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Taurine restores the exploratory behavior following alcohol withdrawal and decreases BDNF mRNA expression in the frontal cortex of chronic alcohol-treated rats

Alana Witt Hansen[a,*], Felipe Borges Almeida[b], Solange Bandiera[a], Rianne Remus Pulcinelli[a], Ana Luiza Rodrigues Fragoso[a], Ricardo Schneider Jr[a], Helena Maria Tannhauser Barros[b], Rosane Gomez[a,b]

[a] Programa de Pós Graduação em Ciências Biológicas, Farmacologia e Terapêutica, Laboratório de Álcool e Tabaco (LAT), Universidade Federal do Rio Grande do Sul – UFRGS, Sarmento Leite, 500, 90050-170 Porto Alegre, RS, Brazil

[b] Programa de Pós Graduação de Ciências da Saúde, Universidade Federal de Ciências da Saúde de Porto Alegre – UFCSPA, Sarmento Leite, 245, 90050-170 Porto Alegre, RS, Brazil

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ABSTRACT

Alcohol use disorder is an alarming health problem, and the withdrawal symptoms increase the risk of relapse. We have hypothesized that taurine, a multitarget substance acting as a gamma-aminobutyric acid A receptor ($GABA_AR$) positive modulator and a partial inhibitor of *N*-methyl-D-aspartate (NMDA) glutamate receptors, may reduce the withdrawal symptoms or modify behaviors when combined with alcohol. Therefore, we investigated the effects of taurine on behavior in the open field test (OFT), the $GABA_AR$ α_2 subunit and BDNF mRNA expression in the frontal cortex of rats after chronic alcohol treatment or upon withdrawal. Rats received alcohol 2 g/kg (alcohol and withdrawal groups) or water (control group) twice daily by oral gavage for 28 days. On day 29, the withdrawal rats received water instead of alcohol, and all groups were reallocated to receive 100 mg/kg taurine or vehicle intraperitoneally, once a day for 5 days. On day 33, the rats were exposed to OFT; 18 h later, they were euthanized, and the frontal cortex was dissected for $GABA_AR$ α_2 subunit detection and BDNF mRNA expression determination by real-time quantitative PCR. Taurine administration restored rearing behavior to the control levels in the withdrawal rats. Taurine also showed anxiolytic-like effects in control rats and did not change the behaviors in the chronic alcohol group. Chronic alcohol treatment or withdrawal did not change the $GABA_AR$ α_2 subunit or BDNF mRNA expression in the frontal cortex, but taurine decreased the α_2 subunit level in control rats and to the BDNF levels in the alcohol rat group. We conclude that taurine restored exploratory behavior after alcohol withdrawal but that this effect was not related to the $GABA_AR$ α_2 subunit or BDNF mRNA expression in the frontal cortex of the rats.

1. Introduction

Alcohol use disorder is a public health problem that is associated with millions of deaths each year worldwide (World Health Organization, 2014). Massive campaigns and policies to decrease alcohol dependence have resulted in little success, probably because the positive reward of alcohol use and negative symptoms of its withdrawal maintain its continuous use and increases the risk of relapse (Gilpin and Koob, 2008).

Alcohol is mainly known as a depressor of the central nervous system (CNS), acting as a positive modulator of the gamma-aminobutyric acid A receptor ($GABA_AR$). $GABA_AR$ is a ligand-gated ion channel with five subunits that are combined according to the function and brain area (Jacob et al., 2008). Alcohol dependence is associated with changes in the α_2 subunit in the limbic brain areas, such as the frontal cortex, hippocampus, and amygdala (Kumar et al., 2009).

Reinstatement after alcohol withdrawal has been linked to the glutamatergic pathway from the prefrontal cortex to NAcc overactivity, lower activity of the dopamine projection from the VTA to the medial prefrontal cortex, as well as lower activity of the GABA projection from the NAcc to the ventral pallidum (Koob and Volkow, 2010). Craving, which is a key component of relapse, is related to overactivity in the glutamatergic pathway, from the frontal cortex to the basolateral amygdala, which projects itself to the ventral striatum (Koob and

* Corresponding author at: Rua Sarmento Leite, 500, Room 313, 90050-170 Porto Alegre, RS, Brazil.
E-mail address: alana.hansen@ufrgs.br (A.W. Hansen).

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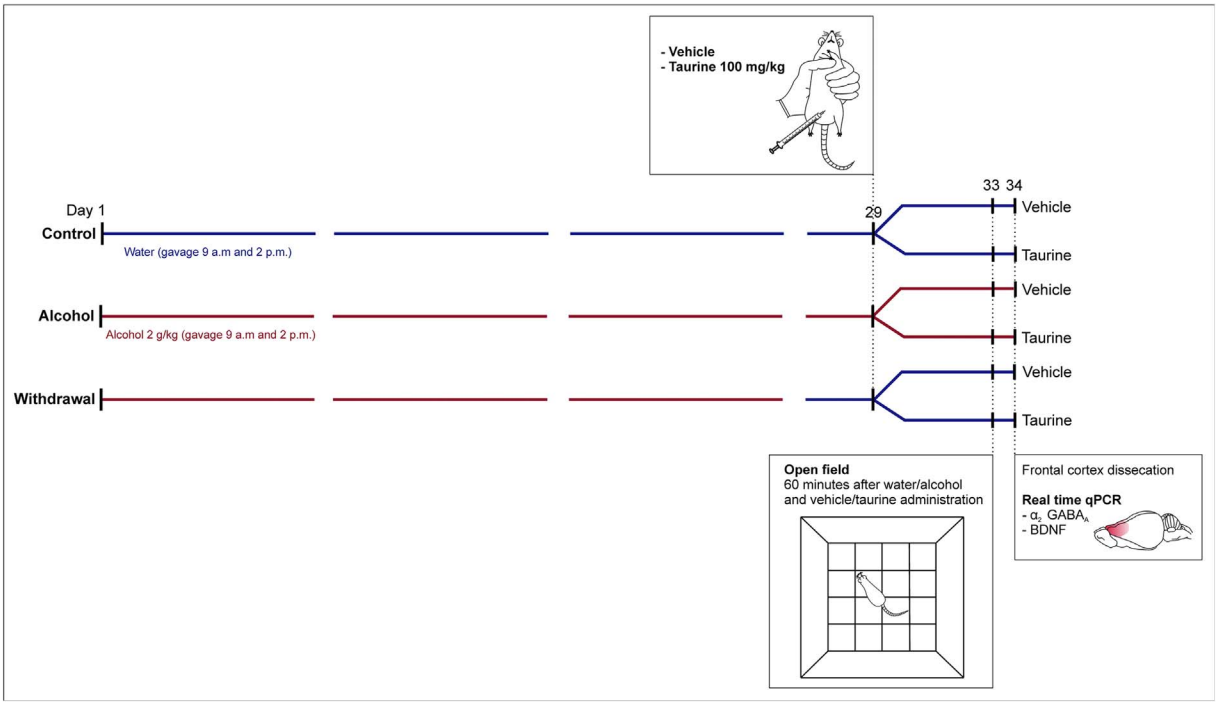

Fig. 1. Experimental Timeline. Wistar rats were treated with 2 g/kg alcohol or distilled water, via oral gavage, twice a day (9 AM and 2 PM), 5 days/week, for 28 days. On day 29, alcohol was interrupted in the withdrawal group, and rats received 100 mg/kg taurine or vehicle, via i.p., once/day. On day 33, they were exposed to the open field test, after 1 h from the last alcohol/water or taurine/vehicle administration. Rats were euthanatized 18 h later under the same treatment, and the frontal cortex was dissected.

Volkow, 2010). Indeed, alcohol withdrawal decreases the inhibitory function of GABA and increases the excitatory function of glutamate, leading to rebound hyper-neuronal excitability. This is related to behavioral changes such as seizures and anxiety, which increase the risk of relapse (Modesto-Lowe et al., 2005). Therefore, novel pharmacological strategies to restore dopamine, GABA, and the glutamate balance during alcohol withdrawal may decrease craving episodes and the risk of relapse in alcoholics.

Alcohol and other drug abuse have been described to regulate brain-derived neurotrophic factor (BDNF), known for its role in the growth, survival, and differentiation of developing neurons (Logrip et al., 2015; Russo et al., 2009). Indeed, the chronic effects of moderate alcohol consumption increases the BDNF levels in the dorsal striatum of rats by activating the genomic mechanisms (Logrip et al., 2015). Until now, little is known about the meaning of changes in BDNF expression during alcohol dependence and withdrawal.

Taurine, a sulfonated amino acid, acts as an agonist of $GABA_AR$, hyperpolarizing the cells by increasing the Cl^- influx (Albrecht and Schousboe, 2005). Additionally, taurine presents osmoregulatory, antioxidant, and neuroprotective properties (Jong et al., 2012; Lambert et al., 2015). Acute taurine administration shows an anxiolytic-like effect in mice and zebrafish (El Idrissi et al., 2009; Mezzomo et al., 2016). Chronic treatment induces an antidepressant-like effect in diabetic rats (Caletti et al., 2015). Taurine also prevents glutamate-induced neurotoxicity and inflammation in animal models of hypoxia (Albrecht and Schousboe, 2005; Schuller-Levis and Park, 2004). Alcohol administration increases the endogenous taurine levels in the NAcc of both alcohol-preferring and non-preferring rats (Quertemont et al., 2000). However, the taurine levels were higher in alcohol-non-preferring rats in this brain area, suggesting that taurine may attenuate the neurotoxic effects of alcohol in rats (Quertemont et al., 2000). However, the multi-target mechanisms of taurine are not completely understood. Few studies have explored taurine's effects in combination with alcohol drinking on the withdrawal symptoms in rats.

Therefore, the aim of this study was to investigate the effects of taurine on behavior and the mRNA expression of the $GABA_AR$ α_2 subunit and BDNF in the frontal cortex after chronic alcohol treatment or withdrawal in rats.

2. Methods

2.1. Animals

Adult male Wistar rats (n = 72), with a body weight of 250–280 g, were born and reared at the animal facility of Universidade Federal do Rio Grande do Sul (UFRGS), Brazil and were housed in polypropylene cages (3 rats/cage, 33 × 40 × 17.8 cm) under controlled environmental conditions (22 ± 2 °C, 12 h light/dark (lights on at 7 a.m.), with free access to water and food (Nuvilab, Colombo, Brazil). All the procedures were performed according to international and local policies for experimental animal handling and had been approved by the Ethics Committee for Animal Experimentation (CEUA-UFRGS #28722).

2.2. Saline, ethanol, and taurine solutions

Ethanol (98%) (Nuclear, São Paulo, Brazil) was diluted to 20% (w/v) in distillated water. Alcohol solution was prepared daily and was administered as 10 mL/kg via oral (gavage). The alcohol dose (2 g/kg twice a day) was chosen based on the literature and from a previous study in our group (Schneider et al., 2015; Gilpin et al., 2009; Gomez and Luine, 2014). This 2 g/kg dose increases blood alcohol concentration (BAC) up to 120 mg/dL at 60 min from the administration (Gilpin et al., 2009; Gomez and Luine, 2014). BAC levels of 0.08 g/dL are considered binge drinking and typically occurs after 4–5 drinks for humans (Drinking Levels Defined, n.d.). Control rats received the same volume of distilled water. Taurine (100 mg/kg; Biofarma, Porto Alegre, Brazil) was diluted in saline 0.9% and was administered intraperitoneally (i.p.). The control group received the same volume of saline 0.9% (vehicle), i.p. This dose of taurine was chosen based on the antidepressant and neuroprotective effects in rats (Caletti et al., 2015) and is the same dose that reduces voluntary alcohol consumption after acute administration (Olive and Hodge, 2001). Taurine treatment