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Review

Alcohol impairs hippocampal function: From NMDA receptor synaptic transmission to mitochondrial function

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ABSTRACT

Many studies have reported that alcohol produces harmful effects on several brain structures, including the hippocampus, in both rodents and humans. The hippocampus is one of the most studied areas of the brain due to its function in learning and memory, and a lot of evidence suggests that hippocampal failure is responsible for the cognitive loss present in individuals with recurrent alcohol consumption. Mitochondria are organelles that generate the energy needed for the brain to maintain neuronal communication, and their functional failure is considered a mediator of the synaptic dysfunction induced by alcohol. In this review, we discuss the mechanisms of how alcohol exposure affects neuronal communication through the impairment of glutamate receptor (NMDAR) activity, neuroinflammatory events and oxidative damage observed after alcohol exposure, all processes under the umbrella of mitochondrial function. Finally, we discuss the direct role of mitochondrial dysfunction mediating cognitive and memory decline produced by alcohol exposure and their consequences associated with neurodegeneration.

1. Introduction

Alcohol is the main licit drug worldwide, and its abusive consumption affects social interactions and severely damages the health of populations (Jung and Namkoong, 2014). The onset of alcohol consumption can occur at a young age, and excessive consumption is toxic to adult development, especially at brain level (Tapia-Rojas et al., 2017). The main risk of drinking alcohol is the appearance of alcohol use disorders (AUDs), such as alcoholism. However, the toxic effects of alcohol on the brain appear long before the development of these pathologies (Mukherjee, 2013). Therefore, it is vital to understand the negative effects of alcohol on the central nervous system (CNS). The hippocampus is a central memory and learning processing area of the forebrain, which contains CA1 and CA3 regions, and includes dentate gyrus (DG). The synaptic circuit includes vast excitatory and inhibitory transmission, where N-methyl-D-Aspartate receptor (NMDAR), an ionotropic glutamate receptor, is a central player in memory consolidation and spatial processing in the hippocampus (Cerpa et al., 2016). This area is vulnerable to toxic effects of ethanol, and when is damaged it can induce learning and memory impairment in alcoholic individuals (Parsons and Nixon, 1993), becoming an important model for study.

Diverse mechanisms have been proposed to explain ethanol-induced toxicity in the brain. The most accepted mechanism involves a cascade of excitotoxicity events because of the deregulation of neurotransmitter release and synaptic function. This deregulation could lead to an imbalance in excitatory/inhibitory currents, which leads to neurotoxicity (Crews and Nixon, 2009). Oxidative and inflammatory damage due to excessive alcohol intake also has been proposed to contribute to neuronal dysfunction (Albano, 2006; Syapin et al., 2005). Alcohol exposure increases the production of reactive oxygen species (ROS), caused mainly by alterations in mitochondria performance (Manzo-Avalos and

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Saavedra-Molina, 2010). Furthermore, ethanol promotes the production of inflammatory molecules in the brain, contributing to neuronal dysfunction (Crews and Nixon, 2009; Pascual et al., 2014). In this review, we summarize the effects of ethanol on excitotoxicity, focusing on NMDAR signaling impairment and oxidative stress and inflammation produced by alcohol exposure. Finally, we describe the importance of mitochondria, such as a master switch, in ethanol-induced neurodegeneration and the role played by this organelle in the mechanism of alcohol intoxication.

2. NMDAR and excitotoxicity by ethanol in the hippocampus

2.1. NMDAR inhibition and withdrawal hyperexcitability

Functional alterations in hippocampal synapses principally involve changes in the presynaptic compartment and excitatory transmission in different key elements, including ionotropic channels, like NMDA receptors. This ionotropic glutamate receptor is involved in fast excitatory transmission and synaptic plasticity events. NMDAR is a heterotetramer, composed of obligatory two GluN1 subunits and other two subunits (GluN2A, GluN2B, GluN2C, GluN2D, GluN3A or GluN3B). This receptor shows high affinity for glutamate, uses glycine or D-serine as a co-agonist, and it is blocked by magnesium ions. Once open, NMDAR let sodium and calcium entry inside the neuron, depolarizing it (Cerpa et al., 2016; Chandrasekar, 2013).

At the level of presynaptic compartment, treatment of ex vivo slices with 100 mM ethanol did not affect neurotransmitter (L-glutamate, L-aspartate, and GABA) release under basal conditions; but, KCl-induced neurotransmitter release was impaired for those three amino acids (Martin and Swartzwelder, 1992), as well as, ethanol treatment in animals also reduced glutamate levels in the dorsal hippocampus (Shimizu et al., 1998).

In the case of postsynaptic domain, hippocampal neurons recorded in the presence of ethanol (50 mM), an acute treatment, suppressed currents evoked by NMDA receptors (NMDAR currents), with less appreciable effects on other excitatory ionotropic glutamate receptors (AMPARs and kainate receptors) (Lovinger et al., 1989), as well as in rat *ex* vivo brain slices (Lovinger et al., 1990). However, spontaneous activity of the NMDAR, measured as miniature postsynaptic currents, increase after chronic ethanol treatment (Carpenter-Hyland et al., 2004), indicating a differential effect on acute and chronic treatments. Chronic intermittent alcohol exposure (CIE) produces a decrease in post-tetanic potentiation (PTP) and long-term potentiation (LTP) magnitude, indicating impairment on synaptic plasticity processes in the hippocampus (Roberto et al., 2003). Ethanol treatment decrease the expression of GluN1 and GluN2A in juvenile rats but increase them in adult rats (Pian et al., 2010), suggesting the role of NMDAR positioning and trafficking in ethanol toxicity with developmental differences between adolescent and adult animals.

Binge drinking is a pattern of alcohol consumption in which high amounts of ethanol are consumed in a short period, with gaps of abstinence before a new binge episode (Kuntsche et al., 2005). Many binge-like models of exposure have been developed to study the effects of high alcohol treatment followed by a withdrawal period. This pattern increases the expression of subunit receptor mRNA (GluN2A and GluN2B), and protein, but withdrawal restores mRNA and proteins levels (Follesa and Ticku, 1995; Kalluri et al., 1998). NMDAR inhibition in a binge drinking rodent model is not sufficient to inhibit CA1 neurodegeneration, indicating the existence of other mechanisms of alcohol toxicity, rather than excitotoxicity *per se* (Corso et al., 1998).

Interestingly, withdrawal, the process during which the blood ethanol concentration is drastically reduced, increases the susceptibility of neurons to NMDA exposure. In organotypic hippocampal-entorhinal cortex slice cultures (HEC), NMDA in bath media during withdrawal period induces neuronal death, more pronouncedly that NMDA treatment in non-ethanol exposed cultures, which indicates that neurons are more susceptible to excitotoxicity, or glutamate-induced neuronal death in withdrawal period (Thomas and Morrisett, 2000). Tetrodotoxin (sodium channel blocker) or MK801 (NMDAR blocker) treatment during withdrawal decrease neurotoxicity observed in CA1 hippocampal region, suggesting that neuronal activity mediated by NMDARs plays a role in ethanol-induced neuronal death (Grant et al., 1990; Prendergast et al., 2004). Electrophysiological recordings and biochemistry support this evidence, since ethanol withdrawal induce seizure activity, which is blocked with an NMDAR antagonist (APV). Part of these effects is through the increase of GluN1, GluN2A and GluN2B NMDAR subunits proteins in dendritic spines (Hendricson et al., 2007). Indeed, CIE treatment increase GluN1, GluN2A, and GluN2B receptor subunits after two weeks of withdrawal in juvenile rats (Nelson et al., 2005; Pian et al., 2010), and induce neurodegeneration impeded by APV (Reynolds et al., 2015). Interestingly, treatment with an antagonist of metabotropic glutamate receptor 5 (mGluR5) and NMDARs (MK-801) prevented the neurotoxicity induced by ethanol withdrawal, which also indicates a role played by metabotropic and ionotropic glutamate receptors in this process (B. R. Harris et al., 2003).

2.2. NMDAR localization and signaling

NMDARs are separated in two subdomains of the dendrites, the postsynaptic density (PSD) or synaptic NMDAR, and distal from the PSD or extrasynaptic NMDAR. Both types of NMDAR are identical at the molecular level but trigger different signaling pathways when activated. Synaptic NMDAR triggers calcium entry and the activation of pro-survival signals through the activation of cAMP response element-binding protein (CREB) transcription factor and extracellular signal-regulated kinase (ERK) signaling pathways. On the other hand, calcium entry through extrasynaptic NMDAR triggers pro-death signals, such as calpain activation, CREB, and ERK shut off, and pro-apoptotic pathways (Hardingham and Bading, 2010).

Four days of ethanol treatment *in vitro* increases membrane recruitment and clustering of GluN1 and GluN2B receptor subunits and increase co-localization of GluN1 with synapsin (Carpenter-Hyland et al., 2004), indicating a synaptic localization.

Ethanol 100 mM (for 10 min) in hippocampal slices produced a decrease in phosphorylation of tyrosine 1472 of the GluN2B subunit, a mark of synaptic localization of NMDAR, indicating a decrease in synaptically located GluN2B. Coadministration with a tyrosine phosphatase inhibitor (bpV(phen)) decreased the inhibition percentage of the NMDAR-mediated field excitatory postsynaptic potentials (fEPSPs) in hippocampal slices suggesting the contribution of phosphatase activity to the NMDAR inhibition induced by ethanol (Alvestad et al., 2003). Striatal enriched protein tyrosine phosphatase (STEP) appears as the key phosphatase in Tyr-1472 dephosphorylation, which induces the endocytosis of the receptor. In STEP knock out (KO) mice ethanol is unable to inhibit NMDAR currents and decrease tyrosine 1472 activity (Hicklin et al., 2011). However, three hours of withdrawal increase the synaptic availability of NMDAR increasing Tyr-1472 phosphorylation in GluN2B subunit in a CIE experimental model. Prolonged withdrawal (21 days) restore protein levels of all NMDAR subunits (Staples et al., 2015), indicating that STEP is a key molecular component which mediates ethanol's inhibitory effects on NMDARs.

Intermittent alcohol exposure (vapor) decreases protein levels of ERK phosphorylated (pERK), but 24 h of withdrawal increase phosphorylated protein levels (Sanna et al., 2002), indicating a decrease synaptic signaling through NMDAR in the hippocampus and compensation during withdrawal. Similar results have been observed for continuous chronic alcohol treatment in vapor chambers (Sanna et al., 2002). Free-choice ethanol treatment in mice upregulates brain-derived neurotrophic factor (BDNF) signaling, the main effector of CREB and synaptic NMDAR activity, increasing phosphorylated form of ERK, AKT (protein kinase B) and CREB proteins. The increase in these proteins

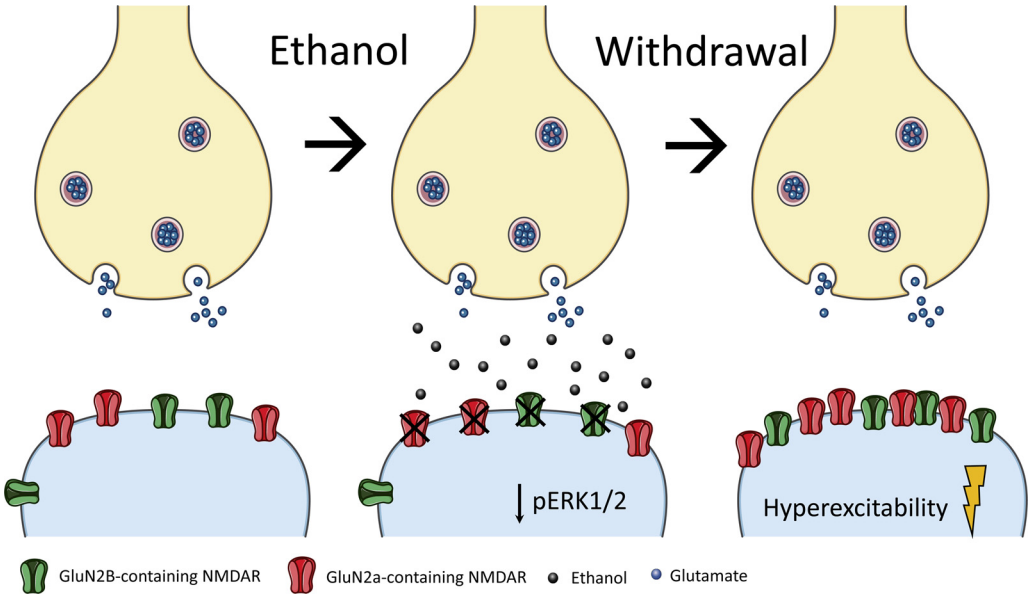

Fig. 1. Alcohol affects glutamatergic synapses. In postsynaptic terminals, NMDARs are inhibited by ethanol, decreasing ERK signaling and related pathways. Ethanol withdrawal increases the number of NMDA receptors at the surface of the postsynaptic membrane, increasing the vulnerability of neurons to excitotoxicity and generating hyperexcitability.

levels was suppressed by adding a TrkB (BDNF receptor) antagonist, which suggest the role of the BDNF pathway (Stragier et al., 2015).

2.3. Summary

Thus, ethanol rearranges the glutamatergic synapses. Ethanol blocked the NMDAR directly, with the absence of effect in other ionotropic glutamate receptors. As a feedback loop, the number of NMDAR increase during withdrawal producing hyperexcitability and seizure patterns in the hippocampus. Inhibition and changes in the trafficking of membrane NMDARs are mediated by the phosphorylation of tyrosine residues on the cytoplasmic tails of the subunit GluN2B. This increase in membrane synaptic receptors contributes to hyperexcitability during early withdrawal and makes neurons more vulnerable to excitotoxicity. The direct inhibition of NMDAR and changes in trafficking suggest a possible mechanism of neurotoxicity and hippocampal dysfunction, altering synaptic plasticity at the molecular level and becoming hippocampal neurons vulnerable to excitotoxicity and glutamate overstimulation (Fig. 1). However, it has been suggested that excitotoxicity and NMDAR are not the central mediators of cytotoxicity induced by alcohol, and additional mechanisms contribute to neuronal dysfunction (Collins and Neafsey, 2012a). Oxidative stress and neuroinflammation have been widely described as important neurotoxic mechanisms involved in ethanol toxicity as we developed in the next section.

3. Alcohol exposure affects brain function through the inflammatory and oxidative responses

Oxidative stress and neuroinflammation are interconnected pathways which have been indicated as mediators of ethanol toxicity in the brain, and particularly in the hippocampus (Fig. 2). These mechanisms involved molecular processes in neurons and glial cells, the reason why it is important to consider the close relationship between them in bran tissue. In this section, we will mention some issues in radical oxygen and nitrogen production and damage to biomolecules that they cause, and the complex neuroinflammatory pathways involved in ethanol toxicity since enzyme induction to transcriptional regulation.

3.1. Alcohol and oxidative damage

As a consequence of normal biological processes of cellular metabolism, oxygen and nitrogen free radicals are produced in the cell. These reactive chemical species are produced mainly in the mitochondria, or it can be synthesized by enzymes during normal cell processes. Oxidative stress, on the other hand, is the imbalance between reactive free radical species and anti-oxidant components of the cell. The overproduction of reactive oxygen and nitrogen species (ROS and RNS respectively) produce a chemical modification in biomolecules such as lipids, proteins and nucleic acids leading to aggregation of these biomolecules and loss of normal function. Many neurological diseases like Alzheimer's disease (AD), Parkinson's disease (PD) or amyotrophic lateral sclerosis (ALS) are characterized by ROS and RNS overproduction and oxidative stress (Islam, 2017; Losada-Barreiro and Bravo-Diaz, 2017; Ortiz et al., 2017).

Previous studies by Borges et al. showed that rats chronically exposed to ethanol showed an increase in the staining of lipofuscin (oxidative marker) in the hippocampus, which suggests the induction of oxidative damage (Borges et al., 1986). In general, ethanol treatment affects most of the cellular antioxidant systems (Casanas-Sanchez et al., 2016), like glutathione reduced/oxidized (GSH-GSSG) ratio and reduced superoxide dismutase (SOD) expression, a superoxide scavenger enzyme (reviewed in (Collins and Neafsey, 2012b).

Ethanol exposure for 8 days decreased the hippocampal GSH content (Johnsen-Soriano et al., 2007) and administration via oral gavage for 10 weeks produced an increase in nitrosative stress and a decrease in antioxidant components, such as lipid peroxidase, GSH, SOD, and catalase in the hippocampus (Tiwari et al., 2009). Ethanol exposure during development led to GSH depletion in the DG, accompanied by increased lipid peroxidation, decreased catalase activity, and increased glutathione reductase and SOD activity (Cesconetto et al., 2016).

Additionally, ethanol exposure induces the expression of enzymes such as nitric oxide synthase (NOS), cyclooxygenase 2 (COX2) and NADPH oxidase (NOX). NOS activity was primarily associated with the toxic effects of ethanol due to its relationship with NMDAR activation in physiological and pathological scenarios (reviewed in (Lancaster, 1992)). The use of two NOS inhibitors, L-NAME and 7-NI, not only failed to protect against ethanol-induced damage but also promoted further neurodegeneration (J. Y. Zou et al., 1996), illustrating the complex role of the enzyme in redox signaling. Under pathological conditions, large amounts of NO are produced by astrocytes via inducible nitric oxide synthase (iNOS; reviewed in (Sun and Sun, 2001)). iNOS expression has been observed in organotypic HEC slices (J. Zou and Crews, 2010) after ethanol exposure and in the hippocampus after binge ethanol exposure (Pascual et al., 2007). Interestingly, the induction of iNOS was abolished by anti-inflammatory treatment with indomethacin, a COX-2 inhibitor (Pascual et al., 2007).

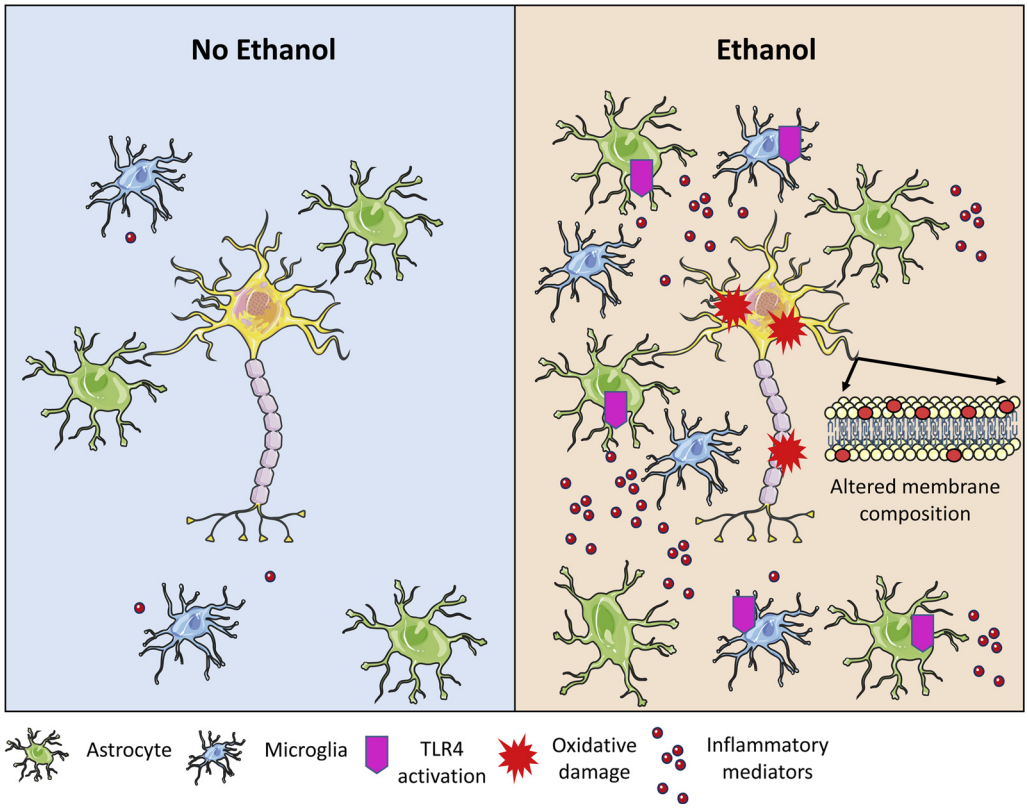

Fig. 2. Alcohol exposure increases oxidative and inflammatory responses in the hippocampus. Ethanol exposure increases oxidative stress, with the consequent modification of proteins, lipids, and nucleic acids. Moreover, the immune response is activated after ethanol exposure, partially activating microglia and astrocytes, releasing proinflammatory cytokines and activating the TLR4 signaling pathway.

3.2. Alcohol and the inflammatory response in the brain

3.2.1. Enzymes induction

Another important mechanism of the response to oxidative stress and inflammation is COX2 signaling, which is involved in the production of prostaglandins, important inflammatory mediators (O'Banion, 1999). Acute treatment of rats with ethanol-induced the expression of COX2 in the CA4 region of the hippocampus, while chronic ethanol treatment induces COX2 expression in CA3 and CA4 after withdrawal (Knapp and Crews, 1999). Further studies showed the induction of COX2 expression after ethanol treatment in the DG (Simonyi et al., 2002), and after binge drinking in juvenile rats (Pascual et al., 2007). COX2 produces prostaglandins and thromboxanes from arachidonic acid released from membrane phospholipids, which is mediated by phospholipase A2 (PLA2) (Hsieh and Yang, 2013). Ethanol exposure alters the expression of several members of the PLA family (N. F. Tajuddin et al., 2013; N. Tajuddin et al., 2014). Furthermore, a PLA2 inhibitor was able to abolish oxidative damage induced by ethanol in HEC cultures (Moon et al., 2014), indicating that ethanol exerts part of its effect by altering PLA signaling related to oxidative stress but also generates changes in the lipid content (Gustavsson and Alling, 1989), and phospholipid composition (Akbar et al., 2006; Wen and Kim, 2004, 2007). NADPH oxidase (NOX) is an enzyme responsible for the formation of the superoxide ion (O_2^-). The induction of NOX after ethanol exposure occurs in several brain areas, such as the hypothalamus and cerebellum (Cohen et al., 2007). The upregulation of $gp91^{phox}$ (catalytic subunit of NOX) was induced by ethanol in the DG of mice, accompanied by increased ROS levels. The NOX inhibitor, Diphenyleneiodonium (DPI), reduced ROS and caspase-3 immunoreactivity, suggesting that NOX mediates the oxidative damage and neuronal death induced by ethanol binge exposure (Qin and Crews, 2012).

3.2.2. Cytokines production

Complementary studies in humans with alcoholism showed increased monocyte chemoattractant protein 1 (MCP-1) levels in the brain, including the hippocampus. MCP-1 is a chemokine that causes the migration and activation of microglia, suggesting the occurrence of a neuroinflammatory process after ethanol exposure (He and Crews, 2008). In mice, ten days of alcohol exposure induce inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin 1 beta (IL-1β) and MCP-1 (Qin et al., 2008). Repeated binge drinking increased TNF-α and IL-1β levels in the hippocampus (Marshall et al., 2016; Zhao et al., 2013) only 1 h after ethanol treatment (Zhao et al., 2013), as well as increment in these cytokines can be observed also in ethanol treatment in neonatal period (Topper et al., 2015). Organotypic HEC cultures have shown that ethanol exposure increased the mRNA levels of proinflammatory cytokines TNF-α, IL-1β, and MCP-1. Moreover, TNF-α was colocalized with $GFAP^+$ (GFAP positive, astrocytes) cells and $NeuN^+$ (NeuN positive, neurons) cells in the dentate gyrus, and MCP-1 was colocalized with $GFAP^+$ cells (J. Zou and Crews, 2010), indicating that pro-inflammatory mediators are produced by both astrocytes and neurons.

3.2.3. Microglial inflammatory response

Microglial activation is another inflammatory process observed after ethanol binge treatment (Nixon et al., 2008). Ethanol binge drinking induces morphological changes in the microglial processes and increases activation markers like OX-6 in the rat hippocampus (Ward et al., 2009). Microglial activation was also observed using CD11b/c (portion of complement receptor 3) marker in the CA1 and CA2/3 areas and the DG after binge drinking (Marshall et al., 2013), as well as the proliferation of $Iba\text{-}1^+$ (Iba-1 positive, microglia) cells in the CA1 and CA2/3 areas and the DG, suggesting microglia activation in the hippocampus (Zhao et al., 2013). Finally, Marshall et al. studied the hypothesis of microglial priming, defined as follows: *Microglial priming is a second interruption in the brain microenvironment that induces an exaggerated or heightened microglial response compared to the first interruption, referring to "microglial activation", and primed microglia in the CNS are more sensitive to potentially minor stimuli* (Li et al., 2018); they further demonstrated that OX-42 (microglial activation marker)

immunoreactivity increased after one cycle and increased even more in the CA1 and CA2/3 areas of the rat hippocampus after two cycles of binge ethanol drinking (Marshall et al., 2016). Therefore, microglia that have been previously activated by ethanol can be further exacerbated by a second application of the alcohol binge cycle or another type of stressor.

3.2.4. Nuclear Factor-κB pathway

One of the major transcription factors mediating immune and inflammatory responses is nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB). In organotypic HEC slice cultures, ethanol increased NF-κB DNA binding, an effect that was enhanced by increasing the ethanol concentration (J. Y. Zou and Crews, 2005). Additionally, CREB a transcription factor that is regulated by ethanol treatment decreased their DNA binding in a concentration-dependent manner (J. Zou and Crews, 2006). Additionally, the effects of ethanol on DNA binding to transcription factors are potentiated by TNF-α and glutamate (J. Zou and Crews, 2006). Increased ethanol-mediated NF-κB DNA binding has been shown to be related to increased expression of DNA-binding NF-κB subunit p50 (J. Zou and Crews, 2010). NF-κB DNA binding after ethanol treatment increased in vivo in a rat model of binge drinking (Crews et al., 2006). In NF-κB-GFP mice, it was observed that the transcription factor colocalized with ROS in neurons, astrocytes, and microglial cells after ethanol exposure for 10 days (Qin and Crews, 2012). Therefore, ethanol promotes an inflammatory response in the brain, which induces changes in genetic expression modulated by the activity of transcription factors, including NF-κB.

Interestingly, further studies have suggested that Toll-like receptor 4 (TLR4) plays a role in NF-κB activation (Blanco et al., 2005). Using organotypic HEC slices, increased levels of IL-1β was reported after ethanol exposure; however, using siRNA against TLR4 ethanol treatment was unable to induce IL-1β production (Crews et al., 2013). Ethanol treatment in mice impaired recognition memory after 5 months of ethanol exposure followed by 2 weeks of withdrawal, while in TLR4 KO mice alterations are absent (Pascual et al., 2011), strongly suggesting that TLR4 is involved in the inflammatory response and behavioral deficits induced by ethanol. However, TLR4 KO, or inhibition with naloxone, does not alter either, ethanol self-administration nor ethanol consumption in drinking in the dark paradigm in mice (R. A. Harris et al., 2017), indicating that probably TLR4 is a mediator of neuroinflammation caused by ethanol but not responsible for the behavior of consumption itself.

3.3. Summary

Ethanol induces the overproduction of ROS and impaired antioxidant response leading to oxidative stress in the hippocampus, which could modify the structure of key biomolecules like lipids, proteins, and nucleic acids. On the other hand, ethanol also induces neuroinflammation triggering the production of pro-inflammatory cytokines such as TNF-α and IL-1β and activating the microglia and astrocytes in the hippocampus. One common effector in the oxidative damage and inflammatory response is the mitochondria. Mitochondrial dysfunction is the major contributor to oxidative stress through the electron transport chain, becoming a key organelle in the process of alcohol-induced toxicity.

4. Role of mitochondrial injury in the synaptic impairment induced by alcohol

Mitochondrial injury observed after excessive alcohol intake could contribute to synaptic failure, cognitive impairment, and motor and behavioral alterations in animals (Levy et al., 2003; Tapia-Rojas et al., 2018). Ethanol promotes ROS production and inflammation as previously described and reduces energy availability in the brain (Heaton et al., 2013; Liu et al., 2014; Ramachandran et al., 2001). Therefore, it is conceivable that some of the effects induced by alcohol are mediated by mitochondrial injury.

Mitochondria are highly regulated organelles that are responsible for energy production and calcium and redox homeostasis (Picone et al., 2014). Accumulating evidence indicates that alcohol exposure affects mitochondrial function (Ramachandran et al., 2003; Tapia-Rojas et al., 2017). Mitochondrial dysfunction is particularly important, as mitochondria are responsible for providing ATP for synaptic processes and maintaining the calcium buffer capacity involved in the neuronal electrical activity (Cabezas-Opazo et al., 2015). Therefore, it is important to understand how alcohol exposure can affect mitochondria and the implications of these effects in neuronal communication.

Indeed, ethanol treatment reduced PPAR-γ activation by reducing PGC1-α promoter activity (Liu et al., 2014). PGC1-α participates in the antioxidant response and fat metabolism and generally controls mitochondrial biogenesis (Liang and Ward, 2006; St-Pierre et al., 2006). Interestingly, the same studies showed that PGC1-α overexpression prevented mitochondrial dysfunction and neuronal loss induced by ethanol (Liu et al., 2014) in cell cultures.

4.1. Alcohol exposure affects mitochondrial dynamics

Mitochondrial dynamics actively control the quality and size of mitochondria (Chen and Chan, 2009; Mishra and Chan, 2014) which are altered in response to stress and metabolic changes (Han et al., 2012). This process involves the regulation of fission and fusion events by a set of GTPase proteins, including dynamin-related protein 1 (Drp1) and Fission protein 1 (Fis1), which control fission (Mishra and Chan, 2014), and mitofusin 1/2 (Mfn1, Mfn2) and Opa1, which are responsible for the fusion process (Mopert et al., 2009). Accumulating evidence indicates that impairments in mitochondrial dynamics are involved in neurodegeneration (Chen and Chan, 2009). However, the effects of alcohol exposure on this mechanism have been poorly described. Our group has recently observed important evidence indicating that alcohol can negatively affect the brain by deregulating mitochondrial dynamics (Tapia-Rojas et al., 2018). We performed studies using adolescent binge drinking model of exposure where we observed an increase in the expression of mitochondrial fission proteins accompanied by reduced levels of fusion components, suggesting that binge-like ethanol exposure promotes mitochondrial fragmentation at 1–3 weeks post-treatment in the hippocampus. Interestingly, at 7 weeks after ethanol treatment, the impairment in mitochondrial dynamics had been completely restored (Tapia-Rojas et al., 2018). Simultaneously, we observed reduced ATP production and increased inflammation (Tapia-Rojas et al., 2018). These observations suggest that binge ethanol exposure could affect mitochondrial function by impairing mitochondrial dynamics, which in turn may affect neuronal function. Ethanol disrupts mitochondrial cristae integrity in cholinergic axonal terminals (Dymecki et al., 1982) and induces fission proteins in *vitro* epithelial cell line (Bonet-Ponce et al., 2015). These alterations in mitochondrial dynamics could distinct features of the ethanol neurotoxicity resulting from binge ethanol exposure.

4.2. Alcohol exposure impairs mitochondrial bioenergetics

Mitochondria are considered the cell´s powerhouse due to their functions in ATP production, cellular metabolism, and redox balance (Putti et al., 2015).

Ethanol impairment of mitochondrial bioenergetics have not been extensively studied in the brain, and neither in the hippocampus specifically. Other models of neuron or astrocyte function have indicated that ethanol impaired mitochondrial membrane potential and reduces ATP production (Liu et al., 2014). Decrease ATP production, decrease expression and activity of mitochondrial respiratory complexes have also been described in cerebellum, cortex, and whole-brain tissue (Budd and Nicholls, 1996; Bustamante et al., 2012; Haorah et al., 2013; M. E.

Jung, 2015; Karadayian et al., 2015; Luo, 2015; Reddy et al., 2013). In the hippocampus, binge drinking alcohol treatment in rats decreases ATP production up to 7 weeks after alcohol exposure, indicating mitochondrial dysfunction (Tapia-Rojas et al., 2018). Additionally, binge alcohol exposure induces mitochondrial membrane depolarization and decreases OXPHOS complex expression (Tapia-Rojas et al., 2019), indicating that mitochondrial bioenergetics is compromised by ethanol as well as other brain regions. Collectively, these reports indicate that ethanol is toxic to mitochondria and thus leads to impaired ATP production and contributes to synaptic failure and cognitive impairment.

4.3. Alcohol administration disrupts mitochondrial permeability

Interesting studies have also shown that alcohol affects mitochondrial function through the deregulation of calcium buffering (Ramachandran et al., 2001). Ethanol increase cytosolic calcium (Gonzalez et al., 2007; Kouzoukas et al., 2013) in cerebellar neurons and astrocytes, leading to ROS production. In the brain of alcoholic rats, cytosolic Ca^{2+} uptake resulted in increased mitochondrial calcium levels during synaptic communication, which in turn led to the overproduction of ROS and a decreased antioxidant response (M. E. Jung, 2015). In the hippocampus, adolescent binge alcohol treatment did not change total calcium content but increases mitochondrial calcium as seen by increasing Rhod2 fluorescence, indicating loss of calcium buffering properties (Tapia-Rojas et al., 2019). High Ca^{2+} concentrations in mitochondria can ultimately lead to mitochondrial membrane transition pore (mPTP) opening and eventually to neuronal death (Friberg and Wieloch, 2002; Perez and Quintanilla, 2017).

The mPTP is a nonspecific channel sensitive to disturbances in intracellular calcium and, in some cases, to increases in ROS (Mnatsakanyan et al., 2016). Under normal conditions, the mPTP remains closed, and in the presence of stressors, the pore components rapidly assemble and form a mega-channel that increases the permeability of the mitochondrial membrane (Haworth and Hunter, 1979; Hunter and Haworth, 1979a, 1979b). This channel favors mitochondrial permeability to small solutes, which leads to the collapse of the chemiosmosis gradient (Galluzzi et al., 2009). Therefore, impairment of the oxidative phosphorylation process leads to decreased ATP production (Budd and Nicholls, 1996), increased ROS generation (Hou et al., 2014), calcium overload (Elrod et al., 2010), and finally cell death (Galluzzi et al., 2009). In a healthy neuron, mitochondria regulate local calcium levels during neurotransmission, ensuring cell signaling and maintenance of the action potential (Friberg and Wieloch, 2002). However, under pathological conditions in which the mPTP is active, calcium regulation is impaired, and this event may contribute to synaptic loss and neuronal death (Friberg and Wieloch, 2002).

Studies of isolated brain mitochondria found that treatment with ethanol did not induce opening of the mPTP, suggesting that ethanol does not directly affect mitochondrial permeability in neurons (Lamarche et al., 2013). However, cultured neurons treated with ethanol open mPTP permanently, and it is blocked by cyclosporine A and nortriptyline (Lamarche et al., 2013), and a transient opening of the mPTP after ethanol exposure, possibly through an indirect mechanism (Galluzzi et al., 2009; Lamarche et al., 2013). A similar effect was observed in chronic ethanol treatment and withdrawal conditions in brain tissue, suggesting that opening of the mPTP persists even when alcohol is removed (Almansa et al., 2009; Karadayian et al., 2015). Additionally, binge alcohol exposure in adolescent rats likely altered mPTP activity in the hippocampus, as indicated by a decrease in the expression of mPTP protein components, such as VDAC, ANT and cyclophilin D (Tapia-Rojas et al., 2018).

Together, these findings indicate that alcohol exposure triggers important defects in the control of mitochondrial dynamics, possibly through the involvement of the mPTP opening. These mitochondrial morphological changes could alter the bioenergetics, generating dysfunctional mitochondria (Fig. 3). Besides, these defects can affect the viability of mitochondria in areas of high energy demand, such as synaptic terminals. These findings support the idea that mitochondrial dysfunction is a principal contributor to alcohol-induced neurotoxicity.

4.4. Summary

Despite lack of vast studies in ethanol-induced hippocampal mitochondrial dysfunction, there is some evidence in whole-brain which suggest impaired mitochondrial functions, including impaired bioenergetics and decrease ATP production, impaired calcium buffering and mPTP opening, and impaired mitochondrial structure and dynamics. In the hippocampus, our group has suggested that binge alcohol treatment alters mitochondrial dynamics, bioenergetics and calcium homeostasis, indicating the mitochondria as an important contributor to ethanol-induced neuronal dysfunction.

5. Discussion and conclusions

The NMDAR dysfunction, ROS production, and neuroinflammation concomitantly have been indicated in several neurological diseases as common mechanisms (Hsieh and Yang, 2013; Kamat et al., 2016; Niedzielska et al., 2016). Neuroinflammation processes in the hippocampus could lead to astrocytic dysfunction which facilitates excitotoxicity (Malarkey and Parpura, 2008). Binge drinking ethanol exposure in adolescent rats activates hemichannels and pannexins in hippocampal astrocytes (Gomez et al., 2018), which could mediate the release of glutamate to synaptic cleft inducing excitotoxicity mediated by NMDARs. Also, ethanol acting over the NMDAR could modulate the localization of the receptor. In early stages after ethanol exposure, the feed-back loop that increases the synaptic localization of NMDAR in synaptic membrane and glutamate release from reactive astrocytes could modulate ethanol-induced neurotoxicity. At the same time, excitotoxicity involves calcium overload which produces ROS production and oxidative stress-inducing enzymes like PLA2 and NOS (Mehta et al., 2013). As well as, ROS production could chemically modify the NMDAR, altering its function as demonstrated in depressive-like behaviors (Ibi et al., 2017). We could hypothesize that this cross-talk between NMDAR inhibition and withdrawal-hyperexcitability, neuroinflammation mediated by astrocytes and ROS production are the major contributors to ethanol-induced neurotoxicity.

Mitochondria is the major contributor in the ROS production from leakage of electrons from electron transport chain. Ethanol-induced oxidative stress seems to be mediated by a mitochondrial component related to electron transport chain dysfunction (and decrease ATP production) and non-mitochondrial component involving the induction of enzymes like NOX, NOS, COX-2 and impairing antioxidant response at the level of glutathione, SOD, and catalase. Mitochondria is also well-established calcium buffering compartment, important in synaptic transmission. Calcium influx into the mitochondria through mitochondrial calcium uniporter (MCU) and efflux via sodium/calcium exchanger (NCLX) are key components in glutamate receptor-mediated calcium fluxes in neurons. The inhibition of these components has shown to regulate the magnitude of calcium permeability in glutamate receptors (Strokin and Reiser, 2016).

Moreover, in hippocampal cell cultures, excitotoxic events induce mitochondrial swelling due to long-lasting activation of CaMKII (Otmakhov et al., 2015), and Aβ oligomers plus NMDA induce mitochondrial depolarization and dysfunction, effects mediated by GluN2B NMDAR subunit (Ferreira et al., 2015). However, in cortical neurons, ethanol could inhibit uncoupling protein 2 (UCP2), inhibiting calcium influx after excitotoxic events, preventing cell death (Fukumori et al., 2013). Thus, ethanol could induce NMDAR mediated excitotoxicity which induces mitochondrial dysfunction through altering calcium buffering, which in turns, leads to ROS overproduction and decrease ATP synthesis. Ethanol probably alters mitochondrial physiology inhibiting UCP2, mitigating at least in part excitotoxic damage.

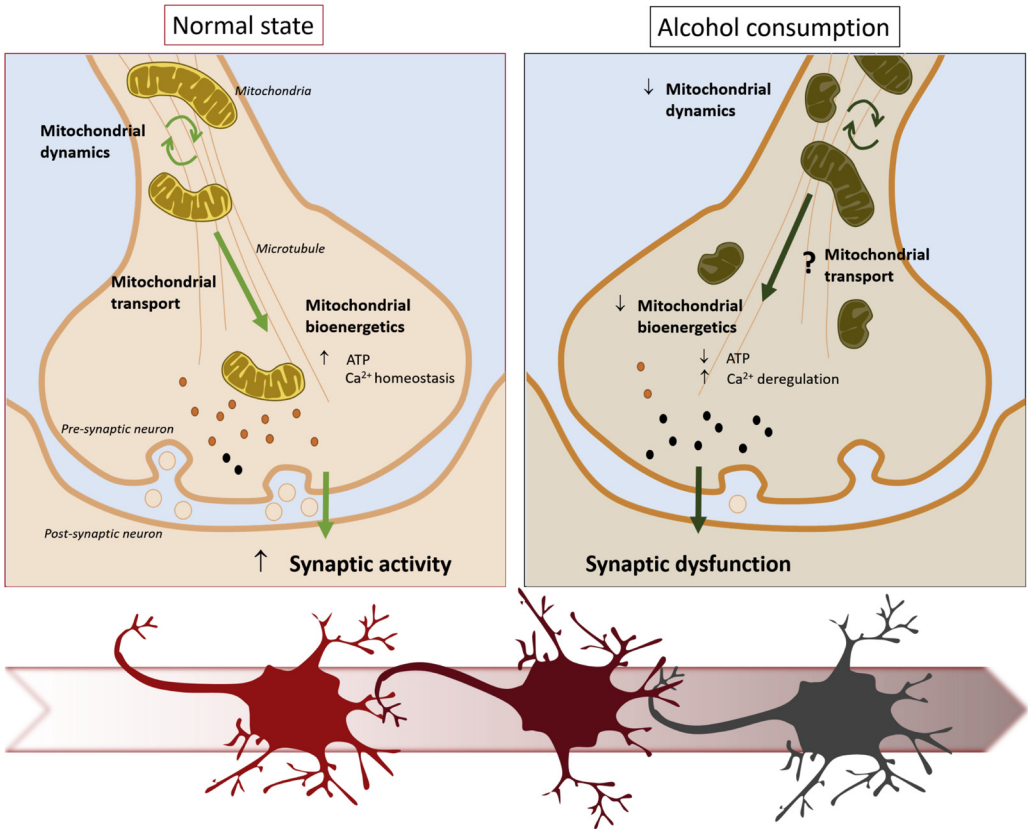

Fig. 3. Alcohol exposure affects mitochondrial function. In the absence of ethanol (normal condition), mitochondria are transported to synapses, where they regulate calcium fluctuations (black circles) and produce the necessary ATP (orange circles). In contrast, ethanol exposure seriously affects these functions, producing a decrease in the mitochondria calcium buffer response and reducing ATP production. These changes finally lead to synaptic failure, which could eventually contribute to neurodegeneration and memory loss.

The astrocyte response to ethanol, including pro-inflammatory environment and release of different mediators through hemichannels are also components of ethanol toxicity in the hippocampus which leads to neurotoxicity and cognitive impairment. There is still a lack of evidence on how these different toxic mechanisms talk to each other in response to ethanol in the hippocampus. Recently the mitochondria are taking place in ethanol neurotoxicity research and open a broad field of possible unknown neuron dysfunction mechanisms and new possible pharmacological targets to reduce ethanol-induced neuronal loss.

Alcohol has been studied for decades, and the mechanisms involved in ethanol-induced neurotoxicity include oxidative stress, inflammation, and alterations in excitatory and inhibitory synapses. However, over the last year, mitochondrial dysfunction has been identified as a crucial event in alcohol-induced toxicity due to its implications in synaptic transmission and memory. Hippocampal dysfunction induced by ethanol and consequent learning and memory impairment exhibit a broad spectrum of molecular events, each related to each other, which determines neuron damage and death. How NMDAR mediated excitotoxicity, oxidative stress, neuroinflammation, and mitochondrial dysfunctions cross-talk and the temporality of these changes are still unrevealed questions on ethanol research in the hippocampal physiology and probably drives future directions in the field.

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Contributors

Rodrigo G. Mira wrote a main part of the manuscript and made the figures.

Cheril Tapia-Rojas wrote part and reviewed the manuscript.

María Jose Pérez wrote a part of the manuscript.

Claudia Jara wrote a part of the manuscript.

Erick H. Vergara wrote a part of the manuscript.

Rodrigo A. Quintanilla wrote part and reviewed the manuscript.

Waldo Cerpa design structure of the manuscript and wrote part and reviewed the manuscript.

All authors contributed to and approved of the final version of the manuscript.

Declaration of Competing Interest

No conflict declared.

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