DOI: 10.1002/bdr2.1172

REVIEW ARTICLE

WILEY Birth Defects Research THE TERATOLOGY SOCIETY EST. 1960

Alcohol consumption during adolescence: A link between mitochondrial damage and ethanol brain intoxication

Cheril Tapia-Rojas[1,2] | Rodrigo G. Mira[1,3] | Angie K. Torres[1,2] | Claudia Jara[1,2] | María José Pérez[1,2] | Erick H. Vergara[1,2] | Waldo Cerpa[1,3] | Rodrigo A. Quintanilla[1,2]

[1] Centro de Investigación y Estudio del Consumo de Alcohol en Adolescentes (CIAA), Santiago, Chile

[2] Laboratory of Neurodegenerative Diseases, Universidad Autónoma de Chile, Chile

[3] Laboratorio de Función y Patología Neuronal, Departamento de Biología Celular y Molecular, Facultad de Ciencias Biológicas, Pontificia Universidad Católica de Chile, Santiago 8331150, Chile

Correspondence
Rodrigo A Quintanilla, Laboratory of Neurodegenerative Diseases, CIB, Universidad Autónoma de Chile, El llano Subercaseaux 2801, 5to Piso, San Miguel 8910000, Santiago, Chile.
Email: rodrigo.quintanilla@uautonoma.cl

Funding information
Fondo Nacional de Desarrollo Científico y Tecnológico, Grant/Award Number: 1140968, 1170441; Comisión Nacional de Investigación Científica y Tecnológica, Grant/Award Number: ACT1411.

Abstract

Adolescence is a period of multiple changes where social behaviors influence interpersonal-relations. Adolescents live new experiences, including alcohol consumption which has become an increasing health problem. The age of onset for consumption has declined in the last decades, and additionally, the adolescents now uptake greater amounts of alcohol per occasion. Alcohol consumption is a risk factor for accidents, mental illnesses or other pathologies, as well as for the appearance of addictions, including alcoholism. An interesting topic to study is the damage that alcohol induces on the central nervous system (CNS) in the young population. The brain undergoes substantial modifications during adolescence, making brain cells more vulnerable to the ethanol toxicity. Over the last years, the brain mitochondria have emerged as a cell organelle which is particularly susceptible to alcohol. Mitochondria suffer severe alterations which can be exacerbated if the amount of alcohol or the exposure time is increased. In this review, we focus on the changes that the adolescent brain undergoes after drinking, placing particular emphasis on mitochondrial damage and their consequences against brain function. Finally, we propose the mitochondria as an important mediator in alcohol toxicity and a potential therapeutic target to reduce or treat brain conditions associated with excessive alcohol consumption.

KEYWORDS

adolescence, alcohol, alcoholism, binge-drinking, mitochondria, oxidative stress

1 | INTRODUCTION

Adolescence is known as the transition period between childhood and adulthood, which is characterized by physical, psychological, and social modifications. These changes make adolescence a very vulnerable period in terms of addictions, especially alcohol dependence (Dawson, Goldstein, Chou, Ruan, & Grant, 2008). Alcohol is one of the most common licit drug consumed by teenagers, between 14- and 20-years old (Dawson et al., 2008). This excessive consumption has increased over the last years, from 4.6% to 13.0% in Americans females and from 17.9% to 29.4% in Americans males, making excessive alcohol consumption a principal cause of death (PAHO, 2015). Moreover, alcohol consumption contributes to the development of social, mental, and physical diseases such as depression, suicidality, liver cirrhosis and other health risk behaviors including driving accidents after drinking (PAHO, 2015). Excessive alcohol intake can also impair decision-making and unplanned sexual conduct (Townshend, Kambouropoulos, Griffin, Hunt, & Milani, 2014). It increases all cause-mortality, such as heart failure and stroke (Stewart, Han, Doran, & McCambridge, 2017) and there is evidence that people who start drinking during adolescence are more

likely to be become an alcohol dependent person during the adulthood (SAMHSA, 2013).

Studies show that teenagers drinks with less frequency than adults, but they drink higher amounts on each occasion (Faden and Goldman, 2004). In 2013, 52.2% of Americans with 12 years old or older reported being current drinkers and 23% had a binge drinking pattern of consumption (SAMHSA, 2013). This drinking pattern is defined by The Substance Abuse and Mental Health Services Administration (SAMHSA) as consuming at least five drinks for males and at least four drinks for females on the same occasion (in a period of 2 hr) over the past month. Another adverse effect of underage drinking is that current drinkers in the United States aged 20 or younger are more likely to use other drugs, such as marijuana (SAMHSA, 2013), cocaine and tobacco (Bonnie and O'Connell, 2004), increasing the possibility of developing a series of addictions. In particular, in South of America, Chile has one of the highest Alcohol Per Capita consumption values with an average of 5.5 L for females and 13.9 L for males, of pure alcohol (PAHO, 2015). The prevalence of alcohol consumption in the Chilean population increased in 2014 compared with 2012, from 40.8% to 48.9% (SENDA, 2014). In 2014, 22.9% of drinkers were aged between 12 and 18 (SENDA, 2014). In 2010, 5% of the population presented alcohol disorders and 2.5% had alcohol dependence, independent of sex. Also in 2012, a 3.4% of road traffic accidents caused by females were attributable to alcohol consumption and this percentage was even worse in males (9.2%) (WHO, 2014). Recent reports show that in 2016, 205 deaths were caused by drivers under the influence of alcohol, drivers in a drunkenness state, or walkers in a drunkenness state (CONASET, 2016).

All these reports suggest that even though countries are making national policies and action plans (e.g., controlling the legal age for purchasing alcohol) (WHO, 2014), the problem of underage drinking has not yet been solved (Paschall, Grube, & Kypri, 2009). Many teenagers consume excess alcohol, making them susceptible to multiple risks, including the development of alcoholism (Squeglia, Jacobus, & Tapert, 2014). High ethanol consumption, even on a single occasion, triggers adverse effects on the CNS, which can remain over time (Kyzar and Pandey, 2015). Ethanol is a small molecule. Therefore, it can easily cross the plasmatic membrane and diffuse rapidly; affecting brain tissues, interfering with neuronal communication and depressing the neuronal activity of excitatory synapses (Oscar-Berman and Marinkovic, 2007). In neural cells, several structures are also modified by ethanol toxicity (Mukherjee, 2013), and among these, the mitochondria is an organelle that is particularly sensitive (Garcia-Ruiz, Kaplowitz, & Fernandez-Checa, 2014; Manzo-Avalos and Saavedra-Molina, 2010). Although the exact mechanism by which alcohol exerts its toxicity in the brain is not clear (Crews and Nixon, 2009; Guerri and Pascual, 2010), it is widely accepted that it induces oxidative stress (Albano, 2006) and promotes inflammation in neurons (Syapin, Hickey, & Kane, 2005). Mitochondria are the main producer of reactive oxygen species (ROS) in the brain (Gandhi and Abramov, 2012) and can also contribute to the inflammatory processes (Lopez-Armada, Riveiro-Naveira, Vaamonde-Garcia, & Valcarcel-Ares, 2013). In this review, we will focus on discussing the effects of alcohol on mitochondrial structure and function, highlighting the fact that mitochondrial alterations correlate with the time or amount of alcohol consumed. Finally, we propose that the mitochondria act as an important mediator in alcohol-induced toxicity; positioning it as a potential therapeutic target for the treatment of diseases associated with alcohol abuse during adolescence and their persistence until adulthood.

2 | ALCOHOL CONSUMPTION DURING ADOLESCENCE

In general, the first experiences involving alcohol consumption occur during adolescence (Spear, 2015). It is common that on this occasion the amount of ethanol consumed is excessive due to a lack of ethylic awareness (Spear and Varlinskaya, 2005). This high alcohol uptake leads to a rapid increase of blood alcohol concentration (BAC), which is usually measured as the percentage of alcohol in the blood (milliliter of ethanol per 1,000 milliliters of blood) (Jung and Namkoong, 2014). The velocity of alcohol ingest is also very important since adolescents often drink higher amounts in a short time; inducing a quick rise in the ethanol blood levels (Spear and Varlinskaya, 2005). This drinking habit generates higher transient damage to the CNS and could eventually produce consequences that persist over time (Mukherjee, 2013). Normally, a blood ethanol value of 0.10% is considered legally drunk (Jung and Namkoong, 2014); however in several countries, the legal normative is often stricter, considering a drunken state at 0.08% (Fell and Voas, 2014). Some countries even have a "zero-tolerance" rule, which applies to adolescents under 21-years old. In this case, the presence of alcohol in the blood is intolerable and corresponds to an infraction against the law (Chamberlain and Solomon, 2008).

When alcohol consumption is persistent, the BAC also increases. At a BAC of 0.02%, consumers begin to show the first effects of intoxication, including the sensation of relaxing, happiness and disinhibition (Jung and Namkoong, 2014). These symptoms progress and the person become more sociable and communicative (BAC 0.04%) (Donovan, 2004). Later, the BAC reaches 0.05%, compromising judgment, attention and some motor functions (Dry, Burns, Nettelbeck, Farquharson, & White., 2012). At this point the person becomes incapable of controlling their reactions, and

they become emotionally unstable, and their perception is altered, making driving impossible (Dry et al., 2012). At 0.08% coordination abilities are lost, hindering speech and walking, and at 0.1% there is a severe impairment of corporal control and reaction (Friedman, Robinson, & Yelland, 2011). The mental symptoms are immediately accompanied by vomiting at 0.15%. Other senses are also reduced, including vision (Jung and Namkoong, 2014). At 0.18%–0.25% the most prominent responses are confusion, disorientation, impulsivity or apathy, and lethargy (Dry et al., 2012). At these stages, as BAC continues to increase leading to complete loss of motor abilities, limited reactions and incontinence (0.25%–0.30%), and possibly loss of consciousness; reducing body temperature, circulation and respiration (0.30%–0.50%) (Jung and Namkoong, 2014). At levels of 0.37% or higher, this could leave to die. In general, BACs over 0.45% are lethal (Vonghia et al., 2008). All the symptoms described in response to ethanol intoxication are the result of severe alterations to the CNS (Dry et al., 2012). Alcohol directly inhibits excitatory synapses in the brain (Mukherjee, 2013), producing a depressant effect in critical regions that control responses, such as behavior and judgment (Abernathy, Chandler, & Woodward, 2010); movement and coordination (Oscar-Berman and Marinkovic, 2007); sleep and vital functions (Brower, 2001). These cerebral structures include the ventral striatum and prefrontal cortex (Abernathy et al., 2010), the cerebellum (Luo, 2015); the reticular activating system (Ali et al., 2013), and the medulla (Vonghia et al., 2008), respectively.

Adolescents experience several physiological symptoms the day after excessive alcohol consumption, even when blood alcohol levels have returned to zero (Spear and Varlinskaya, 2005). These symptoms are commonly known as a "hangover" which is characterized by a headache, nausea, fatigue, muscular pain, and decreased physical and mental abilities (Penning, van Nuland, Fliervoet, Olivier, & Verster, 2010). At the cerebral level, alterations as a result of intoxication by ethanol can be found (Penning et al., 2010). However, these physical symptoms disappear approximately 24 hours later, and adolescents are then willing to drink again (Squeglia et al., 2014). Among adults, alcohol is consumed at a slower rate, since it is linked to socialization and friendship (Bullers, Cooper, & Russell, 2001). Nowadays, alcohol consumption in adolescents has another purpose; to get drunk fast to have fun (Kuntsche et al., 2005). This is troubling behavior because this heavy drinking is recurrent, two or three times per week, especially during the weekend (Petit et al., 2014). This characteristic pattern of alcohol consumption among adolescents is known as "binge-drinking" and has severe consequences for brain function, which can remain throughout adulthood (Squeglia et al., 2014; Tapia-Rojas et al., 2017; Zahr et al., 2010).

Adolescents are often unaware of the risks associated with high alcohol consumption (Marshall, 2014). Regularly, alcohol produces two main problems in the brain: first, irreparable damage to brain cells (Squeglia et al., 2014); and second, this high alcohol consumption is the main risk for developing pathologies associated with excessive drinking, such as alcoholism (Marshall, 2014). Teens do not talk about alcoholism since they usually drink only on the weekend (Spear and Varlinskaya, 2005). However, the alcohol consumption during all weekends also can develop dependence and could be considered a type of alcoholism, leading to addiction (Garcia-Moreno, Exposito, Sanhueza, & Angulo, 2008). Some young people feel that they must drink to have fun, relate with others, and to feel safer (Donovan, 2004). Adolescents who depend on alcohol gradually start drinking during the week changing their habits and responsibilities (Donovan, 2004; Marshall, 2014). At this stage, the neuronal damage is greater, and some brain functions are lost as a consequence of the neurodegeneration observed in specific brain regions (Spanagel, 2009). Finally, alcohol dependence results in symptoms associated with "withdrawal syndrome" during periods when intake is limited (Bayard, McIntyre, Hill, & Woodside, 2004). Common symptoms include anxiety, irritability, sweating, insomnia, loss of appetite and in more severe cases fever, hallucinations and seizures (Kattimani and Bharadwaj, 2013). All these symptoms can be attributed to alterations observed in cerebral cells that persist even in the absence of alcohol (Hashimoto and Wiren, 2008).

In the following section, we will discuss the changes observed in neuronal cells after alcohol intoxication, either after a single episode of consumption or in more severe conditions of addiction and abstinence. We will highlight the effects of ethanol on the mitochondria under each scenario and how this compromises their function in the brain.

3 | MITOCHONDRIA: A CONTRIBUTOR TO ETHANOL TOXICITY

Mitochondria is an organelle whose main function is to carry out aerobic cellular respiration to produce energy in the form of ATP (Friedman and Nunnari, 2014). In aerobic organisms >90% of ATP originates in the mitochondria through the oxidative phosphorylation (OXPHOS), and the remaining 10% by anaerobic glycolysis (Ly and Verstreken, 2006). However, this is not the only role of the mitochondria, since it is also an important regulator ROS production(Murphy, 2009), redox cell balance, calcium homeostasis (Giorgi et al., 2012), and cell death (Estaquier, Vallette, Vayssiere, & Mignotte, 2012).

This organelle constitutes a complex, interconnected and highly dynamic network, maintained by opposing and

balanced events of mitochondrial fusion and fission (Archer, 2013) In mammals, mitochondrial fission is regulated by the Dynamin-related protein- 1 (Drp-1) and fission protein 1 (Fis1). These proteins are actively involved in the cleavage of membranes from the mitochondria by construction (Otera et al., 2013). The main regulators of mitochondrial fusion are the mitofusin proteins (Mfn 1 and 2) and the optical atrophy 1 protein (OPA1) (Liesa et al., 2009). Mfn 1 and 2 interact to coordinate the fusion of the outer mitochondrial membrane. Meanwhile, OPA1 is located in the intermembrane space and participates in the remodeling of mitochondrial ridges and fusion of the internal mitochondrial membrane (van der Bliek et al., 2013). Mitochondrial fusion and fission events usually occur in all cells under normal conditions (Liesa et al., 2009). However, mitochondrial fission is associated with conditions of metabolic stress, cellular damage and apoptosis (Reddy, 2014), whereas fusion is a related to cell repair and survival (Ni et al., 2015). Loss of the regulation in mitochondrial fission/fusion process is associated with alterations in mitochondrial function in certain neurodegenerative conditions (Mishra, 2016).

Increase in mitochondrial permeability is a characteristic symptom of mitochondrial impairment in the brain (Marzo et al., 1998; Perez and Quintanilla, 2017). This process is produced by the mitochondrial permeability transition pore (mPTP), which is a nonspecific high-conductance channel that is permeable to molecules up to 1.5 KDa; increasing membrane permeability to ions and small solutes (Haworth and Hunter, 1979; Hunter and Haworth, 1979a, 1979b). This structure consists of at least three proteins, the voltage-dependent anion channel (VDAC), an outer membrane protein of the mitochondria; the adenine nucleotide transporter, located on the internal membrane; and the mitochondrial matrix protein, cyclophilin D (CypD) (Halestrap, 2009). mPTP is opened by mitochondrial calcium overload, oxidative stress, and changes in the pH (Tsujimoto and Shimizu, 2007). Transient openings of this pore induce the release of excess calcium that accumulates in the mitochondrial matrix (Perez and Quintanilla, 2017). However, when mPTP is constantly open provokes permeabilization of the mitochondria and induce the release of pro-apoptotic factors leading, to cellular death (Rao et al., 2014).

Our brain consumes approximately 20% of the total energy pool produced by mitochondria (Grimm and Eckert, 2017). Neurons possess a large number of mitochondria throughout the dendrites and axons, and their correct function is necessary for the synapse (Sheng, 2014). Axonal mitochondria are very abundant, especially in the axonal terminals, due to the high energy demand of the presynaptic processes, the release of neurotransmitters, calcium regulation, and other synaptic processes (Cheng et al., 2010; Hollenbeck, 2005; Ly and Verstreken, 2006).

Regarding alcohol toxicity in the brain, ethanol uses several action mechanisms that explain its multiple effects on the body (Crews and Nixon, 2009). At the synapse, alcohol acts on the gamma-Aminobutyric acid (GABA) neurotransmitter, increasing chloride conductance, and thus decreasing neuronal activity (Wilcox et al., 2014). Alcohol also reacts with other neurotransmitters such as dopamine, norepinephrine, and serotonin (Sullivan, Harris, & Pfefferbaum, 2010). Since alcohol increases the production of free radicals, oxidative stress has also been reported as a molecular mechanism of ethanol neurotoxicity (Albano, 2006; Das and Vasudevan, 2007; Wu, Zhai, & Shi, 2006). Likewise, ethanol triggers inflammatory processes (Syapin et al., 2005) and reduces the expression and response to trophic factors (Crews, 2008). Over the last years, several studies have shown that alcohol can affect neurons by altering the mitochondrial function through the impairment of electron transport chain; generating oxidative stress and reducing energy production (Almansa et al., 2009; Manzo-Avalos and Saavedra-Molina, 2010). Here, we will discuss the toxic effects of ethanol on mitochondrial structure and function, and we will suggest that these mitochondrial alterations could be associated with the severity of alcohol intoxication. Principal changes produced in the mitochondria by ethanol intoxication are also summarized (Table 1).

3.1 | Heavy episodic drinking

Diverse studies have shown that adolescents are less sensitive to the toxic effects of ethanol compared with adults (Varlinskaya and Spear, 2004). These effects could be due to the high alcohol intake consumed by adolescents (Spear and Varlinskaya, 2005), and neuromaturation and neuronal adaptations process produced in the young brain (Arain et al., 2013; Spear, 2000). According to the National Institute on Alcohol Abuse and Alcoholism Advisory Council, the intake of around four or five alcoholic drinks on one occasion, in a short time lapse, is defined as a heavy drinking episode (Piasecki, Trela, & Mermelstein, 2017). This type of consumption is a common pattern in current adolescent drinkers, especially among teenagers, as shown in an international study; were 4.711 of 31.336 (13%) current drinkers reported heavy episodic drinking, and they were more likely to be young males (Smyth et al., 2015). In 2014, approximately 60.9 million of US drinkers presented this pattern, and a 23% of these people are 12-years old or older. The majority of episodic drinkers were young adults aged between 18 and 25 with a 37.7% (Hedden, 2015). In the Chilean population, studies showed that 16.2% reported heavy episodic drinking, where 28.3% were male drinkers and a 4.3% were female drinkers (Pena et al., 2017).

During alcohol intoxication, ethanol affects the inhibitory centers of the brain (Davies, 2003), and individuals can show

TABLE 1 Defects in mitochondrial health induced by different alcohol consumption patterns

Mitochondrial effect	Heavy episodic drinking	Alcohol hangover	Binge-drinking	AUDs	EW
Oxidative stress	Increased (Lee et al., 2005; Ozkol et al., 2017; Ramachandran et al., 2003; Schlorff et al., 1999)	Increased (Bustamante et al., 2012; Karadayian et al., 2015; Karadayian et al., 2017)	Increased (Ewenczyk et al., 2012; Pascual et al., 2007; Tapia-Rojas et al., 2017)	Increased (Auta et al., 2017; Casanas-Sanchez et al., 2016; Das and Vasudevan, 2007; Ji, 2012; Yan et al., 2016)	Increased (Jung, 2015; Jung et al., 2008; Parthasarathy et al., 2015)
Antioxidant defenses	Decreased (Ramachandran et al., 2003)	Decreased (Bustamante et al., 2012; Karadayian et al., 2015; Karadayian et al., 2017)	*No determined*	Decreased (Casanas-Sanchez et al., 2016; Das and Vasudevan, 2007; Ji, 2012)	*No determined*
Changes in mitochondrial dynamics	*No determined*	*No determined*	Altered (Tapia-Rojas et al., 2017)	*No determined*	*No determined*
Mitochondrial membrane potential	Loss (Ramachandran et al., 2001)	Loss (Karadayian et al., 2015)	Loss (Tapia-Rojas et al., manuscript in preparation)	Loss (Almansa et al., 2009)	Loss (Jung, 2015; Jung et al., 2008)
Changes in OXPHOS activity/expression	*No determined*	Reduced activity complex I-II-III and IV (Bustamante et al., 2012; Karadayian et al., 2015)	Increased expressions after 1–3 weeks; decreased expression after 7 weeks (Tapia-Rojas et al., manuscript in preparation)	Reduced expression Complexes I and V (Haorah et al., 2013)	Reduced expression Complex V (Jung and Metzger, 2015)
ATP production	Decreased (Budd and Nicholls, 1996; Liu et al., 2014)	Decreased (Bustamante et al., 2012)	Decreased (Tapia-Rojas et al., 2017)	Decreased (Casanas-Sanchez et al., 2016; Haorah et al., 2013; Reddy et al., 2013; Yan et al., 2016).	Decreased Increased (Jung, 2015; Jung et al., 2008; Parthasarathy et al., 2015)
Calcium concentrations	Increased (Elrod et al., 2010)	*No determined*	Increased (Tapia-Rojas et al., manuscript in preparation)	Increased (Ji, 2012)	Increased (Jung et al., 2008)
Opening mPTP	Yes, transient (Galluzzi et al., 2009; Lamarche et al., 2013)	Yes (Karadayian et al., 2015)	Decreased expression of mPTP proteins (Tapia-Rojas et al., 2017)	Yes (Almansa et al., 2009)	Yes, prolonged (Jung et al., 2008)
Apoptosis	Yes (Galluzzi et al., 2009; Guadagnoli et al., 2016; Heaton et al., 2013)	Yes (Bustamante et al., 2012)	Yes (Lacaille et al., 2015)	Yes (Auta et al., 2017; Haorah et al., 2013; Yan et al., 2016)	Yes (Hashimoto and Wiren, 2008; Jung et al., 2008)

This table summarizes the mitochondrial changes that result from heavy episodic drinking; hangover; binge-drinking; AUDs and EW. Among the mitochondrial alterations, we found changes in oxidative stress; reduction of antioxidant defenses; deregulation of mitochondrial dynamics; mitochondrial depolarization; defects in OXPHOS activity/expression, calcium deregulation and mPTP opening, loss of ATP production, and apoptosis.

signs of mental excitation (Avegno et al., 2016). As the blood alcohol levels rise, intoxication becomes more severe and central nervous system (CNS) depression becomes prevalent (Marshall, 2014; Mukherjee, 2013). At the cellular level, neural cells are also affected which has been described mainly through *in vitro* studies. Reports in cortical neurons (DIV6) show that acute ethanol intoxication induces changes in cell structure (Guadagnoli, Caltana, Vacotto, Gironacci, & Brusco, 2016). At this time *in vitro*, neurons undergo a period of constant adaptation to form mature synapses. Therefore alcohol toxicity could inhibit this process (Guadagnoli et al., 2016) and could even induce neuronal apoptosis (Guadagnoli et al., 2016). In glial cells, alcohol provokes the activation of signaling pathways related to the toll-like receptor 4, leading to neuroinflammation (Pla, Pascual, & Guerri , 2016) and impaired autophagy (Pla et al., 2016).

Oxidative stress was also significantly increased after acute ethanol exposure both in vitro and *in vivo* (Lee et al., 2005; Ozkol, Bulut, Balahoroglu, Tuluce, & Ozkol, 2017; Ramachandran et al., 2003; Schlorff, Husain, & Somani, 1999). For example, Wistar rats exposed for 1 hr to 1mL of absolute ethanol showed increased oxidative stress markers in the brain (Ozkol et al., 2017). A similar effect was observed in primary cultures of cortical neurons treated with 2.5 mg/mL ethanol for 24 hr. In these cells, ethanol induces a rapid oxidative stress response, which could be a consequence of mitochondrial damage that finally leads to apoptotic cell death (Lee et al., 2005; Ramachandran et al., 2003). Oxidative damage induced by ethanol is proposed to be the result of an imbalance between the oxidant response and antioxidant pathways (Ramachandran et al., 2003); since pretreatment with an antioxidant glutathione precursor prevented ROS production and finally inhibited alcohol-mediated apoptotic death (Ramachandran et al., 2003). Both oxidative stress and apoptosis are mitochondria-dependent processes (Estaquier et al., 2012; Murphy, 2009); therefore, the previously described reports highlight the importance of this organelle in ethanol toxicity. Complementary studies in cortical primary culture suggest that ethanol alters the mitochondrial membrane integrity, and these alterations could also contribute to cell death (Ramachandran et al., 2001). Altogether, these changes in the mitochondrial membrane and increased ROS production could result in decreased ATP production (Lopez-Armada et al., 2013). In fact, acute ethanol treatment of a neuronal cell line for 24 hr reduced ATP formation (Liu et al., 2014).

Mitochondria normally undergo degradation and biogenesis processes. An important regulator of mitochondrial biogenesis is the transcriptional co-activator peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PCG-1α) (Liu et al., 2014), which also regulates mitochondrial metabolism, antioxidant response, and energy function (Perez and Quintanilla, 2015; St-Pierre et al., 2006; Wareski et al., 2009). Interestingly, high ethanol exposure reduces PCG-1α expression, which could partially explain, the loss of mitochondrial function; since its overexpression protects against ethanol toxicity (Liu et al., 2014).

Several studies suggest that acute alcohol intoxication could lead to the opening of mPTP, inducing a loss of mitochondrial depolarization (Galluzzi, Blomgren, & Kroemer, 2009), alterations to calcium concentrations (Elrod et al., 2010), ROS production (Hou et al., 2014), reduced ATP formation (Budd and Nicholls, 1996), and finally cell death (Galluzzi et al., 2009). Interestingly, permeability induced by mPTP is an indirect effect of ethanol toxicity, because alcohol exposure of isolated mitochondria does not induce mPTP opening (Lamarche et al., 2013). Therefore, mPTP opening is only observed when intact neuronal cells are treated with alcohol (Lamarche et al., 2013). Additional studies showed that neuronal cultures present permanent mPTP opening after treatment with ethanol, leading to neuronal death (Lamarche et al., 2013); however, this effect is not observed in astrocyte cultures. In astrocytes, ethanol induces a transient, and not permanent, opening of mPTP (Lamarche et al., 2013). *In vivo* studies showed that ethanol treatment reduced oxygen consumption in the brain, an effect that persists over time while ethanol is present in the blood (Lamarche et al., 2013). During this period, animals showed cognitive alterations including impaired spatial learning and memory (Wozniak et al., 2004), and a decreased nociceptive response (Lamarche et al., 2013). The relation between the loss of cognitive abilities with mPTP opening is supported by treatment with mPTP opening inhibitors before to ethanol injection which effectively prevented these behavior alterations (Lamarche et al., 2013).

Finally, when mitochondrial and cellular damage is irreparable, neuronal cells may activate the apoptotic pathways (Estaquier et al., 2012). For example, neuronal cultures challenged with heavy alcohol concentrations presented a translocation of the apoptotic factor Bax to the mitochondria (Heaton et al., 2013). This event alters mitochondrial membrane potential (Heaton et al., 2013) and blocking the effect of anti-apoptotic proteins including Bcl-2 and Bcl-xl (Siler-Marsiglio et al., 2005). Similar effects were observed in other cellular models both *in vivo* and *in vitro* (Bhave, Snell, Tabakoff, & Hoffman, 1999; Hamre and West, 1993; Moore, Walker, & Heaton, 1999).

Altogether, these observations indicate that single exposure to heavy ethanol concentrations, as occurs in heavy episodic drinking, is sufficient to trigger harmful effects in the brain, affecting neuronal cells and their organelles including mitochondria. Most importantly, adverse changes in the mitochondria could lead to bioenergetics deficits and finally an ethanol-induced cellular death, if a high alcohol concentration is maintained for several hours (see Table 1).

3.2 | Alcohol hangover

Currently, there is no consensus regarding the definition of the hangover. However, this state it is characterized by a collection of different unpleasant symptoms that appears the day after an episode of heavy alcohol consumption when blood alcohol concentration return to zero (Van Schrojenstein Lantman, van de Loo, Mackus, & Verster, 2017c). The symptoms include a headache, diarrhea, anorexia, fatigue, nausea (Wiese, Shlipak, & Browner, 2000), and more frequently, feeling tired (Score 8.0), sleepiness (Score 7.6) and concentration/attention problems (Score 6.6) (van Schrojenstein Lantman, Mackus, van de Loo, & Verster, 2017b). Hangover is also related to problems on job performance, studying, physical activities and mood (van Schrojenstein Lantman et al., 2017b). Studies have shown that in the United States, hangover symptoms carry losses of 148 billion pounds due to decreased industrial productivity (Van Schrojenstein Lantman et al., 2017c). Other studies report that Dutch students aged 20 experienced approximately 2.7 hangover days per month, which had a duration of approximately 18 hr after their last drink (van Schrojenstein Lantman Mackus, Roth, & Verster, 2017a). Interestingly some ethanol effects, including hangover symptoms, are relatively less frequent in adolescents compared with adults (Spear and Varlinskaya, 2005; Squeglia et al., 2014). Interestingly, these same effects have been reported in rodents, whose adolescents are less sensitive than adults to acute ethanol effects, such as motor impairment and sedation, social inhibition and hangover-related hyperthermia as well as anxiety (Varlinskaya and Spear, 2004). Then, this could be one of the reasons why teens frequently repeat these drinking habits compared with adults (Squeglia et al., 2014); who experience alcohol adversity following a severe hangover episode (Moos, Schutte, Brennan, & Moos, 2009)

The effects of a hangover have been reported in different study models and showed substantial physiological and behavioral hangover-associated alterations (Gauvin et al., 1997; Gauvin, Cheng, & Holloway, 1993), including decreased locomotor activity and loss of motivation(Lal, Prather, & Rezazadeh, 1991). At the cellular level, the ethanol metabolite acetaldehyde is responsible for many of these alterations (Penning et al., 2010). Acetaldehyde has different adverse effects on the liver, including mitochondrial dysfunction (Helander and Tottmar, 1988). A similar effect is observed in the brain, where a loss of mitochondrial function is directly associated with the hangover (Bustamante, Karadayian, Lores-Arnaiz, & Cutrera, 2012; Karadayian et al., 2015; Karadayian et al., 2017). Interestingly, impaired motor activity observed in a hangover mice model is linked to a bioenergetics deficit as a consequence of mitochondrial dysfunction (Bustamante et al., 2012).

The control center for movement and coordination in the brain is the cerebellum; therefore most studies evaluating hangover have been carried out in cerebellar cells (Luo, 2015; Oscar-Berman and Marinkovic, 2007). The analysis of mitochondria isolated from the cerebellum of hangover mice reveals severe changes associated to mitochondrial damage (Karadayian et al., 2015). For example, in these mice, redox balance is dysregulated after ethanol intoxication. Also, superoxide dismutase (SOD) and the monoamine oxidase (MAO) activity was increased (Karadayian et al., 2015), instead both catalase (CAT), glutathione peroxidase (GPx), and nitric oxide synthase was decreased (Karadayian et al., 2015). Thus, ethanol in a hangover state induces a loss of oxidative defenses. Also, increased malate-glutamate and succinate-supported oxygen uptake, simultaneous to reduced activity of the mitochondrial Complex (I–IV) and loss of the mitochondrial membrane potential (Karadayian et al., 2015) was reported in the hangover. Altogether, these alterations finally lead to mPTP opening in the mitochondria in the cerebellum (Karadayian et al., 2015).

Among the hangover symptoms, we also found changes in judgment, attention, motivation, and mood (van Schrojenstein Lantman et al., 2017b) which functions are related to the brain cortex. Further studies in cortical isolated mitochondria showed redox imbalance, indicated by increased hydrogen peroxide (H2O2) levels, decreased NO expression (Bustamante et al., 2012) and decreased CAT and SOD enzyme activity. Also, hangover protocol increased MAO activity, and decreased GSH/GSSG ratio in synaptic mitochondria, accompanied by reduced GPx and Glutathione reductase (GR) enzymes and increased Glutathione S-transferase (Karadayian et al., 2017). The relevance of the oxidative damage during hangover (Marino, Aksenov, & Kelly, 2004) is supported by treatment with a MAO inhibitor (Karadayian et al., 2017), melatonin (Cardinali and Pevet, 1998; Karadayian et al., 2014; Manda, Ueno, & Anzai, 2007; Reiter, Paredes, Korkmaz, Manchester, & Tan, 2008; Tan et al., 2000), or by treatment with natural antioxidant products that prevent oxidative stress and negative motor changes (Wang, Li, Zhang, Zhou, Li, & Li, 2016).

In addition to oxidative stress observed during the hangover, other mitochondrial alterations have been described such as the reduced activity of the mitochondrial Complexes I–III, II–III, and IV (Bustamante et al., 2012), as well as the mitochondrial membrane potential (Bustamante et al., 2012). Finally, these changes make the mitochondria more sensitive to damage, inducing the opening of mPTP and reducing neuronal survival (Bustamante et al., 2012). Interestingly, melatonin pre-treatment also prevented the impairment of mitochondrial function during alcohol hangover (Karadayian et al., 2014).

Therefore, ethanol hangover is a state where neural cells and the mitochondria are particularly vulnerable to damage,

even in ethanol absence. In this condition the mitochondria produce high levels of ROS, reducing ATP production and activating mPTP, leading to cell death (Table 1). All these events contribute to altered behavior and deficient motor activity during the hangover condition.

3.3 | Binge-drinking

This alcohol consumption pattern is characterized by drinking five or more alcoholic beverages, during consecutive days followed by nondrinking days, intermittently (Merrill and Carey, 2016; SAMHSA, 2007). Studies show that in the United States, 1% of the population aged between 12 and 15 had this type of alcohol pattern, and this percentage increased with age, reaching values of 10.8% in adolescents between 18 and 25 years old (Gass et al., 2014). In fact, this is a recurrent pattern of alcohol consumption during the weekend, were adolescents consume higher amounts of alcohol in a short period (Garcia-Moreno et al., 2008). Survey data from the US shows that approximately 24.5% of the population reported to being binge-drinkers, with Native Americans and Alaskan Natives having the highest percentage (30.6%). Reports also showed that the prevalence of current drinking with binge drinking in the United States is not significantly different between boys and girls (29.5% and 27.9%, respectively) (Miller, Naimi, Brewer, & Jones, 2007). In the Chilean National Health Survey (2010), 89.07% of males and a 70.83% of females presented binge-drinking patterns over the last month. Even though binge drinking is becoming an increasingly common consumption pattern (Schulteis, Archer, Tapert, & Frank, 2008), and little is known about its effects and the mechanism involved in ethanol toxicity. Therefore, it is important to understand the harmful effects of this consumption (Orellana et al., 2017), since the adolescent brain is more vulnerable to ethanol toxicity (Slawecki, Thorsell, & Ehlers, 2004; Spear, 2015) and the cellular impairment could persist over time and affects the brain function in adulthood.

Ethanol consumption in a binge-drinking pattern is associated with depression (Briones and Woods, 2013), possibly by a mechanism implicating increased death of hippocampal neural progenitor cells, resulting in decreased adult neurogenesis (Briones and Woods, 2013). Likewise, ethanol binge drinking can activate the inflammatory process by activating innate immune receptors TLRs and potentiate the expression of cytokines such as TNFα and IL-1β (Pascual, Pla, Minarro, & Guerri, 2014). Also, alcohol provokes demyelination, reducing myelin basic protein and myelin oligodendrocyte glycoprotein expression levels in the cortex of an animal model of binge-drinking (Pascual et al., 2014). All the molecular alterations caused by a binge-drinking could contribute to the loss of cognitive abilities associated with the prefrontal cortex and hippocampus function in adult animals (Gass et al., 2014; Ledesma, Miquel, Pascual, Guerri, & Aragon, 2014). Molecular alterations were also found in the circuits associated to reward, and addiction since binge drinking rodents increased their resistance to the extinction of ethanol-seeking behavior (Gass et al., 2014). Further studies in adolescent rats exposed to a binge drinking protocol by intraperitoneal (i.p) injections of alcohol (3.0 g/kg) (Pascual, Blanco, Cauli, Minarro, & Guerri, 2007) had impaired conditional learning, motor performance and recognition memory 24-hr post-treatment and also during the adulthood (Pascual et al., 2007).

At the molecular level, the binge-drinking administration increased cyclooxygenase and inducible NOS (iNOS) protein levels and activates processes associated with cell death in the cortex, hippocampus, and cerebellum, 24 hr after injection (Pascual et al., 2007). Also, detrimental effects have been found in the insulin, and IGF signaling, which could be associated with the reduced motor abilities described (Ewenczyk, Ziplow, Tong, Le, & de la Monte, 2012). Also, binge-drinking induced a transient increase of the ventricular brain volume, decreasing N-acetyl aspartate (NAA) and creatine levels, and increasing the number of compounds formed by choline in the hippocampus (Zahr et al., 2010). Binge-drinking also stimulates the expression of apoptotic factors both in adolescent and adult mice (Lacaille et al., 2015). All the molecular defects described could be directly or indirectly associated with mitochondrial damage. In fact, alterations in insulin/IGF-1 signaling are related to oxidative stress as a consequence of mitochondrial dysfunction (Ewenczyk et al., 2012) as well as the changes observed in NAA production (Zahr et al., 2010); however, studies that focus on mitochondrial function during ethanol binge-drinking are scarce.

We recently performed a detailed study evaluating the mitochondrial changes induced by a binge-drinking episode during adolescence and its repercussions in adulthood (Tapia-Rojas et al., 2017). In this study, we exposed adolescent rats PND25to a single binge-like ethanol episode though i.p injections (Tapia-Rojas et al., 2017). The hippocampus of treated rats was evaluated at 1, 3, or 7 weeks after the binge-protocol. Our findings showed that binge-drinking induce a rapid oxidative response 1-week post-treatment (Tapia-Rojas et al., 2017) and altered Drp1, Fis1, Mfn1, Mfn2, and Opa1 proteins levels (Tapia-Rojas et al., 2017). These results suggest an imbalance in both the oxidative response and mitochondrial fission/fusion events 1–3 weeks post-treatment (Tapia-Rojas et al., 2017). Interestingly, these alterations were compensated 7 weeks post-treatment. In contrast, reduced ATP formation was reported, reaching its peak 7 weeks post-binge-ethanol exposure, indicating a loss of the bioenergetics function of the mitochondria over time (Tapia-Rojas et al., 2017). Finally, we observed activation of inflammatory processes in adulthood, 7 weeks after treatment (Tapia-Rojas et al., 2017). These findings suggest that in the

absence of ethanol mitochondrial damage progresses over time, and highlight the importance of preventing heavy ethanol consumption during adolescence.

We also detected changes that could be related to both cellular and mitochondrial protection. We observed reduced VDAC and Cyp-D protein expression, suggesting that mPTP opening may be reduced (Tapia-Rojas et al., 2017); likewise, we report increased Nuclear factor erythroid-2 related factor 2 (Nrf2) levels (Tapia-Rojas et al., 2017). This transcription factor is associated with the regulation of oxidant balance, inflammatory process, and repair of mitochondrial function (Dinkova-Kostova and Abramov, 2015), therefore, suggesting that it could also be restoring oxidative balance.

In summary, our reports et al. indicate that the mitochondria play a fundamental role in alcohol toxicity during binge-drinking consumption; and most importantly, mitochondrial damage persists and can progress over time, even until adulthood when ethanol is absent.

3.4 | Alcohol use disorders

Alcohol use disorders (AUDs) consisting of a pattern of drinking habits characterized by an intense intake of alcohol (Mehta, 2016; Walter, Denmark, Kozell, & Buck, 2016), which causes damage to health, and even physical or mental harm (Haorah, Rump, & Xiong, 2013; Linhart, Bartsch, & Seitz, 2014; Mehta, 2016; Wu et al., 2006). This is considered a synonym of alcoholism, a disease which generally results in the development of tolerance and dependence (Mehta, 2016; Rando et al., 2011; Trantham-Davidson and Chandler, 2015), and according to the US Centers for Disease Control and Prevention is the third cause of preventable death in the United States (NIAAA, 2007). The global prevalence of AUDs in 2010 was 4.1%, being Europe the continent with the highest percentage, reaching values of 7.5% (WHO, 2014). Also, AUDs are significantly more prevalent among males, with the highest prevalence (12.6%) in Europe, while the highest prevalence among females (3.2%) is seen in the Americas (WHO, 2014). In the United States, the prevalence of AUDs is 7.8%. Meanwhile, this value is lower in Chile (5.0%) (WHO, 2014). It seems that the adolescent population is more vulnerable to chronic alcohol exposure than adults (Varlinskaya and Spear, 2004). Adolescents begin to show the first symptoms of alcohol abuse and dependence after 7 months of initiating regular drinking; meanwhile, adults present these symptoms approximately 3 years after persistent ethanol consumption (Deas, Riggs, Langenbucher, Goldman, & Brown, 2000). Also, adolescents are more prone to develop AUDs when they drink at least once a month for 6 months or more (Deas et al., 2000).

Increased impulsiveness, anxiety, and loss of control of behavior affecting executive functions are among the neurobiological changes induced by chronic ethanol consumption (Wackernah, Minnick, & Clapp, 2014), as a consequence of the cerebral activity damage produced in several brain cortex regions (Abernathy et al., 2010). Also, motor problems were observed which were caused by the neurodegenerative processes, which are activated in neural cells (Fitzpatrick, Jackson, & Crowe, 2008), involving oxidative signaling pathways and excitotoxicity events (Wackernah et al., 2014). Activation of inflammatory pathways in the brain also contributes to ethanol toxicity (Alfonso-Loeches et al., 2016; Fernandez, Lew, Vedder, & Savage, 2017). All these deleterious effects result in altered synaptic transmission, inducing changes in the synthesis and release of glutamate, dopamine and GABA neurotransmitters and, therefore, in the activation of its respective receptors (Fernandez et al., 2017; Ji, 2012; Trantham-Davidson and Chandler, 2015).

Due to the high energy demand of the synapses, behavior impairment is linked to deficient mitochondrial performance (Almansa et al., 2009; Haorah, Padmavathi, Kavitha, Saradamma, & Varadacharyulu, 2013; Reddy et al., 2013). As part of the ethanol metabolism, acetaldehyde is formed and is the main responsible for the severe damage observed in neuronal cells. Acetaldehyde promotes ROS formation and induces apoptotic cell death (Auta, Zhang, Pandey, & Guidotti, 2017; Yan, Zhao, & Zhang, 2016), which finally results in brain function damage (Casanas-Sanchez, Perez, Quinto-Alemany, & Diaz, 2016; Reddy et al., 2013). Supporting the idea that the mitochondria mediate ethanol toxicity, chronic ethanol treatment in rats promotes the production of ROS and reactive nitrogen species (Casanas-Sanchez et al., 2016; Das and Vasudevan, 2007; Ji, 2012). These events favor lipidic peroxidation of neural membranes (Das and Vasudevan, 2007), increasing the activity of NADPH oxidase and NOS enzymes and reducing the activity of SOD, CAT, GPx, and GR enzymes (Casanas-Sanchez et al., 2016; Das and Vasudevan, 2007; Ji, 2012). Normally, the high production of oxidative molecules is associated with a reduced efficiency of the respiratory chain activity. In fact, this was also observed in chronic ethanol treated rats (Casanas-Sanchez et al., 2016; Das and Vasudevan, 2007; Ji, 2012).

Another mitochondrial function is the maintenance of calcium homeostasis. Interestingly, chronic ethanol administration also altersCa^{+2} regulation, increasing cytoplasmic Ca^{+2} levels, which in turn induces more mitochondrial damage through ROS formation and impairs phosphorylative respiration (Ji, 2012). Finally, all these events result in changes in the expression of mitochondrial Complexes I and V (ATP synthase) (Haorah et al., 2013), leading to a bioenergetics deficit as is indicated by low ATP concentrations (Casanas-Sanchez et al., 2016; Das and Vasudevan, 2007; Haorah et al., 2013; Reddy et al., 2013; Yan et al., 2016).

Along with the mitochondria's reduced capacity to produce ATP, reduced glucose availability during chronic

ethanol exposure can also be observed (Haorah et al., 2013). Altogether, these negative mitochondrial effects, mediated by ethanol exposure, promote cytochrome-c release (Haorah et al., 2013), suggesting that ethanol induces irreparable damage to the cell and results in neuronal death (Table 1). AUDs could act via this mechanism, shown by a gradual loss of cognitive and motor abilities.

3.5 | Ethanol withdrawal

Chronic ethanol consumption can cause the ethanol withdrawal (EW) syndrome when alcohol intake is suddenly stopped or decreased (Bayard et al., 2004; Jung and Mallet, 2017; Spanagel, 2009). This syndrome includes tremors, seizures, and other neurological sequelae, and makes alcoholics relapse into heavy drinking due to their lack of tolerance (Prakash, Setlur, & Saini, 2010; Spanagel, 2009; Walter et al., 2016). The symptoms are diverse, depending on the severity and time of AUD before the withdrawal episode (Bayard et al., 2004). In general, whereas more young appear the alcoholism, more severe is the ethanol syndrome manifestation (Bayard et al., 2004). In the brain, studies have reported that EW reduces the number of post-synaptic structures (dendritic spines) in cerebral regions, including the amygdala and prefrontal cortex (Kyzar and Pandey, 2015; Rando et al., 2011); explaining the cognitive alterations observed during the abstinence period.

In regards to cellular mechanisms that explain alcohol withdrawal, the effects are a consequence of excitatory processes activated in neurons of cerebral regions such as the cerebellum (Hoffman, 1995). Excitotoxicity observed during withdrawal is the result of a primary activation of inhibitory GABA synapses by ethanol (Carta, Mameli, & Valenzuela, 2004). Over time, ethanol concentration gradually decreases due to the metabolization of this molecule, which then leads to over-activation of excitatory transmission (Li, Chin, & Chueh, 2004). Thus, excessive activity of the glutamatergic synapses induces the activation of both α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid and N-methyl-D-aspartate receptors (Li et al., 2004). The direct outcome of high glutamate concentrations in the synapses, and binding to its receptor, is increased Ca^{2+} concentration within the cell (Nguyen et al., 2011), even greater than the concentration observed in the presence of alcohol (Netzeband, Schneeloch, Trotter, Caguioa-Aquino, & Gruol, 2002; Virmani, Majchrowicz, Swenberg, Gangola, & Pant, 1985). Also, withdrawal leads to ROS overproduction and decreased antioxidant defenses (Jung, 2015). Thus, excitotoxicity can finally result in neuronal death (Nguyen et al., 2011).

Interestingly, the effects previously described during a withdrawal episode also could be linked to mitochondrial alterations (Jung, 2015; Luo, 2015). Calcium homeostasis and neuronal death are two key mitochondrial functions. Therefore, the drastic increase in Ca^{2+} impedes the mitochondria's ability to buffer calcium levels. Complementary studies support mitochondrial dysfunction since increased lipid peroxidation, and mitochondrial protein oxidation is detected in the cortex, hippocampus and mainly in the cerebellum (Jung, Yan, Forster, & Simpkins, 2008). In the latter, a bioenergetics deficit is detected, indicated by reduced expression of the mitochondrial complex V (Jung and Metzger, 2015) and ATP production in neurons (Follesa et al., 2003). Finally, the higher calcium concentrations associated with increased oxidative stress induce mPTP opening in a permanent and nontransient manner (Jung et al., 2008), and activate pro-apoptotic genes (Hashimoto and Wiren, 2008). Therefore, during withdrawal, as well as during other alcohol consumption patterns, the mitochondria play a major role in ethanol toxicity (Table 1).

3.6 | Mitochondrial damage as an indicator of ethanol intoxication severity

As discussed in the previous section and summarized in Table 1, ethanol exposure induces negative changes that affect mitochondrial function. These alterations include (a) increased ROS production (Albano, 2006; Das and Vasudevan, 2007), (b) calcium deregulation, (Giorgi et al., 2012), (c) mitochondrial respiration impairment (Bustamante et al., 2012; Jung and Metzger, 2015; Karadayian et al., 2015), (4) reduced ATP production (Jung, 2015; Ramachandran et al., 2001; Reddy et al., 2013); and finally, (5) mPTP opening (Jung, 2015; Karadayian et al., 2015). All these events, in turn, could result in neuronal death (Bustamante et al., 2012; Heaton et al., 2013; Lacaille et al., 2015).

Interestingly, alcohol-induced changes indicate that mitochondrial damage correlates with the amount and time of alcohol consumption. For example, in heavy episodic drinking the acute ethanol intoxication promotes redox state imbalance (Lee et al., 2005; Ramachandran et al., 2003) and reduce ATP production (Budd and Nicholls, 1996; Liu et al., 2014), which in turn induces a transient opening of mPTP (Galluzzi et al., 2009; Lamarche et al., 2013) and neural death (Galluzzi et al., 2009) (Fig. 1). When drinking stops, the BAC is gradually reduced until it disappears. Thus, during a hangover, in the absence of ethanol (Penning et al., 2010), the mitochondrial modifications persist over time, inducing the loss of mitochondrial membrane potential (Karadayian et al., 2015), and reducing the activity of the mitochondrial Complexes I, III, and IV(Bustamante et al., 2012; Karadayian et al., 2015) necessary for ATP formation (Bustamante et al., 2012). Additionally, heavy episodic drinking can also generate dependence, developing AUDs such as alcoholism (Mehta, 2016). In this condition, mitochondrial damage is exacerbated and adds to the alterations described after excessive ethanol exposure the loss of the membrane

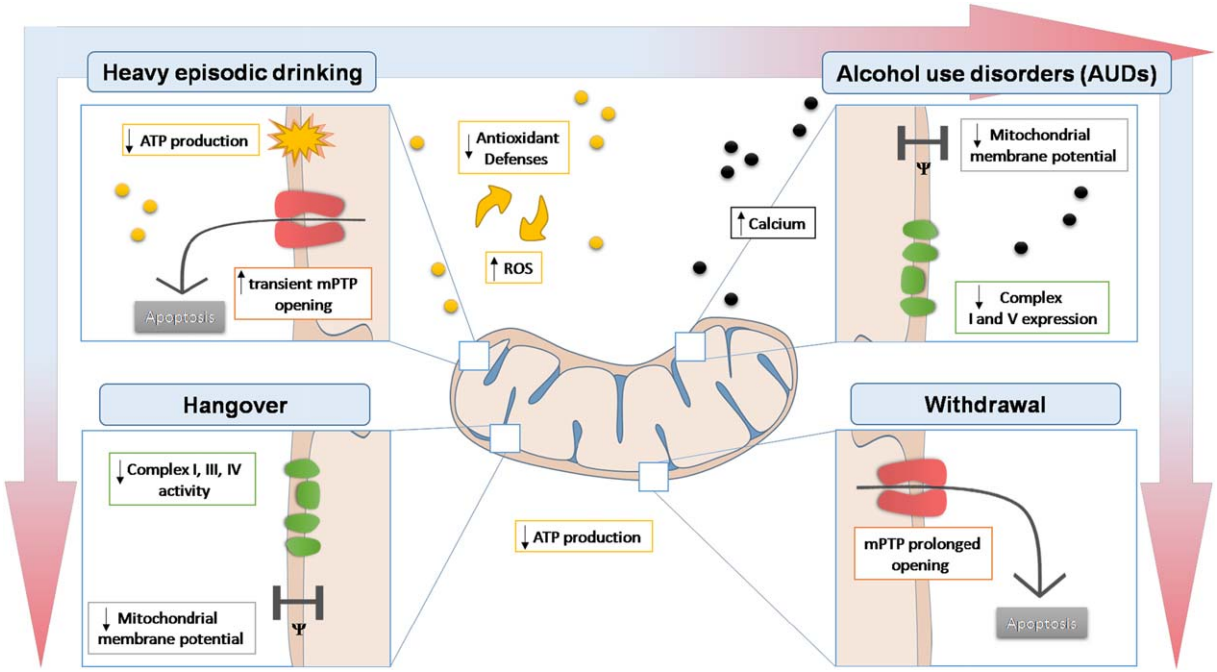

FIGURE 1 Mitochondrial damage induced by ethanol consumption. Representative scheme highlights the mitochondrial changes in response to ethanol exposure. As is indicated by the arrows, there is a relation between mitochondrial dysfunction and the severity of ethanol exposure; heavy episodic drinking results in increased ROS decreased ATP production and a temporary opening of the mPTP. In hangover condition (BAC 0.0%), decreased activity of several complexes from the electron transporter chain and the loss of mitochondrial membrane potential also appear, aggravating the mitochondrial dysfunction. When the alcohol uptake persists, AUDs are developed, and higher mitochondrial Ca + 2 concentrations are described; and finally, in EW syndrome, the prolonged opening of mPTP is present, indicating an irreparable mitochondrial damage

mitochondrial potential (Almansa et al., 2009) and reduced expression of I and V complexes (Haorah et al., 2013). Finally, during alcohol withdrawal state, mitochondrial damage is severe, leading to the prolonged opening of mPTP (Jung et al., 2008) that triggers neuronal death (Hashimoto and Wiren, 2008). With all these antecedents, we could propose the mitochondrial alterations as a potential indicator of the severity of alcohol intoxication, and eventually, could be used as a potential therapeutic target to treat disorders ethanol-related or prevent its apparition.

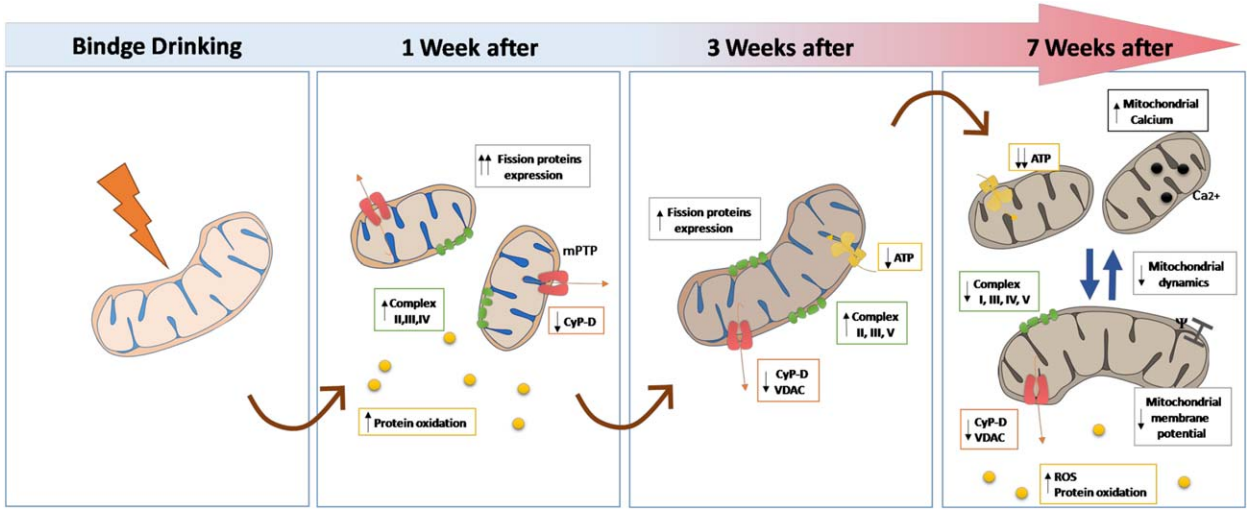

FIGURE 2 Ethanol binge-drinking episode during adolescence damages the mitochondrial structure and function over time. Binge-drinking ethanol consumption during the adolescence is sufficient to induce detrimental changes in the mitochondria, which occur until 7 weeks after alcohol exposure. During 1 week after the binge protocol, hippocampal cells have increased protein oxidation, suggesting a pro-fission state and possessing reduced levels of Cyp-D. After 3 weeks is detected a decreased ATP production and a reduced expression of VDAC. Finally, 7 weeks post-treatment, a more severe mitochondrial dysfunction is suggested, due to a decreased mitochondrial dynamic state, loss of mitochondrial membrane potential, increased mitochondrial calcium, reduced expression of mitochondrial complexes, and a higher deficiency in ATP production

A particular situation is observed after binge-drinking, because mitochondrial alterations observed after binge drinking are more drastic compared with one heavy drinking episode, and persist over time, without generating dependence as occurs in AUDs. We discuss this point in Figure 2 where ethanol binge-drinking exposure triggers effects that appear up to 7 weeks after the consumption has stopped (Tapia-Rojas et al., 2017). The primary negative changes are observed at 1-week post-exposure, rapidly inducing ROS production and mitochondrial fission events (Tapia-Rojas et al., 2017). Subsequently, at 3 weeks post-ethanol treatment, a deficiency in ATP production is evident (Tapia-Rojas et al., 2017) and finally, at 7 weeks post-ethanol-binge, mitochondria presented a deregulation in mitochondrial dynamics (Tapia-Rojas et al., 2017), depolarization, calcium deregulation and reduced expression of mitochondrial Complexes I, III–V (data not shown, Tapia-Rojas et al., manuscript in preparation). These changes are suggesting that binge-drinking ethanol consumption is a rapid transition between acute and chronic ethanol intoxication in the absence of addictive behaviors. It is important to highlight this state, especially since this is a normal condition is becoming more frequent in the adolescent population. In most cases, teenagers believe that heavy alcohol consumption will not have further repercussions. However, mitochondrial alterations persist apparently as innocuous changes but likely have significant influences on the neural circuits and finally in brain function over an extended period (Hollenbeck, 2005; Ly and Verstreken, 2006; Tong, 2007).

4 | CONCLUSIONS

Adolescence is a transition period between childhood and adulthood, in which multiple physical and social changes occur. In the adolescent brain, diverse cellular and molecular adaptations occur as part of the neuromodulation process. Therefore, adolescence is a stage particularly sensitive to the use and abuse of drugs, mainly alcohol. Excessive alcohol uptake among adolescents is worrying, since the age for initiating consumption has declined, and the amount of alcohol consumed has increased. It is fundamental that the young population is aware of the effects of ethanol intoxication on brain cells. Here we proposed the mitochondria as an important target of alcohol toxicity and we also suggested that mitochondrial alterations could be evaluated as an indicator of the severity of alcohol-induced brain damage. Additionally, all the antecedents summarized in our review place the mitochondria as a therapeutic target to treat the detrimental effects of alcohol abuse. Future efforts in our laboratory will focus on evaluating potential signaling pathways that could be involved in mitochondrial dysfunction, and we will place particular emphasis on the melanocortin system that participates in reward and addictive behaviors (Orellana et al., 2017).

ORCID

Cheril Tapia-Rojas http://orcid.org/0000-0002-7084-0318

REFERENCES

Abernathy, K., Chandler, L. J., & Woodward, J. J. (2010). Alcohol and the prefrontal cortex. *International Review of Neurobiology*, *91*, 289–320.

Albano, E. (2006). Alcohol, oxidative stress and free radical damage. *The Proceedings of the Nutrition Society*, *65*(3), 278–290.

Alfonso-Loeches, S., Urena-Peralta, J., Morillo-Bargues, M. J., Gomez-Pinedo, U., & Guerri, C. (2016). Ethanol-induced TLR4/NLRP3 neuroinflammatory response in microglial cells promotes leukocyte infiltration across the BBB. *Neurochemical Research*, *41*(1–2), 193–209.

Ali, S., Nathani, M., Jabeen, S., Yazdani, I., Mouton, C. D., Bailey, R. K., … Riley, W. J. (2013). Alcohol: The lubricant to suicidality. *Innovations in Clinical Neuroscience*, *10*(1), 20–29.

Almansa, I., Fernandez, A., Garcia-Ruiz, C., Muriach, M., Barcia, J. M., Miranda, M., … Romero, F. J. (2009). Brain mitochondrial alterations after chronic alcohol consumption. *Journal of Physiology and Biochemistry*, *65*(3), 305–312.

Arain, M., Haque, M., Johal, L., Mathur, P., Nel, W., Rais, A., … Sharma, S. (2013). Maturation of the adolescent brain. *Neuropsychiatric Diseas and Treatment*, *9*, 449–461.

Archer, S.L. (2013). Mitochondrial dynamics–mitochondrial fission and fusion in human diseases. *The New England Journal of Medicine*, *369*, 2236–2251.

Auta, J., Zhang, H., Pandey, S. C., & Guidotti, A. (2017). Chronic Alcohol Exposure Differentially Alters One-Carbon Metabolism in Rat Liver and Brain. *Alcoholism, Clinical and Experimental Research*, *41*(6), 1105–1111.

Avegno, E. M., Salling, M. C., Borgkvist, A., Mrejeru, A., Whitebirch, A. C., Margolis, E. B., … Harrison, N. L. (2016). Voluntary adolescent drinking enhances excitation by low levels of alcohol in a subset of dopaminergic neurons in the ventral tegmental area. *Neuropharmacology*, *110*, (Pt A):386–395.

Bayard, M., McIntyre, J., Hill, K. R., & Woodside, J. Jr. (2004). Alcohol withdrawal syndrome. *American Family Physician*, *69*(6), 1443–1450.

Bhave, S. V., Snell, L. D., Tabakoff, B., & Hoffman, P. L. (1999). Ethanol sensitivity of NMDA receptor function in developing cerebellar granule neurons. *European Journal of Pharmacology*, *369*(2), 247–259.

Bonnie, R. J., & O'connell, M. E. (2004). Reducing Underage Drinking: A Collective Responsibility. National Research Council (US) and Institute of Medicine (US) Committee on Developing a Strategy to Reduce and Prevent Underage Drinking. AQ: Please provide complete information for reference Bonnie & O'connell (2004), CONASET CNdSdT (2016), NIAAA NIoHNIoAAaA (2007), SAMHSA (2013), SENDA OCdD (2014), WHO (2014).]

Briones, T. L., & Woods, J. (2013). Chronic binge-like alcohol consumption in adolescence causes depression-like symptoms possibly mediated by the effects of BDNF on neurogenesis. *Neuroscience*, *254*, 324–334.

Brower, K. J. (2001). Alcohol's effects on sleep in alcoholics. *Alcohol Res Health*, *25*(2), 110–125.

Budd, S. L., & Nicholls, D. G. (1996). Mitochondria, calcium regulation, and acute glutamate excitotoxicity in cultured cerebellar granule cells. *Journal of Neurochemistry*, *67*(6), 2282–2291.

Bullers, S., Cooper, M. L., & Russell, M. (2001). Social network drinking and adult alcohol involvement: A longitudinal exploration of the direction of influence. *Addictive Behaviors*, *26*(2), 181–199.

Bustamante, J., Karadayian, A. G., Lores-Arnaiz, S., & Cutrera, R. A. (2012). Alterations of motor performance and brain cortex mitochondrial function during ethanol hangover. *Alcohol*, *46*(5), 473–479.

Cardinali, D. P., & Pevet, P. (1998). Basic aspects of melatonin action. *Sleep Medicine Reviews*, *2*(3), 175–190.

Carta, M., Mameli, M., & Valenzuela, C. F. (2004). Alcohol enhances GABAergic transmission to cerebellar granule cells via an increase in Golgi cell excitability. *Journal of Neuroscience*, *24*(15), 3746–3751.

Casanas-Sanchez, V., Perez, J. A., Quinto-Alemany, D., & Diaz, M. (2016). Sub-toxic ethanol exposure modulates gene expression and enzyme activity of antioxidant systems to provide neuroprotection in hippocampal HT22 Cells. *Frontiers in Physiology*, *7*, 312.

CONASET CNdSdT. (2016). Causas de siniestros (2000 – 2016).

Crews, F. T. (2008). Alcohol-related neurodegeneration and recovery: Mechanisms from animal models. *Alcohol Research & Health*, *31*(4), 377–388.

Crews, F. T., & Nixon, K. (2009). Mechanisms of neurodegeneration and regeneration in alcoholism. *Alcohol and Alcoholism*, *44*(2), 115–127.

Chamberlain, E., & Solomon, R. (2008). Zero blood alcohol concentration limits for drivers under 21: Lessons from Canada. *Injury Prevention*, *14*(2), 123–128.

Cheng, A., Hou, Y., & Mattson, M. P. (2010). Mitochondria and neuroplasticity. *ASN Neuro*, *2*, e00045.

Das, S. K., & Vasudevan, D. M. (2007). Alcohol-induced oxidative stress. *Life Sciences*, *81*(3), 177–187.

Davies, M. (2003). The role of GABAA receptors in mediating the effects of alcohol in the central nervous system. *Journal of Psychiatry & Neuroscience*, *28*(4), 263–274.

Dawson, D. A., Goldstein, R. B., Chou, S. P., Ruan, W. J., & Grant, B. F. (2008). Age at first drink and the first incidence of adult-onset DSM-IV alcohol use disorders. *Alcoholism: Clinical and Experimental Research*, *32*(12), 2149–2160.

Deas, D., Riggs, P., Langenbucher, J., Goldman, M., & Brown, S. (2000). Adolescents are not adults: Developmental considerations in alcohol users. *Alcoholism: Clinical and Experimental Research*, *24*(2), 232–237.

Dinkova-Kostova, A. T., & Abramov, A. Y. (2015). The emerging role of Nrf2 in mitochondrial function. *Free Radical Biology & Medicine*, *88*(Pt B), 179–188.

Donovan, J. E. (2004). Adolescent alcohol initiation: A review of psychosocial risk factors. *Journal of Adolescent Health*, *35*(6), 529 e527-518.

Dry, M. J., Burns, N. R., Nettelbeck, T., Farquharson, A. L., & White, J. M. (2012). Dose-related effects of alcohol on cognitive functioning. *PLoS One*, *7*(11), e50977.

Elrod, J. W., Wong, R., Mishra, S., Vagnozzi, R. J., Sakthievel, B., Goonasekera, S. A., … Molkentin, J. D. (2010). Cyclophilin D controls mitochondrial pore-dependent Ca(2+) exchange, metabolic flexibility, and propensity for heart failure in mice. *The Journal of Clinical Investigation*, *120*(10), 3680–3687.

Estaquier, J., Vallette, F., Vayssiere, J. L., & Mignotte, B. (2012). The mitochondrial pathways of apoptosis. *Advances in Experimental Medicine and Biology*, *942*, 157–183.

Ewenczyk, A., Ziplow, J., Tong, M., Le, T., & de la Monte, S. M. (2012). Sustained impairments in brain insulin/igf signaling in adolescent rats subjected to binge alcohol exposures during development. *Journal of Clinical and Experimental Pathology*, *2*(2), 106. doi: 10.4172/2161-0681.1000106

Faden, V. B., & Goldman, M. (2004). Alcohol and development in youth–a multidisciplinary overview. Introduction. *Alcohol Research & Health*, *28*(3), 107–108.

Fell, J. C., & Voas, R. B. (2014). The effectiveness of a 0.05 blood alcohol concentration (BAC) limit for driving in the United States. *Addiction*, *109*(6), 869–874.

Fernandez, G. M., Lew, B. J., Vedder, L. C., & Savage, L. M. (2017). Chronic intermittent ethanol exposure leads to alterations in brain-derived neurotrophic factor within the frontal cortex and impaired behavioral flexibility in both adolescent and adult rats. *Neuroscience*, *348*, 324–334.

Fitzpatrick, L. E., Jackson, M., & Crowe, S. F. (2008). The relationship between alcoholic cerebellar degeneration and cognitive and emotional functioning. *Neuroscience & Biobehavioral Reviews*, *32*(3), 466–485.

Follesa, P., Mancuso, L., Biggio, F., Mostallino, M. C., Manca, A., Mascia, M. P., … Biggio, G. (2003). Gamma-hydroxybutyric acid and diazepam antagonize a rapid increase in GABA(A) receptors alpha(4) subunit mRNA abundance induced by ethanol withdrawal in cerebellar granule cells. *Molecular Pharmacology*, *63*(4), 896–907.

Friedman, J. R., & Nunnari, J. (2014). Mitochondrial form and function. *Nature*, *505*(7483), 335–343.

Friedman, T. W., Robinson, S. R., & Yelland, G. W. (2011). Impaired perceptual judgment at low blood alcohol concentrations. *Alcohol*, *45*(7), 711–718.

Galluzzi, L., Blomgren, K., & Kroemer, G. (2009). Mitochondrial membrane permeabilization in neuronal injury. *Nature Reviews Neuroscience*, *10*(7), 481–494.

Gandhi, S., & Abramov, A. Y. (2012). Mechanism of oxidative stress in neurodegeneration. *Oxidative Medicine and Cellular Longevity*, *2012*, 428010.

Garcia-Moreno, L. M., Exposito, J., Sanhueza, C., & Angulo, M. T. (2008). [Prefrontal activity and weekend alcoholism in the young]. *Adicciones*, *20*(3), 271–279.

Garcia-Ruiz, C., Kaplowitz, N., & Fernandez-Checa, J. C. (2014). Role of Mitochondria in Alcoholic Liver Disease. *Current Pathobiology Reports*, *1*(3), 159–168.

Gass, J. T., Glen, W. B., Jr., McGonigal, J. T., Trantham-Davidson, H., Lopez, M. F., Randall, P. K., … Chandler, L. J. (2014). Adolescent alcohol exposure reduces behavioral flexibility, promotes disinhibition, and increases resistance to extinction of ethanol self-administration in adulthood. *Neuropsychopharmacology*, *39*(11), 2570–2583.

Gauvin, D. V., Briscoe, R. J., Baird, T. J., Vallett, M., Carl, K. L., & Holloway, F. A. (1997). Cross-generalization of an EtOH "hangover" cue to endogenously and exogenously induced stimuli. *Pharmacology Biochemistry Behavior*, *57*(1–2), 199–206.

Gauvin, D. V., Cheng, E. Y., & Holloway, F. A. (1993). Recent developments in alcoholism:biobehavioral correlates. *Recent Developments in Alcoholism*, *11*, 281–304.

Grimm, A., & Eckert, A. (2017). Brain aging and neurodegeneration: from a mitochondrial point of view. *Journal of Neurochemistry.*

Giorgi, C., Agnoletto, C., Bononi, A., Bonora, M., De Marchi, E., Marchi, S., … Pinton, P. (2012). Mitochondrial calcium homeostasis as potential target for mitochondrial medicine. *Mitochondrion*, *12*(1), 77–85.

Guadagnoli, T., Caltana, L., Vacotto, M., Gironacci, M. M., & Brusco, A. (2016). Direct effects of ethanol on neuronal differentiation: An in vitro analysis of viability and morphology. *Brain Research Bulletin*, *127*, 177–186.

Guerri, C., & Pascual, M. (2010). Mechanisms involved in the neurotoxic, cognitive, and neurobehavioral effects of alcohol consumption during adolescence. *Alcohol*, *44*(1), 15–26.

Halestrap, A. P. (2009). What is the mitochondrial permeability transition pore? *Journal of Molecular and Cellular Cardiology*, *46*, 821–831.

Hamre, K. M., & West, J. R. (1993). The effects of the timing of ethanol exposure during the brain growth spurt on the number of cerebellar Purkinje and granule cell nuclear profiles. *Alcoholism, Clinical and Experimental Research*, *17*(3), 610–622.

Haorah, J., Rump, T. J., & Xiong, H. (2013). Reduction of brain mitochondrial beta-oxidation impairs complex I and V in chronic alcohol intake: The underlying mechanism for neurodegeneration. *PloS One*, *8*(8), e70833.

Hashimoto, J. G., & Wiren, K. M. (2008). Neurotoxic consequences of chronic alcohol withdrawal: Expression profiling reveals importance of gender over withdrawal severity. *Neuropsychopharmacology*, *33*(5), 1084–1096.

Haworth, R. A., & Hunter, D. R. (1979). The Ca2+-induced membrane transition in mitochondria. II. Nature of the Ca2+ trigger site. *Archives of biochemistry and biophysics*, *195*, 460–467.

Heaton, M. B., Siler-Marsiglio, K., Paiva, M., Kotler, A., Rogozinski, J., Kubovec, S., … Madorsky, V. (2013). Ethanol influences on Bax associations with mitochondrial membrane proteins in neonatal rat cerebellum. *Developmental Neurobiology*, *73*(2), 127–141.

Hedden, S. L. (2015). Behavioral health trends in the United States: Results from the 2014 National Survey on Drug Use and Health. Substance Abuse and Mental Health Services Administration, Department of Heath & Human Services.

Helander, A., & Tottmar, O. (1988). Effect of acute ethanol administration on human blood aldehyde dehydrogenase activity. *Alcohol Clin Exp Res*, *12*(5), 643–646.

Hoffman, P. L. (1995). Glutamate receptors in alcohol withdrawal-induced neurotoxicity. *Metab Brain Dis*, *10*(1), 73–79.

Hollenbeck, P. J. (2005). Mitochondria and neurotransmission: Evacuating the synapse. *Neuron*, *47*(3), 331–333.

Hou, Y., Ghosh, P., Wan, R., Ouyang, X., Cheng, H., Mattson, M. P., & Cheng, A. (2014). Permeability transition pore-mediated mitochondrial superoxide flashes mediate an early inhibitory effect of amyloid beta1–42 on neural progenitor cell proliferation. *Neurobiology of Aging*, *35*(5), 975–989.

Hunter, D. R., & Haworth, R. A. (1979a). The Ca2+-induced membrane transition in mitochondria. I. The protective mechanisms. *Archives of biochemistry and biophysics*, *195*, 453–459.

Hunter, D. R., & Haworth, R. A. (1979b). The Ca2+-induced membrane transition in mitochondria. III. Transitional Ca2+ release. *Archives of biochemistry and biophysics*, *195*, 468–477.

Ji, C. (2012). Mechanisms of alcohol-induced endoplasmic reticulum stress and organ injuries. *Biochemistry Research International*, *2012*, 216450.

Jung, M. E. (2015). Alcohol Withdrawal and Cerebellar Mitochondria. *Cerebellum*, *14*(4), 421–437.

Jung, M. E., & Mallet, R. T. (2017). Intermittent hypoxia training: Powerful, non-invasive cerebroprotection against ethanol withdrawal excitotoxicity. *Respiratory Physiology & Neurobiology*, pii: S1569-9048(17)30181–301817. doi: 10.1016/j.resp.2017.08.007

Jung, M. E., & Metzger, D. B. (2015). Aberrant histone acetylation promotes mitochondrial respiratory suppression in the brain of alcoholic rats. *Journal of Pharmacology and Experimental Therapeutics*, *352*(2), 258–266.

Jung, M. E., Yan, L. J., Forster, M. J., & Simpkins, J. W. (2008). Ethanol withdrawal provokes mitochondrial injury in an estrogen preventable manner. *Journal of Bioenergetics and Biomembranes*, *40*(1), 35–44.

Jung, Y. C., & Namkoong, K. (2014). Alcohol: Intoxication and poisoning - diagnosis and treatment. *Handbook of Clinical Neurology*, *125*, 115–121.

Karadayian, A. G., Bustamante, J., Czerniczyniec, A., Cutrera, R. A., & Lores-Arnaiz, S. (2014). Effect of melatonin on motor performance and brain cortex mitochondrial function during ethanol hangover. *Neuroscience*, *269*, 281–289.

Karadayian, A. G., Bustamante, J., Czerniczyniec, A., Lombardi, P., Cutrera, R. A., & Lores-Arnaiz, S. (2015). Alcohol hangover induces mitochondrial dysfunction and free radical production in mouse cerebellum. *Neuroscience*, *304*, 47–59.

Karadayian, A. G., Malanga, G., Czerniczyniec, A., Lombardi, P., Bustamante, J., & Lores-Arnaiz, S. (2017). Free radical production and antioxidant status in brain cortex non-synaptic mitochondria and synaptosomes at alcohol hangover onset. *Free Radical Biology & Medicine*, *108*, 692–703.

Kattimani, S., & Bharadwaj, B. (2013). Clinical management of alcohol withdrawal: A systematic review. *Industrial Psychiatry Journal*, *22*, 100–108.

Kuntsche, E., Knibbe, R., Gmel, G., & Engels, R. (2005). Why do young people drink? A review of drinking motives. *Clinical Psychology Review*, *25*, 841–861.

Kyzar, E. J., & Pandey, S. C. (2015). Molecular mechanisms of synaptic remodeling in alcoholism. *Neuroscience Letters*, *601*, 11–19.

Lacaille, H., Duterte-Boucher, D., Liot, D., Vaudry, H., Naassila, M., & Vaudry, D. (2015). Comparison of the deleterious effects of binge drinking-like alcohol exposure in adolescent and adult mice. *Journal of Neurochemistry*, *132*(6), 629–641.

Lal, H., Prather, P. L., & Rezazadeh, S. M. (1991). Anxiogenic behavior in rats during acute and protracted ethanol withdrawal: Reversal by buspirone. *Alcohol*, *8*(6), 467–471.

Lamarche, F., Carcenac, C., Gonthier, B., Cottet-Rousselle, C., Chauvin, C., Barret, L., ... Fontaine, E. (2013). Mitochondrial permeability transition pore inhibitors prevent ethanol-induced neuronal death in mice. *Chemical Research in Toxicology*, *26*(1), 78–88.

Ledesma, J. C., Miquel, M., Pascual, M., Guerri, C., & Aragon, C. M. (2014). Induction of brain cytochrome P450 2E1 boosts the locomotor-stimulating effects of ethanol in mice. *Neuropharmacology*, *85*, 36–44.

Lee, R. D., An, S. M., Kim, S. S., Rhee, G. S., Kwack, S. J., Seok, J. H., ... Park, K. L. (2005). Neurotoxic effects of alcohol and acetaldehyde during embryonic development. *Journal of Toxicology and Environmental Health Part A*, *68*(23–24), 2147–2162.

Li, C. Y., Chin, T. Y., & Chueh, S. H. (2004). Rat cerebellar granule cells are protected from glutamate-induced excitotoxicity by S-nitrosoglutathione but not glutathione. *American Journal of Physiology - Cell Physiology*, *286*(4), C893–C904.

Liesa, M., Palacin, M., & Zorzano, A. (2009). Mitochondrial dynamics in mammalian health and disease. *Physiological Reviews*, *89*, 799–845.

Linhart, K., Bartsch, H., & Seitz, H. K. (2014). The role of reactive oxygen species (ROS) and cytochrome P-450 2E1 in the generation of carcinogenic etheno-DNA adducts. *Redox Biology*, *3*, 56–62.

Liu, Z., Liu, Y., Gao, R., Li, H., Dunn, T., Wu, P., ... Fang, X. (2014). Ethanol suppresses PGC-1alpha expression by interfering with the cAMP-CREB pathway in neuronal cells. *PLoS One*, *9* (8), e104247.

Lopez-Armada, M. J., Riveiro-Naveira, R. R., Vaamonde-Garcia, C., & Valcarcel-Ares, M. N. (2013). Mitochondrial dysfunction and the inflammatory response. *Mitochondrion*, *13*(2), 106–118.

Luo, J. (2015). Effects of ethanol on the cerebellum: Advances and prospects. *Cerebellum*, *14*(4), 383–385.

Ly, C. V., & Verstreken, P. (2006). Mitochondria at the synapse. *Neuroscientist*, *12*(4), 291–299.

Manda, K., Ueno, M., & Anzai, K. (2007). AFMK, a melatonin metabolite, attenuates X-ray-induced oxidative damage to DNA, proteins and lipids in mice. *Journal of Pineal Research*, *42*(4), 386–393.

Manzo-Avalos, S., & Saavedra-Molina, A. (2010). Cellular and mitochondrial effects of alcohol consumption. *International Journal of Environmental Research and Public Health*, *7*(12), 4281–4304.

Marino, M. D., Aksenov, M. Y., & Kelly, S. J. (2004). Vitamin E protects against alcohol-induced cell loss and oxidative stress in the neonatal rat hippocampus. *International Journal of Developmental Neuroscience*, *22*(5–6), 363–377.

Marshall, E. J. (2014). Adolescent alcohol use: Risks and consequences. *Alcohol & Alcoholism*, *49*(2), 160–164.

Marzo, I., Brenner, C., Zamzami, N., Susin, S. A., Beutner, G., Brdiczka, D., Remy, R., Xie, Z. H., Reed, J.C., & Kroemer, G. (1998). The permeability transition pore complex: a target for apoptosis regulation by caspases and bcl-2-related proteins. *The Journal of experimental medicine*, *187*, 1261–1271.

Mehta, A. J. (2016). Alcoholism and critical illness: A review. *World Journal of Critical Care Medicine*, *5*(1), 27–35.

Merrill, J. E., & Carey, K. B. (2016). Drinking over the lifespan: Focus on college ages. *Alcohol Research*, *38*(1), 103–114.

Miller, J. W., Naimi, T. S., Brewer, R. D., & Jones, S. E. (2007). Binge drinking and associated health risk behaviors among high school students. *Pediatrics*, *119*(1), 76–85.

Mishra, P. (2016). Interfaces between mitochondrial dynamics and disease. *Cell Calcium*, *60*, 190–198.

Moore, D. B., Walker, D. W., & Heaton, M. B. (1999). Neonatal ethanol exposure alters bcl-2 family mRNA levels in the rat cerebellar vermis. *Alcoholism, Clinical and Experimental Research*, *23*(7), 1251–1261.

Moos, R. H., Schutte, K. K., Brennan, P. L., & Moos, B. S. (2009). Older adults' alcohol consumption and late-life drinking problems: A 20-year perspective. *Addiction*, *104*(8), 1293–1302.

Mukherjee, S. (2013). Alcoholism and its effects on the central nervous system. *Current Neurovascular Research*, *10*(3), 256–262.

Murphy, M. P. (2009). How mitochondria produce reactive oxygen species. *Biochemical Journal*, *417*(1), 1–13.

Netzeband, J. G., Schneeloch, J. R., Trotter, C., Caguioa-Aquino, J. N., & Gruol, D. L. (2002). Chronic ethanol treatment and withdrawal alter ACPD-evoked calcium signals in developing Purkinje neurons. *Alcoholism: Clinical and Experimental Research*, *26*(3), 386–393.

Nguyen, D., Alavi, M. V., Kim, K. Y., Kang, T., Scott, R. T., Noh, Y. H., ... Ju, W. K. (2011). A new vicious cycle involving glutamate excitotoxicity, oxidative stress and mitochondrial dynamics. *Cell Death Disease*, *2*, e240.

NIAAA NIoHNIoAAaA. (2007). Alcohol across the lifespan. Five year strategic plan FY08–13.

Orellana, J. A., Cerpa, W., Carvajal, M. F., Lerma-Cabrera, J. M., Karahanian, E., Osorio-Fuentealba, C., & Quintanilla, R. A. (2017). new implications for the melanocortin system in alcohol drinking behavior in adolescents: The glial dysfunction hypothesis. *Frontiers in Cell Neuroscience*, *11*, 90.

Oscar-Berman, M., & Marinkovic, K. (2007). Alcohol: Effects on neurobehavioral functions and the brain. *Neuropsychol Rev*, *17*(3), 239–257.

Otera, H., Ishihara, N., & Mihara, K. (2013). New insights into the function and regulation of mitochondrial fission. *Biochimica et Biophysica Acta (BBA) - Molecular Cell Research*, *1833*, 1256–1268.

Ozkol, H., Bulut, G., Balahoroglu, R., Tuluce, Y., & Ozkol, H. U. (2017). Protective effects of selenium, N-acetylcysteine and vitamin E against acute ethanol intoxication in rats. *Biological Trace Element Research*, *175*(1), 177–185.

PAHO PAHO. (2015). Regional Status Report on Alcohol and Health in the Americas. http://iris.paho.org/xmlui/handle/123456789/123457670.

Pascual, M., Blanco, A. M., Cauli, O., Minarro, J., & Guerri, C. (2007). Intermittent ethanol exposure induces inflammatory brain damage and causes long-term behavioural alterations in adolescent rats. *European Journal of Neuroscience*, *25*(2), 541–550.

Pascual, M., Pla, A., Minarro, J., & Guerri, C. (2014). Neuroimmune activation and myelin changes in adolescent rats exposed to high-dose alcohol and associated cognitive dysfunction: A review with reference to human adolescent drinking. *Alcohol & Alcoholism*, *49*(2), 187–192.

Paschall, M. J., Grube, J. W., & Kypri, K. (2009). Alcohol control policies and alcohol consumption by youth: A multi-national study. *Addiction*, *104*(11), 1849–1855.

Pena, S., Makela, P., Valdivia, G., Helakorpi, S., Markkula, N., Margozzini, P., & Koskinen, S. (2017). Socioeconomic inequalities in alcohol consumption in Chile and Finland. *Drug and Alcohol Dependence*, *173*, 24–30.

Penning, R., van Nuland, M., Fliervoet, L. A., Olivier, B., & Verster, J. C. (2010). The pathology of alcohol hangover. *Current Drug Abuse Reviews*, *3*(2), 68–75.

Perez, M. J., & Quintanilla, R. A. (2015). Therapeutic actions of the thiazolidinediones in Alzheimer's disease. *PPAR Research*, *2015*, 957248.

Perez, M. J., & Quintanilla, R. A. (2017). Development or disease: duality of the mitochondrial permeability transition pore. *Developmental Biology*, *426*, 1–7.

Petit, G., Maurage, P., Kornreich, C., Verbanck, P., & Campanella, S. (2014). Binge drinking in adolescents: a review of neurophysiological and neuroimaging research. *Alcohol Alcohol*, *49*, 198–206.

Piasecki, T. M., Trela, C. J., & Mermelstein, R. J. (2017). Hangover symptoms, heavy episodic drinking, and depression in young adults: A cross-lagged analysis. *Journal of Studies on Alcohol Drugs*, *78*(4), 580–587.

Pla, A., Pascual, M., & Guerri, C. (2016). Autophagy constitutes a protective mechanism against ethanol toxicity in mouse astrocytes and neurons. *PloS One*, *11*(4), e0153097.

Prakash, J., Setlur, R., & Saini, R. K. (2010). Symptom triggered therapy in delirium tremens. *Medical Journal, Armed Forces India*, *66*(2), 180–181.

Ramachandran, V., Perez, A., Chen, J., Senthil, D., Schenker, S., & Henderson, G. I. (2001). In utero ethanol exposure causes mitochondrial dysfunction, which can result in apoptotic cell death in fetal brain: A potential role for 4-hydroxynonenal. *Alcoholism: Clinical and Experimental Research*, *25*(6), 862–871.

Ramachandran, V., Watts, L. T., Maffi, S. K., Chen, J., Schenker, S., & Henderson, G. (2003). Ethanol-induced oxidative stress precedes mitochondrially mediated apoptotic death of cultured fetal cortical neurons. *J Neuroscience Research*, *74*(4), 577–588.

Rao, V. K., Carlson, E. A., & Yan, S. S. (2014). Mitochondrial permeability transition pore is a potential drug target for neurodegeneration. *Biochimica et Biophysica Acta (BBA) - Molecular Cell Research*,*1842*, 1267–1272.

Rando, K., Hong, K. I., Bhagwagar, Z., Li, C. S., Bergquist, K., Guarnaccia, J., & Sinha, R. (2011). Association of frontal and posterior cortical gray matter volume with time to alcohol relapse: A prospective study. *The American Journal of Psychiatry*, *168*(2), 183–192.

Reddy, V. D., Padmavathi, P., Kavitha, G., Saradamma, B., & Varadacharyulu, N. (2013). Alcohol-induced oxidative/nitrosative stress alters brain mitochondrial membrane properties. *Molecular and Cellular Biochemistry*, *375*(1–2), 39–47.

Reddy, P. H. (2014). Inhibitors of mitochondrial fission as a therapeutic strategy for diseases with oxidative stress and mitochondrial dysfunction. *Journal of Alzheimers Disease 40*, 245–256.

Reiter, R. J., Paredes, S. D., Korkmaz, A., Manchester, L. C., & Tan, D. X. (2008). Melatonin in relation to the "strong" and "weak" versions of the free radical theory of aging. *Advances in Medical Sciences*, *53*(2), 119–129.

SAMHSA. (2007). Substance Abuse and Mental Health Services Administration. National Survey on Drug Use and Health: National Findings. Rockville: SAMHSA.

SAMHSA. (2013). Results from the 2013 National Survey on Drug Use and Health: Summary of National Findings.

Schlorff, E. C., Husain, K., & Somani, S. M. (1999). Dose- and time-dependent effects of ethanol on plasma antioxidant system in rat. *Alcohol*, *17*(2), 97–105.

Schulteis, G., Archer, C., Tapert, S. F., & Frank, L. R. (2008). Intermittent binge alcohol exposure during the periadolescent period induces spatial working memory deficits in young adult rats. *Alcohol*, *42*(6), 459–467.

SENDA OCdD. (2014). Décimo Primer Estudio Nacional de Drogas en Población General.

Siler-Marsiglio, K. I., Pan, Q., Paiva, M., Madorsky, I., Khurana, N. C., & Heaton, M. B. (2005). Mitochondrially targeted vitamin E and vitamin E mitigate ethanol-mediated effects on cerebellar granule cell antioxidant defense systems. *Brain Research*, *1052* (2), 202–211.

Sheng, Z. H. (2014). Mitochondrial trafficking and anchoring in neurons: New insight and implications. *Journal of Cellular Biology*, *204*, 1087–1098.

Slawecki, C. J., Thorsell, A., & Ehlers, C. L. (2004). Long-term neurobehavioral effects of alcohol or nicotine exposure in adolescent animal models. *Annals of the New York Academy of Sciences*, *1021*, 448–452.

Smyth, A., Teo, K. K., Rangarajan, S., O'donnell, M., Zhang, X., Rana, P., … Yusuf, S. (2015). Alcohol consumption and cardiovascular disease, cancer, injury, admission to hospital, and mortality: A prospective cohort study. *Lancet*, *386*(10007), 1945–1954.

Spanagel, R. (2009). Alcoholism: A systems approach from molecular physiology to addictive behavior. *Physiological Reviews*, *89*(2), 649–705.

Spear, L. P. (2000). The adolescent brain and age-related behavioral manifestations. *Neuroscience & Biobehavioral Reviews*, *24*(4), 417–463.

Spear, L. P. (2015). Adolescent alcohol exposure: Are there separable vulnerable periods within adolescence? *Physiology Behavior*, *148*, 122–130.

Spear, L. P., & Varlinskaya, E. I. (2005). Adolescence. Alcohol sensitivity, tolerance, and intake. *Recent Developmental & Alcohol*, *17*, 143–159.

Squeglia, L. M., Jacobus, J., & Tapert, S. F. (2014). The effect of alcohol use on human adolescent brain structures and systems. *Handbook of Clinical Neurology*, *125*, 501–510.

St-Pierre, J., Drori, S., Uldry, M., Silvaggi, J. M., Rhee, J., Jager, S., … Spiegelman, B. M. (2006). Suppression of reactive oxygen species and neurodegeneration by the PGC-1 transcriptional coactivators. *Cell*, *127*(2), 397–408.

Stewart, D., Han, L., Doran, T., & McCambridge, J. (2017). Alcohol consumption and all-cause mortality: An analysis of general practice database records for patients with long-term conditions. *Journal of Epidemiology in Community Health*, *71*(8), 729–735.

Sullivan, E. V., Harris, R. A., & Pfefferbaum, A. (2010). Alcohol's effects on brain and behavior. *Alcohol and Research Health*, *33* (1–2), 127–143.

Syapin, P. J., Hickey, W. F., & Kane, C. J. M. (2005). Alcohol brain damage and neuroinflammation: Is there a connection? *Alcoholism: Clinical and Experimental Research*, *29*:1080–1089.

Tan, D. X., Manchester, L. C., Reiter, R. J., Qi, W. B., Karbownik, M., & Calvo, J. R. (2000). Significance of melatonin in antioxidative defense system: Reactions and products. *Biological Signals and Receptors*, *9*(3–4), 137–159.

Tapia-Rojas, C., Carvajal, F. J., Mira, R. G., Arce, C., Lerma-Cabrera, J. M., Orellana, J. A., Cerpa, W., & Quintanilla, R. A. (2017). Adolescent binge alcohol exposure affects the brain function through mitochondrial impairment. *Molecular Neurobiology*, 1–19. http://iris.paho.org/10.1007/s12035-017-0613-4

Tong, J. J. (2007). Mitochondrial delivery is essential for synaptic potentiation. *Biological Bulletin*, *212*(2), 169–175.

Townshend, J. M., Kambouropoulos, N., Griffin, A., Hunt, F. J., & Milani, R. M. (2014). Binge drinking, reflection impulsivity, and unplanned sexual behavior: Impaired decision-making in young social drinkers. *Alcoholism: Clinical and Experimental Research*, *38*(4), 1143–1150.

Trantham-Davidson, H., & Chandler, L. J. (2015). Alcohol-induced alterations in dopamine modulation of prefrontal activity. *Alcohol*, *49*(8), 773–779.

Tsujimoto, Y., & Shimizu, S. (2007). Role of the mitochondrial membrane permeability transition in cell death. *Apoptosis*, *12*, 835–840.

van Schrojenstein Lantman, M., Mackus, M., Roth, T., & Verster, J. C. (2017a). Total sleep time, alcohol consumption, and the duration and severity of alcohol hangover. *Nature and Science of Sleep*, *9*, 181–186.

van Schrojenstein Lantman, M., Mackus, M., van de Loo, A. J. A. E., & Verster, J. C. (2017b). The impact of alcohol hangover symptoms on cognitive and physical functioning, and mood. *Human Psychopharmacology*, *32*, e2623. https://doi.org/10.1002/hup.2623

Van Schrojenstein Lantman, M., van de Loo, A. J., Mackus, M., & Verster, J. C. (2017c). Development of a definition for the alcohol hangover: Consumer descriptions and expert consensus. *Current Drug Abuse Reviews*, *9*, 148–154.

van der Bliek, A. M., Shen, Q., & Kawajiri, S. (2013). Mechanisms of mitochondrial fission and fusion. *Cold Spring Harbor Perspective Biology*, *5*.

Varlinskaya, E. I., & Spear, L. P. (2004). Acute ethanol withdrawal (hangover) and social behavior in adolescent and adult male and female Sprague-Dawley rats. *Alcoholism: Clinical Experimental and Research*, *28*(1), 40–50.

Virmani, M., Majchrowicz, E., Swenberg, C. E., Gangola, P., & Pant, H. C. (1985). Alteration in calcium-binding activity in synaptosomal membranes from rat brains in association with physical dependence upon ethanol. *Brain Research*, *359*(1–2), 371–374.

Vonghia, L., Leggio, L., Ferrulli, A., Bertini, M., Gasbarrini, G., & Addolorato, G. (2008). Acute alcohol intoxication. *European Journal of Internal Medicine*, *19*(8), 561–567.

Wackernah, R. C., Minnick, M. J., & Clapp, P. (2014). Alcohol use disorder: Pathophysiology, effects, and pharmacologic options for treatment. *Substance Abuse and Rehabilitation*, *5*, 1–12.

Walter, N. A., Denmark, D. L., Kozell, L. B., & Buck, K. J. (2016). A systems approach implicates a brain mitochondrial oxidative homeostasis co-expression network in genetic vulnerability to alcohol withdrawal. *Frontiers in Genetics*, *7*, 218.

Wang, F., Li, Y., Zhang, Y. J., Zhou, Y., Li, S., & Li, H. B. (2016). Natural products for the prevention and treatment of hangover and alcohol use disorder. *Molecules*, *21*(1), 64.

Wareski, P., Vaarmann, A., Choubey, V., Safiulina, D., Liiv, J., Kuum, M., & Kaasik, A. (2009). PGC-1{alpha} and PGC-1{beta} regulate mitochondrial density in neurons. *J Biol Chem*, *284*(32), 21379–21385.

WHO. (2014). Substance abuse Global status report on alcohol and health.

Wiese, J. G., Shlipak, M. G., & Browner, W. S. (2000). The alcohol hangover. *Annals of the Internal Medicine*, *132*(11), 897–902.

Wilcox, M. V., Cuzon Carlson, V. C., Sherazee, N., Sprow, G. M., Bock, R., Thiele, T. E., … Alvarez, V. A. (2014). Repeated binge-like ethanol drinking alters ethanol drinking patterns and depresses striatal GABAergic transmission. *Neuropsychopharmacology*, *39*(3), 579–594.

Wozniak, D. F., Hartman, R. E., Boyle, M. P., Vogt, S. K., Brooks, A. R., Tenkova, T., … Muglia, L. J. (2004). Apoptotic neurodegeneration induced by ethanol in neonatal mice is associated with profound learning/memory deficits in juveniles followed by progressive functional recovery in adults. *Neurobiology of Disease*, *17*(3), 403–414.

Wu, D., Zhai, Q., & Shi, X. (2006). Alcohol-induced oxidative stress and cell responses. *Journal of Gastroenterology and Hepatology*, *21(Suppl3)*, S26–S29.

Yan, T., Zhao, Y., & Zhang, X. (2016). Acetaldehyde induces cytotoxicity of SH-SY5Y cells via inhibition of akt activation and induction of oxidative stress. *Oxidative Medicine and Cellular Longevity*, *2016*, 4512309.

Zahr, N. M., Mayer, D., Rohlfing, T., Hasak, M. P., Hsu, O., Vinco, S., … Pfefferbaum, A. (2010). Brain injury and recovery following binge ethanol: Evidence from in vivo magnetic resonance spectroscopy. *Biological Psychiatry*, *67*(9), 846–854.

How to cite this article: Tapia-Rojas C, Mira RG, Torres AK, et al. Alcohol consumption during adolescence: A link between mitochondrial damage and ethanol brain intoxication. *Birth Defects Research*. 2017;109:1623–1639. https://doi.org/10.1002/bdr2.1172