed that the daily consumption of approximately four glasses of whisky for 17 days did not affect plasma TNF levels [132]. In individuals with AUD, levels of TNF within cerebrospinal fluid did not differ significantly to control groups [133]. Another study saw no significant differences in TNF plasma levels

Table 1
Ethanol induced changes in TNF gene expression and protein levels in the brain of rodents

Ethanol Treatment	Study	Brain region	mRNA levels	Protein levels
Mice				
Acute – 5, 10 or 15 hours of continuous infusion of EtOH (total amount 156 mg/25 g) into the right internal jugular vein	[220]	Whole brain	↑	↑
Acute – 5 g/kg EtOH via intragastric gavage, 25% EtOH (w/v) daily for 10 days	[221]	Whole brain	↑	↑
Acute – 6 g/kg EtOH via intragastric gavage for 10 days	[222]	Hippocampus, cerebellum or cortex	No change	
Acute – 5 g/kg EtOH via intragastric gavage daily for 10 days	[223]	Whole brain and serum	↑	↑
Chronic – 5% (v/v) EtOH (36% ethanol-derived calories) or an isocaloric control diet for 5 weeks	[46]	Cerebellum	↑	
Chronic – 10% EtOH (v/v) in drinking water and solid diet ad libitum for 5 months	[224]	Striatum		↑ striatum
Rats				
Acute – 7% EtOH (w/v) for either 15 days ad libitum access or 3 intermittent 5 day binges	[225]	Cortex	↓acute ↑ chronic	
Acute – 2 g/kg EtOH injected intraperitoneally at 3, 9, 15, 18 hours	[226]	Hypothalamus, paraventricular nucleus of the hypothalamus, hippocampus, cerebellum	Hypothalamus = ↓ at 3hrs and 9hrs, ↑ 18hrs Hippocampus = ↓ 3, 9 and 18hrs Cerebellum = ↓ at 3hrs, 9hrs PVN = ↓ 3hrs	
Acute (single 14 hour exposure), subchronic (1 week intermittent exposure), chronic (6 week intermittent exposure) EtOH vapor	[227]	Basolateral amygdala, nucleus accumbens, and ventral tegmental area	↑ acute and subchronic in all 3 areas ↑ chronic in the NAC	
Acute – 3 g/kg 25% EtOH (v/v) via intragastric gavage every 8 hours for 4 days	[118]	Anterior cerebellar vermis, cingulate cortex, frontal cortex, hippocampus, hypothalamus, striatum	No difference observed	
Acute – 25% EtOH (w/v) in drinking water or an isocaloric dextrose diet via intragastric gavage every 8 hours over 4 days	[116]	Hippocampus	No difference observed	
Acute – 25% EtOH (w/v) or an isocaloric dextrose diet via intragastric gavage every 8h for 4 days	[117]	Hippocampus and entorhinal cortex	No difference observed	
Chronic – 10 weeks voluntary consumption and 4 g/kg EtOH intragastric challenge	[226]	Paraventricular nucleus of the hypothalamus, hippocampus, amygdala	Paraventricular nucleus of the hypothalamus (PVN) = No change Hippocampus = ↓ at 3hrs Amygdala = Trend for ↓ at 3 hours	
Chronic – 5.0 g/kg via intragastric gavage, 20% EtOH (w/v) on a 2day on/2day off schedule	[228]	Frontal cortex	↑	

between Spanish populations of self-reported alcohol abstainers and light, moderate and heavy drinkers [134]. Similar results were found in AUD patients without AALD and with compensated liver disease in multiple studies [135, 136]. Interestingly, a contrasting study found that elevations in serum TNF predicted decreased long term survival in patients with AALD [137]. Taken together, alcohol related TNF levels in humans show marked differences between studies, even accounting for AALD.

Table 2
Ethanol induced changes in TNF levels in humans

Participants	Study	Method	TNF
7 female and 6 male healthy controls, and 9 females and 19 male participants with AUD	[229]	Cerebrospinal fluid levels collected on days 4 and 25 of abstinence	No differences on day 4, ↓ in alcoholics after 25 days
26 female and 28 male healthy controls, and 27 female and 54 male participants with AUD	[230]	Whole blood plasma	↑
18 healthy male controls and 30 male participants with AUD	[231]	Serum levels collected during withdrawal at 1, 7 and 14 days	↑ consistently elevated during the whole period of withdrawal
30 healthy controls and 30 male participants with AUD	[232]	Blood plasma collected during withdrawal at 15–25 hours	↑
20 healthy controls and 43 participants with AUD	[233]	Blood sample collected during withdrawal at 12–36 hours	No significant differences
16 healthy controls and 40 participants with AUD	[217]	Blood plasma collected during withdrawal at onset and end of 3 weeks	↑ onset ↓ decreases during withdrawal but remains increased compared to controls
23 healthy male subjects consuming 4 standard drinks daily for 17 days	[234]	Blood plasma	No differences seen after 17 days
14 healthy controls and 32 participants with AUD. Some participants had AALD	[235]	Blood plasma collected at time of admission (withdrawal around 3 weeks) and 30 days later	No differences in alcoholic patients without clinically apparent liver disease, with alcoholic cirrhosis, or in non-alcoholic healthy controls ↑severe alcoholic hepatitis
459 participants ranging from non-drinkers to heavy drinkers. 137 of these participants were hospitalized for AUD	[236]	Blood plasma collected across a number of hospitals around Spain	↑ admitted alcoholics ↑ higher TNF levels in alcoholics with liver disease
21 participants with compensated alcoholic liver cirrhosis (ALC) and 23 with decompensated ALC	[237]	Blood sample collected on admission (withdrawal varied)	No difference ↑ decompensated ALC
11 male and 4 female healthy controls, and 11 male and 4 female participants with AUD	[138]	Blood samples collected, peripheral blood mononuclear cells isolated and cultured	No difference was observed with LPS stimulation between groups

The majority of these studies use subjects who enter clinical settings as patients during withdrawal. Therefore, it is possible that variability in the neuroimmune state of the subject could contribute to incompatible results. Recent studies using positron emission tomography (PET) scans to measure translocator protein (TSPO) binding in withdrawn or abstinent individuals with a history of long term AUD show reduced microglial and astrocytic activation in the striatum and hippocampus compared to controls [138, 139]. Another study showed similar results in total brain TSPO binding, but this difference disappeared when both alcohol dependant patients and healthy controls possessed a TSPO rs6971 polymorphism which confers higher binding affinity for TSPO [140]. The same group later showed that *in vitro* autoradiography with the TSPO ligand [^{3}H]PK11195 had higher levels of binding than *in vivo* PET with [^{11}C]PBR28 in the brains of alcohol exposed rats, indicating that observations in the aforementioned human studies may be a result of imaging methodology rather than a true effect [141]. Furthermore, histological results in the brains of humans with alcohol use disorder show region specific increases in microglia immunoreactivity, indicating increased neuroinflammation [142–144]. However, long term alcohol use disorder resulting in a 'blunting' of the neuroimmune response, perhaps due to lowered glial density or glial adaptations, remains a possibility.

Additionally, the reliability of serum TNF as an indicator of brain TNF must be considered. While TNF is able to be transported across the BBB, previous work has shown significant increases in TNF within the brain following a 10 day regiment of intragastric ethanol exposure that were not observed in serum [113]. Similarly, other cytokine changes in response to ethanol have previously been restricted to the CNS with no changes in serum levels being detected [145, 146]. Admittedly, these studies were

both in mice and it is possible that TNF serum levels may be more representative of brain TNF in the human. However, these results imply the probability that increased TNF within the brain may not be apparent when measuring serum.

TNF'S INVOLVEMENT IN AUD

TNF's ability to modulate synaptic strength as discussed in this review has implications with drug associated neuroinflammation and neuroplasticity. However, it is difficult to contextualise the neuroplastic effects of TNF in AUD. Firstly, there are contrasting results on the effect of alcohol on TNF levels in those with AUD, and concentration appears to be pivotal in the effect of TNF on neuroplasticity. Secondly, TNF is a single molecule among a family of neuroimmune signals and inflammatory molecules. These cytokines often act in concert in parallel, possibly redundant, pathways that converge on NF-κB transcription and it is therefore difficult to attribute effect to a single immune molecule [62, 147]. Despite this, TNF is in a relatively privileged position of being a potent inflammatory molecule and a modulator of synaptic plasticity and this section will discuss TNF's role in AUD rather than the collective role of all inflammatory cytokines.

To begin with an unforgiving perspective, ethanol consumption was not significantly decreased in TNFR1 knockout mice [148]. In contrast, interleukin 1 receptor (IL-1R) knockout mice showed significant decreases in ethanol consumption and double knockouts for IL-1R and TNFR1 showed marked decreases in ethanol consumption. However, these results imply that TNF/TNFR1 signalling is not involved in regulating ethanol consumption and do not exclude a contributory effect of TNF on altered neurotransmission, which may affect other aspects of AUD. Demonstrating TNF's effect on drug related adaptation, TNF has been correlated with alcohol craving in humans, associated with ethanol withdrawal-induced anxiety in mice and is involved in cocaine use in mice [33, 130, 149, 150]. In investigations involving cocaine use, mice subjected to maternal separation show increased levels of TNF gene expression in the nucleus accumbens and the prefrontal cortex in a sex dependent manner, with females experiencing no effect [150]. Importantly, mice who experienced maternal separation showed a place preference for cocaine where their control littermates did not. This preference was abolished after administration of Xpro1595, which blocks solTNF. Although this investigation was not related to AUD, it supports TNF as a regulator of drug induced plasticity and highlights the relationship between stress activated neuroimmune signalling and drug use [13].

A proposed mechanism of brain damage in AUD involves adaptations in GABAergic and glutamatergic signalling leading to higher susceptibility to excitotoxic cell death during withdrawal. Although the effect of alcohol on glutamate signalling is complex, it has been proposed that glutamate excitotoxicity during alcohol use disorder is linked to neurodegeneration [151]. Additionally, while evidence supporting this mechanism *in vivo* is not clearly demonstrated, drugs used to reduce withdrawal symptoms such as benzodiazepines work by interacting with GABA receptors to reduce excitatory transmission [152, 153]. TNF's augmentation of excitatory transmission deserves discussion in this context. Theoretically, TNF's effect on susceptibility to excessive calcium influx, through calcium permeable AMPAR expression, and positive enhancement of glutamate release, should create an optimal environment for excitotoxic cell death [57]. Surprisingly, while there are broad associations, there is a lack of definitive evidence implicating TNF in withdrawal related excitotoxic changes. For example, TNF is known to increase GluR2 subunit containing AMPARs in some models, and the brains of individuals with AUD show increased expression of GluR2 and GluR3 subunit containing AMPARs in the cingulate cortex [66, 154]. However, links such as these are tenuous and do not demonstrate a causative role. Due to the role of TNF in potentiating excitotoxicity, its role in AUD withdrawal warrants investigation. The validity of this topic for further investigation is increased by the observation that TNF administration can manifest increased anxiety related withdrawal symptoms following alcohol withdrawal in mice [149].

In regards to human TNF polymorphisms, a meta-analysis found an association between alcohol dependence and TNF polymorphism in individuals with AALD [155]. However, this relationship was not present in those without AALD and further analysis showed this link was more representative of AALD and AUD rather than TNF polymorphisms. Indeed, associations between TNF and AALD are well documented in some populations [134, 155, 156]. In other populations, no links between TNFR1 or TNFR2 polymorphisms and AALD are found

[157]. Therefore, while there is no evidence to support TNF related predisposition to AUD, there is the possibility that TNF polymorphisms could amplify peripheral inflammation, leading to increased TNF levels to exacerbate neurodegeneration and altered neurotransmission. Somewhat nullifying this proposition, a study of common TNF polymorphisms in a Japanese population of alcoholics showed no association between TNF polymorphisms and brain atrophy [158]. An association was found between lymphotoxin, previously known as TNF-β, related alleles and atrophy which is of interest as lymphotoxin signals through both TNFR1 and TNFR2. Polymorphisms involving TNF and brain derived neurotrophic factor (BDNF) genes have been observed to affect spatial memory retention, which is interesting in its own right [159].

Intriguingly, it is possible TNF may play an almost 'invisible' role in AUD. In hippocampal rat neurons, it was shown that the presence of a cannabinoid receptor 1 (CB1R) agonist reduced TNF induced AMPAR membrane expression [160]. In alcoholic patients, CB1R availability as measured through PET was lower both during withdrawal and after alcohol consumption compared to healthy controls [161]. Downregulation of CB1R is also observed in animals chronically exposed to ethanol [162, 163]. Therefore, a possible mechanism exists involving changes in neuronal excitability associated with CB1R and TNF in AUD. Notably, changes in the regulation of TNF could result in strengthening or dampening of synaptic transmission independent of changes in TNF brain or serum level.

While this review highlights TNF's potentiation of excitatory transmission, there is some evidence that TNF protects against excitotoxicity in cortical and hippocampal neurons [66, 164–166]. Of note, investigators showed that pretreatment of murine cortical neurons with ethanol prevented the neuroprotective effects of TNF against excitotoxic challenge [164]. Additionally, it has been suggested that TNF levels, mediated by drug induced neuroinflammation, and their possibly protective effects against excitatory transmission could drop during withdrawal [13]. However, the sum of human and animal studies taken together imply increases of TNF levels after chronic alcohol consumption. Additionally, some of the studies illustrating neuroprotection involve TNFR2, which is not the primary receptor activated during inflammation induced solTNF release [165].

TNF IN NEUROGENESIS

Neurogenesis describes the generation of new neurons from neural stem cells. Neurogenesis occurs during development and continues throughout adulthood where it is restricted to the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone (SGZ) of the hippocampal dentate gyrus. The neurons born in the SVZ migrate through the rostral migratory stream and become granule and periglomerular neurons within the olfactory bulb whereas neurons born in the SGZ migrate into the granular layer of the dentate gyrus of the hippocampus and become dentate granule cells [167]. The regulation of adult neurogenesis is thought to be involved in memory formation and cognition but is also involved in mood and stress. Recent research has emerged suggesting that inflammation and the immune system itself can influence the way adult neurogenesis occurs in the brain.

While TNF production has been linked to decreased neural stem cell proliferation and shown anti-neurogenic properties, it has demonstrated pro-neurogenic properties in other studies [23, 168–170]. In embryonic neural progenitor cell culture, LPS activated microglia and macrophages inhibited neuronal differentiation or induced neuronal cell death [171, 172]. Treatment with pentoxifylline, an inhibitor of TNF, partially restored neurogenesis [171]. The anti-neurogenic role of TNF has also shown to stimulate differentiation of neuronal progenitor cells into astrocytes [172]. In neuronal spheroid culture, it has been shown that TNF has no effect on differentiation or proliferation and instead induces neuronal progenitor cell migration [168, 173].

The effect of TNF on neurogenesis also depends on whether TNFR1 or TNFR2 signalling is involved. In a TNF receptor knockout model, TNFR1 activation reduced hippocampal neurogenesis in normal conditions and after status epilepticus [169]. Although TNFR2 is known for its neuroprotective effects, it can also induce apoptosis and TNFR2 knockout mouse models show increased proliferation and survival of newborn neurons [169, 174–176]. An investigation using a mouse model of irradiation induced chronic inflammation showed reduced neurogenesis in TNFR2 knockout animals while TNFR1 knockout mice showed little difference compared to controls [177]. This result suggests a role of TNFR2 in promoting neurogenesis after injury. *In vivo*, TNF knockout models show reduced hippocampal BDNF

levels and decreased apical dendrite arborization of CA1 and CA3 pyramidal cells [178]. Another study reported that primary hippocampal neurons in culture reduced neurite outgrowth and dendritic branching in response to TNF [179]. Overall, the proposed mechanism of TNF's modulation of neurogenesis that is generally accepted involves disruption of I kappa β kinase/ NF-κβ (IKK/NF-κβ) signalling in neural progenitor cells [173]. This process results in an upregulation of Cyclin D1, an important protein for cell cycle progression, which promotes the passage through the G1/S restriction point therefore encouraging proliferation of neural progenitors cells [172, 173]. However, the literature on TNF's role on neurogenesis varies and further research needs to evaluate the effects of TNF and its receptors on neuronal progenitor cells in neurogenesis.

ALCOHOL'S EFFECT ON TNF AND NEUROGENESIS

Decreased neurogenesis contributes to both anxiety and depression and selective serotonin reuptake inhibitor antidepressants can alleviate and promote hippocampal neurogenesis [180]. Under healthy conditions, stem cells in the brain are under constant stimulation to proliferate, migrate, differentiate and survive. However, pathological conditions like AUD impact these neurogenic stages with differential effects between alcohol intoxication and withdrawal. Ethanol intoxication studies *in vivo* have shown that the consumption of ethanol decreases neurogenesis through ethanol's effect on cell proliferation and cell survival [180–185]. However, studies observing abstinence of ethanol after ethanol dependence show increases in neurogenesis [186]. Some studies conflict with the general consensus that ethanol intoxication inhibits neural stem cell proliferation and have observed no effect after 10 days of ethanol consumption, or an increase in proliferation after chronic ethanol exposure [183, 187, 188].

AUD is known to disrupt neurogenesis and hippocampal integrity [182]. Although the exact mechanism is unknown, numerous mechanisms have been proposed. Ethanol's interaction with neurotransmission may be relevant due to the importance of glutamate and GABA signalling in hippocampal neurogenesis [189]. BDNF is a modulator of neurotransmitters and increases neurogenesis through enhancement of cell birth, survival, and maturation within the hippocampal SGZ [190]. After ethanol consumption, levels of serum BDNF decrease in humans and can return to baseline after alcohol abstinence [191–193]. BDNF levels have also been shown to decrease in rodents in the hippocampus, cortex and hypothalamus [194–196]. Finally, there is considerable evidence suggesting ethanol has significant cellular effects on glia that impact the hippocampal neurogenic niche. Excessive consumption of ethanol results in activation and damage to astrocytes which are primary components of the neural stem cell niche [197–203]. Activation of microglia can also inhibit neurogenesis [204]. Microglial TNF release during neuroinflammation is a key contributor to inflammation induced death of newly formed hippocampal neural progenitor cells in the adult brain after injury [205]. Microglia are activated by ethanol consumption depending on their phenotype and inflammatory environment and the duration, dose, and pattern of alcohol exposure [116, 117, 206–208]. Other cytokines released by microglia such as IL-1β and IL-6 are also thought to contribute to inhibition of neurogenesis [209, 210].

However, limited studies have explored the relationship between alcohol, TNF and adult neurogenesis. Broadly, TNF is usually explored in conjunction with other cytokines and is rarely studied individually. Both LPS and ethanol treated mice have shown to increase proinflammatory cytokines such as TNF, monocyte chemoattractant protein-1 (MCP1) and IL-1β and reduce the proliferation of hippocampal neural progenitors and newly born neuron differentiation in mice [211–213]. However, the role of TNF in neurogenic deficits after alcohol exposure should not be overstated. One study showed reversal of ethanol's inhibition of neurogenesis by neutralising IL-1β and blocking the IL-1β receptor with an antagonist against IL-1R, an effect that could not be replicated with neutralizing antibodies to TNF or MCP1 [214]. Antioxidant drugs have been tested to rescue the neurogenic deficits elicited after ethanol consumption. Butylated hydroxytoluene (BHT) has been shown to restore ethanol inhibition of neurogenesis by blocking NF-κB induction of proinflammatory genes [215, 216]. Rolipram, a phosphodiesterase-4 inhibitor, has also been tested and induced an increase in neurogenesis after ethanol consumption [214]. The success of these treatments supports a role of inflammatory cytokines in mediating ethanol's inhibition of neurogenesis but does not highlight TNF as an essential signal in this process.

CONCLUDING REMARKS

TNF has a demonstrated effect on synaptic plasticity and neurogenesis *in vitro* and in animal models. There is some evidence for TNF having an important role during withdrawal, with associations between alcohol craving and TNF in humans and in animal studies showing a direct effect of TNF on anxiety during withdrawal [149, 217]. This role in anxiety during withdrawal may be important when considering relapse and further studies involving the blocking of TNF during withdrawal may be beneficial. Its possible involvement in excitotoxicity during withdrawal is also an interesting research avenue. Additionally, TNF has prominent involvement in peripheral inflammation during AUD, particularly with AALD, which would exacerbate other neuroimmune signals and their effects [218, 219]. However, there is a lack of definitive evidence for TNF having a clearly defined, unique effect on neuroplasticity and neurogenesis in AUD. Rather, it is likely TNF contributes to neuroimmune signalling within a party of cytokines [32, 62]. Understanding TNF in AUD is also complicated by its differential effects on synaptic strength in different brain regions, which remain to be elucidated. In our opinion, the relevance of TNF in AUD going forward should be decided using animal models of voluntary drinking with inducible knockdowns of TNFR1 or TACE followed by behavioural testing during withdrawal. Furthermore, the roles of TNF should be further investigated to understand its effect on neurotransmission in physiology and pathology.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

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