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## Ethanol Interference on Adenosine System

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### 1. Introduction

It is well documented in literature a wide range of behavioral and physiological effects arising from ethanol intake (Spinetta et al., 2008; Soares et al., 2009; Brust, 2010). Because it is a substance that affects differently and simultaneously several neurotransmitter systems, covering different brain areas (Dahchour & De Witte, 2000; Vasconcelos et al., 2008; Vengeliene et al., 2008), it becomes complex to reveal the mechanism of action that governs its effects, being still a challenge for researchers. In addition, ethanol has a biphasic behavioral presenting an excitatory feature in the early stages and a depressant feature in its chronic use.

Among the wide range of pathways in central nervous system that are modified by ethanol, it is important to highlight those that explain ethanol diverse effects, like the ones releasing gamma-aminobutyric acid (GABA), glutamate, dopamine and norepinephrine (Kaneyuki et al., 1991; Vasconcelos et al., 2004). Moreover, another pathway that is rising on researches about ethanol effects is the adenosinergic system (Prediger et al., 2006; Thorsell et al., 2007).

Adenosine was described as a potent depressor of neuronal activity (Dunwiddie & Haas, 1985), and acts mainly via A1 receptor, which is a presynaptic inhibitor of the release of neurotransmitters such as dopamine, GABA, glutamate, acetylcholine and norepinephrine (Fredholm et al., 2001; Dunwiddie & Masino, 2001). Moreover, adenosine is involved in behavioral processes like motor function, anxiety, depression, reward and drug addiction, and human disorders such as Parkinson disease and schizophrenia (Moreau and Huber, 1999).

In addition, there is strong evidence of an involvement of the adenosinergic system on ethanol effects, including the extracellular increase of adenosine after acute exposure to ethanol (Krauss et al., 1993; Nagy et al., 1990), the accentuation or blockade of ethanol-induced motor incoordination provided by adenosine receptor agonists or antagonists, respectively (Dar, 2001; Soares et al., 2009), and the reduction of anxiogenic-like behavior in acute ethanol withdrawal (Prediger et al., 2006). Adenosine antagonists, like caffeine, are implicated in alcohol tolerance (Fillmore, 2003), and retrograde memory impairment caused by ethanol (Spinetta et al., 2008). Thus, adenosine receptors seem to modulate some of the

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pharmacological properties of ethanol, interacting with it by blocking or accentuating its properties.

## 2. Ethanol and adenosine relation in different neurotransmission systems

It's known in literature that ethanol alone interferes in different neurotransmitter systems, as GABAergic, glutamatergic, dopaminergic, serotonergic, noradrenergic, cholinergic and others, including adenosinic; however, its action on this last system has currently deserved more attention, due to its neuromodulator/neuroprotector action. Thus, in the present topic updates will be discussed on the relationship between ethanol and adenosine and its consequent interference in some systems above.

To better understand the association of ethanol and adenosine on different neurotransmitter systems, it is necessary to explore the likely hypotheses that explain how ethanol interferes with the adenosine system. Carmichael et al. (1991) suggested that a probable mechanism could occur via metabolism of ethanol by acetate, where this would be incorporated into acetyl-coenzyme A with subsequent formation of AMP, thereby directing the synthesis of adenosine.

Another possible mechanism of interaction between these two substances can be related to the fact that ethanol inhibits facilitated diffusion transporters, being the ENT1 (Equilibrative Nucleoside Transporter) an example, increasing the availability of extracellular adenosine (Diamond et al., 1991; Krauss et al., 1993). Finally, ethanol may facilitate the activation of receptors that have adenylate cyclase (AC) as intracellular signaling system (Rabin; Molinoff, 1981; Hoffman; Tabakoff, 1990), which is displayed by adenosine receptors. Therefore, there are different points of possible interference of the increased concentration of extracellular adenosine induced by ethanol on other neurotransmitter systems.

The GABAergic system in the striatum may be modulated by adenosine with regard to the effects of ethanol on motor coordination and sleep, involving cAMP (Meng; Dar, 1995; Meng et al., 1997). It was found that the use of adenosine agonists accentuate the reduction in the motor coordination induced by ethanol, whereas Ro15-4513, a weak partial inverse agonist of the benzodiazepine class of drugs, attenuated by blocking the effect of the first when used in combination (Meng; Dar, 1994, 1995), suggesting a participation via GABA<sub>A</sub> by an alteration in the conductance of chloride ions (Meng et al., 1997, Mohler et al., 1984). A mechanism suggested by Londos et al. (1980) and Van Calk et al. (1970) relates ethanol to alterations in the production of cAMP via AC through the A1 receptor, ie, increased availability of adenosine induced by ethanol leads to greater signs of adenosine on your receptor that has a higher affinity, which is related with inhibitory G protein, reducing cAMP production and concomitant modulation of the GABAergic system that increases chloride conductance.

This ratio adenosine/ethanol with the GABAergic system can still be related to opioid system, where ethanol induces the increased availability of  $\beta$ -endorphin which activates  $\mu$ type receptors, altering the release of GABA in dopaminergic neurons in the ventral tegmental area, an area involved to reward behavior and abuse of ethanol (Mendez et al, 2003; Marinelli et al, 2004; Lam et al, 2008; Jarjour et al, 2009).

Indirectly, this relationship can also occur through ionotropic ATP receptors, that has the function of specific subtypes (P2X4R and P2X2R) inhibited by ethanol (Davies et al., 2002, 2005), altering the modulation of release of different substances such as GABA, glycine and glutamate (Mori et al., 2001; Papp et al., 2004).

Concerning the glutamatergic system, this one demonstrates relationship with the two subtypes of adenosine receptors  $A_1$  and  $A_{2A}$ , once these receptors appear hetero-dimerized in glutamatergic nerve terminals in the striatum, modulating the concentration of glutamate in accordance with the availability of adenosine, where a lower concentration activates  $A_1$ R inhibiting glutamate release, and a higher concentration activates  $A_{2A}$ R, stimulating the release of glutamate and greater activation of the NMDA receptor. This regulates the release of dopamine in the nucleus accumbens stimulating higher consumption of ethanol (Ciruela et al., 2006; Quarta et al., 2004).

Another finding that reinforces the relationship ethanol/adenosine/glutamate is the synergic interaction that occurs between  $A_{2A}$  and mGluR5 receptors (which is related to the consumption of ethanol in the nucleus accumbens) in the striatum, that is, the co-activation of these receptors increases the phosphorylation of proteins regulated by dopamine and cAMP, increased ethanol consumption (Nishi et al., 2003). In addition, NMDA and  $A_1$  receptors present a cross modulation on the negative effects of ethanol, like a reduction on motor coordination in the cerebellum, striatum and motor cortex (Mitchell; Neafsey; Collins, 2009). This relationship could be involved with the altered activity of Protein Kinase C (PKC) (Othman et al., 2002). This enzyme has a modulating function against the concentration of glycine, GABA internalization, externalization of NMDA expression of 5-HT3 (Chapell et al., 1998; Lan et al., 2001; Zhang et al., 1995; Sun et al., 2003).

Regarding the dopaminergic system,  $A_{2A}$  and  $D_2$  receptors (as well as  $A_1$  and  $D_1$ ) exhibit dimerization between them, relating to the reward system in the striatum probably by modulation of AC activity by ethanol, leading to an increase in the concentration of cAMP and the activity of PKA, desensitizing  $D_2$ , and thus leading to an increased consumption of ethanol (Ferre et al., 2008; Mailliard & Diamond, 2004; Yao et al., 2002; 2003). A possible mechanism of the final response of the dimerized activation of these receptors is that ethanol desensitizes receptors linked to the stimulatory G protein ( $\alpha$  subunit), modulating the coupling of  $D_2$  with the AC pathway, which may be related to PKA (Yao et al., 2001; Batista et al., 2005). Inoue et al. (2007) found that co-activation of  $A_{2A}$  and  $D_2$  mediates the transient interaction between nicotine and ethanol, showing an indirect relationship with the cholinergic system, where the use of antagonists of this co-activation can prevent, mitigate or even reverse the use of smoke and ethanol.

Indirectly, the adenosine system also maintains relation to the dopaminergic system via receptors P2XR which were identified in mesolimbic dopaminergic neurons, modulating their activity and, equivalently, the consumption of ethanol (Heine et al., 2007; Xiao et al., 2008).

Adenosine and serotonin systems are related in regard to ethanol via P2X receptors (P2XR). That is, 5-HT3 and P2XR are functionally coupled and both have their actions modulated by ethanol (inhibits P2X2 and P2X4 and stimulates 5-HT3), besides being involved with other neurotransmitter systems such as glycine, GABA, glutamate (mentioned above) and dopamine in the nucleus accumbens and ventral tegmental area (Davies et al., 2006).

Other neurotransmitters still present a few studies involving ethanol and the adenosine system, such as glycine, where ethanol inhibits their specific receptors probably via PKC (Tao & Ye, 2002), and taurine, which normalizes the activity of ATPases in tissues pretreated with ethanol (Pushpakiran et al., 2005), showing some indirect relationship with the system in focus.

### 3. Adenosine agonists and antagonists in the responses induced by ethanol

As widely described, ethanol affects several mechanisms of transmission on the central nervous system, bringing a wide range of behavioral and neurochemical responses. To reduce the risks and to prevent the damages arising from ethanol intake, many researches are engaged in finding other substances that could inhibit or reduce the responses of ethanol in the organism. An alternative for this proposition is to study the relationship of the mechanism of action of ethanol effects and substances that may interfere in these pathways. Adenosine system, as already mentioned, interacts with many effects induced by ethanol, affecting their responses as being influenced by them. This system has gained remarkable interest in research because of its neuromodulator/neuroprotective action (Halbach & Dermietzel, 2006; Wardas, 2002), and may bring about a new target for developing drugs that can interfere with the effects caused by ethanol.

Among the wide range of adenosine receptor agonists and antagonists used in experiments involving ethanol treatment, we will focus on the most common substances, like adenosine, N<sup>6</sup>-[2-(3,5-dimethoxyphenyl)-2-(2-methylphenyl)ethyl]adenosine g(DPMA), 2-chloro-N<sup>6</sup>-cyclopentyladenosine (CCPA), R(-)-N<sup>6</sup>-phenylisopropyladenosine (R-PIA) as agonists, and caffeine, theophylline, 1,3-dipropyl-8-cyclopentylxanthine (DPCPX), 3,7-Dimethyl-1-propargylxanthine (DMPX) as antagonists, these last being well described and characterized in a review performed by Muller & Jacobson (2011).

A moderate alcohol intake may not be harmful and has even beneficial effects in prevention of cardiovascular diseases, for example (Di Castelnuovo et al., 2010), but heavy alcohol consumption could be associated with some risks to the body, like reduced brain mass, neuronal loss, neuropathological changes, and impairment of cognitive functions, amnesia, dementia and even a significant increase in mortality. Furthermore, the consumption of significant quantities of ethanol during pregnancy is responsible for the Fetal Alcohol Syndrome (FAS), and prenatal alcohol exposure in humans, as well as in rodents, leads to an impaired cognitive and behavioral function, resulting from damage to the central nervous system (Chen et al., 2003; Riley et al., 2004; Hamilton et al., 2003). Thus, taking into account the substantial importance of this system, studies looking for the lessening of these various damages caused by ethanol intake are strictly necessary.

High amount of experimental studies, involving ethanol administration, use a chronic treatment as methodology protocol; but subchronic and acute treatments are also well used (Soares et al., 2009; Prediger et al., 2006). While acute treatment simulates hangover, chronic treatment usually refers to the withdrawal symptoms and body's adaptive responses to prolonged consumption of ethanol.

Although many studies have consistently demonstrated increases in anxiety-like behavior during the withdrawal period after chronic exposure to ethanol in rodents (Lal et al., 1991; Knapp et al., 1993; Gatch & Lal, 2001), there are limited experimental findings regarding this



symptom after a single ethanol challenge dose. Prediger et al. (2006) designed an experimental study of acute ethanol withdrawal (hangover) in mice, in which a time-dependent development of anxiety-like behavior after an intraperitoneal administration of a single dose of ethanol (4 g/kg) in mice was assessed, and the potential of adenosine A<sub>1</sub> and A<sub>2A</sub> receptor agonists in reducing this behavior was evaluated. They presented evidence that acute administration of 'nonanxiolytic' doses of adenosine (5–10 mg/kg, i.p.) or the selective adenosine A<sub>1</sub> receptor agonist CCPA (0.05–0.125 mg/kg, i.p.), but not the adenosine A<sub>2A</sub> receptor agonist DPMA (0.1–5.0 mg/kg, i.p.), which reduces the anxiety-like behavior during ethanol hangover in mice, as indicated by a significant increase in the exploration of the open arms of the elevated plus maze. In addition, the effect of CCPA (0.05 mg/kg, i.p.) was prevented by the pretreatment with the selective adenosine A<sub>1</sub> receptor antagonist DPCPX (3.0 mg/kg, i.p.), demonstrating that the activation of adenosine A<sub>1</sub> receptors, but not adenosine A<sub>2A</sub> receptors, reduces the anxiogenic-like behaviour observed during acute ethanol withdrawal in mice.

In general, sensitivity to the adverse effects of ethanol is inversely correlated with alcohol consumption. In a study with mice lacking the A<sub>2A</sub> receptor, Naassila et al. (2002) showed that these animals are less sensitive to the acute effects of ethanol as hypothermia and sedation, and consume more ethanol in a two-bottle choice paradigm compared with wild-type littermate control mice, demonstrating that the A<sub>2A</sub>R is involved in the sensitivity to the hypothermic and sedative effects of ethanol playing a role in alcohol-drinking behavior.

Furthermore, caffeine presents an ability to decrease sensitivity to the stumbling and tiredness associated with drinking large quantities of ethanol. Thus, adenosine receptors antagonists also appear to mediate some of the reinforcement effects of ethanol. This reinforcement is in part mediated via A<sub>2A</sub>R activation and probably associated with intracellular A<sub>2</sub> activation of cAMP/PKA signalling cascades in the nucleus accumbens (Thorsell, et al., 2007; Adams et al., 2008), but the exact mechanism of action remains unclear. Studies in humans examining methylxanthine and ethanol interactions have mostly focused on the influence that caffeine exerts on ethanol intoxication, and have yielded mixed results (Liguori and Robinson 2001; Drake et al. 2003); but a point that needs further attention is the fact that these studies converge upon the point that caffeine consumed in association with ethanol, rather than improving ethanol-induced impairments, would reduce the self-perception of ethanol intoxication (Morelli & Simola, 2011), since human data also show that caffeine enhances tolerance to ethanol (Fillmore, 2003).

In addition to reinforcing effects, adenosine also appears to be related to locomotive effects of ethanol at high dose (6 g/kg) in subchronic treatment during 5 days, as shown in the experimental study of Soares et al. (2009), in which the administration of Aminophylline, a non-selective adenosine receptor antagonist, at low doses (5 and 10 mg/kg) produced some degree of locomotion stimulation, and was able to reverse the depressive effects produced by ethanol on the number of falls and time spent in the bar, in the Rota rod test, suggesting a partial blockage of the action of ethanol. The selective A<sub>1</sub>R agonist N<sup>6</sup>-cyclohexyladenosine (CHA) has also been found to potentiate, and the antagonist DPCPX attenuates ethanol-induced motor incoordination in mice (Meng et al., 1997).

Chronic ethanol intake leads to several changes in the balance of neurotransmitter pathways and its receptors, being studied oftentimes focusing withdrawal symptoms. Accordingly

Concas et al. (1994), the adenosine receptor agonist CCPA produces inhibition of these symptoms, such as tremors and audiogenically induced seizures in rats treated repeatedly with ethanol (12–18 g/kg daily for 6 days), an effect prevented by DPCPX. Similar results about the specificity of the adenosine receptor in the responses of ethanol effects have been reported by Kaplan et al (1999) in mice receiving a 14-day liquid diet containing ethanol and treated with the adenosine  $A_1$  receptor agonist R-PIA during the withdrawal period, indicating the adenosine  $A_1$ R modulate anxiety-like responses in mice, not only in acute, but also in chronic treatment with ethanol.

Thus, adenosine receptor activation seems to be strongly linked with sensitivity and reinforcement properties of ethanol either in  $A_1$ , or in  $A_{2A}R$ , with an opposite relation of activation, whereas the adenosine  $A_1$ R agonists reduce sensitivity,  $A_{2A}R$  antagonists demonstrate to play this role. Despite  $A_{2A}$  knockout mice showed reduced conditioned place preference for ethanol. Houchi et al. (2008) showed that the increased propensity to drink ethanol in  $A_{2A}$  knockout mice was associated with an increase in sensitivity to the motor stimulant and anxiolytic effects of ethanol. Contrasting with these findings, the administration of  $A_{2A}$  antagonist DMPX reduced ethanol reward and consumption, in a study performed by Thorsell et al. (2007), in which a decreased lever-pressing for ethanol in an operant chamber was observed.

Caffeine and selective adenosine receptor antagonists may also reduce the duration of ethanol-induced loss of the righting reflex (El Yacoubi et al., 2003), reverse deficits in motor coordination induced by ethanol (Barwick & Dar, 1998; Connole et al., 2004) and reverse retrograde memory impairment caused by a high dose of ethanol (3 g/kg) (Spinetta et al., 2008). Indeed, the combination of caffeine and ethanol produces a beneficial effect after experimental traumatism brain injury (Dash et al., 2004), projecting its effect on stroke (Aronowski et al., 2003; Belayev et al., 2004) and indicating the importance of the interaction between caffeine and ethanol.

Beyond neurotransmission/neuromodulation, it is important to give attention to other factors that contribute to the relationship between adenosine system and ethanol effects, as indicated in a review performed by Ruby et al. (2011) about adenosine signalling in anxiety, which underlies the importance of the adenosine transporter ENT1. Many aspects of ethanol-related behaviors and anxiety appear to be involved in genetic factors as polymorphism and in the gene encoding ENT1 could be associated with alcoholism and depression in women (Gass et al., 2010). Further, acute ethanol inhibits ENT1, while chronic ethanol treatment leads to decreased ENT1 expression (Short et al., 2006; Sharma et al., 2010). Also, mice lacking this adenosine transporter displayed a decreased  $A_1$  adenosine tone in the nucleus accumbens and elevated levels of ethanol consumption compared with wild-type mice (Choi et al., 2004). In contrast, it has been shown that ethanol operant self-administration is not altered by an  $A_1$ R antagonist while it is bimodally affected by an  $A_{2A}R$  antagonist (Arolfo et al., 2004).

#### 4. Conclusion and future prospects

As noted above, there are many different points of adenosine system interference on the effects of ethanol administration. This interaction is of fundamental importance because it could be a new target for developing drugs that may interfere, reducing the damage caused by ethanol.

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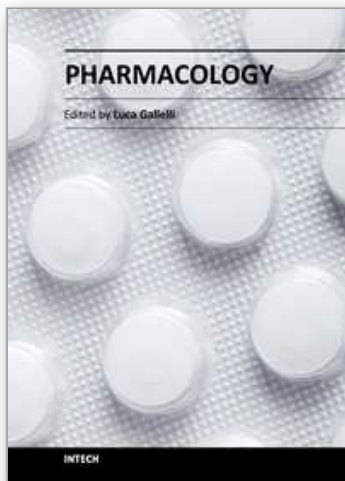
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The history of pharmacology travels together to history of scientific method and the latest frontiers of pharmacology open a new world in the search of drugs. New technologies and continuing progress in the field of pharmacology has also changed radically the way of designing a new drug. In fact, modern drug discovery is based on deep knowledge of the disease and of both cellular and molecular mechanisms involved in its development. The purpose of this book was to give a new idea from the beginning of the pharmacology, starting from pharmacodynamic and reaching the new field of pharmacogenetic and ethnopharmacology.

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