Ethanol versus Adenosine on Emotional and Cognitive Disturbances

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Binge drinking intake is the most common pattern of ethanol consumption by adolescents, which elicits emotional disturbances, mainly anxiety and depressive symptoms, as well as cognitive alterations. Ethanol exposure may act on the adenosine neuromodulation system by increasing adenosine levels, consequently increasing the activation of adenosine receptors in the brain. The adenosine modulation system is involved in the control of mood and memory behavior.

ethanol binge drinking adolescence adenosine caffeine

1. Introduction

Ethanol is the most commonly used drug by adolescents, mainly consumed through a binge drinking pattern. According to the National Institute on Alcohol Abuse and Alcoholism (NIAAA), binge drinking consumption is characterized by approximately 0.08% grams of alcohol/dL, which corresponds to the intake of four drinks for women and five drinks for men during 2 h [1]. Evidence from human and laboratory animal studies highlighted the profound structural and functional neurodevelopment processes modifying synaptic plasticity and dendritic connectivity during adolescence [2]. This on-going neuronal maturation predisposes the central nervous system (CNS) to harmful consequences of drugs (i.e., ethanol), eliciting anxiety and depressive symptoms as well as cognitive deficits [3][4][5]. These ethanol-induced behavioral changes in adolescents result from disturbances in homeostasis of several brain regions, such as the prefrontal cortex, hippocampus, and limbic system, which aggravates adolescent risk behavior [6]. In addition, ethanol also negatively affects the mesocorticolimbic pathway, which is part of the reward and reinforcement circuitry. Activation of the dopaminergic system signaling on the ventral tegmental area and nucleus accumbens, concomitant to hyperactivation of the glutamatergic system in limbic structures, trigger neurotoxicity mechanisms and behavioral alterations, especially in the immature brain [7][8].

Although caffeine has multiple molecular targets, it was first proposed by Bertil Fredholm late last century that caffeine mostly acts through the antagonism of adenosine receptors [9]. Indeed, it was recently confirmed that the ability of caffeine to control synaptic transmission and plasticity in hippocampal circuits is critically and solely dependent on the antagonism of adenosine receptors [10]. Adenosine is a prototypical neuromodulator released in an activity-dependent manner, with a parallel role in fine-tuning neuronal function under physiological conditions

and controlling neurodegeneration in different neuropsychiatric conditions [11]. Adenosine signals through adenosine receptors, namely A1, A2A, A2B, and A3 [12]. These four metabotropic receptors can recruit numerous transduction pathways, in particular, the formation of intracellular cyclic adenosine monophosphate (cAMP). Adenosine A1 and A3 receptors are coupled to Gi/Go protein, resulting in the inhibition of adenylate cyclase activity and consequent reduction of cAMP formation, whereas A2A and A2B receptors are coupled to Gs proteins, activating adenylate cyclase that increases cAMP production [13].

Adenosine receptors have a wide but heterogenous distribution in the brain. Adenosine A1 receptors (A1R) are the most abundant adenosine receptor subtype, with higher levels in the limbic cortex and thalamus. A1R potently inhibit glutamatergic transmission throughout the brain, as well as dopamine release in corticostriatal neurocircuits [14][15]. On the other hand, adenosine A2A receptors (A2AR) are sparsely but widely distributed throughout the brain to selectively control synaptic plasticity processes [16][17][18], and they are more densely located in the basal ganglia to integrate dopaminergic modulation of corticostriatal glutamatergic transmission [19][20][21]. These adenosine receptors interact with dopamine receptors as A1/D1 and A2A/D2 receptor heterodimers, respectively [22], to efficiently regulate the mesocorticolimbic system and control addiction circuits [23].

The molecular mechanisms associated with drug abuse involve multiple processes ranging from neurotransmitter reuptake blockade, increase in excitatory neurotransmitters release, as well as high extracellular monoamine levels in synapses (reviewed in ref. [24]). Ethanol increases the synaptic levels of adenosine through direct and indirect processes [25][26][27]. Physiologically, the bidirectional equilibrative nucleoside transporters (ENT1) regulate adenosine intracellular and synaptic levels, and ethanol inhibits the activity of ENT1 (a direct mechanism), increasing adenosine levels in the synaptic cleft [28]. Chronic exposure to ethanol triggers neuroadaptations in the densities of A1 and A2A receptors, which may contribute to ethanol abuse and neurotoxicity [26][27][29].

The indirect process is a result of ethanol metabolism to acetaldehyde by alcohol dehydrogenase, CYP2E1 and catalase enzymatic systems. Subsequently, acetaldehyde is converted to acetate, catalyzed by aldehyde dehydrogenase [30]. The acetate produced is recycled to form the neurotransmitter acetylcholine by an active process (i.e., adenosine triphosphate consumption), increasing the levels of intracellular adenosine [30].

2. Ethanol versus Adenosine Effects on Anxiety

Ethanol is a drug commonly used in early adolescence, a period where curiosity, novelty, and risk-taking are prevalent [31]. Such early ethanol intake predisposes these adolescent consumers to a higher probability of ethanol abuse or dependence in adulthood since binge drinking leads to an escalating consumption of alcohol, culminating in a heavy drinking pattern of use, aggravating the neurotoxicological effects of ethanol [32][33][34]. Epidemiological studies have demonstrated that binge ethanol drinking induces mood and anxiety disorders in adolescents, either upon daily or episodic consumption [35][36]. Spear [2] reported that ethanol toxicological consequences are intensified among adolescents as a result of modifications in brain maturation and behaviors that are observed in both clinical and experimental studies.

Reduction and disruption of the integrity of the white matter, as well as a decrease of connectivity between the prefrontal cortex and limbic regions, i.e., mesolimbic and mesocortical pathways mediated by dopamine signaling, have been found following adolescent ethanol exposure [2][37]. These structural and molecular dysfunctions trigger long-lasting anxiety-like behavior in adulthood. Previous studies have indicated that anxiety-like behavior in rodents is present in several animal models involving ethanol consumption, including the development of social anxiety in male rodents [38], anxiogenic effects in elevated plus-maze in adolescent animal exposure to adulthood [39][40], in the light-dark box [41], and open field paradigms [42][43][44].

Some studies suggest that ethanol may increase adenosine levels in the brain by acetate-oxidation (acetyl-CoA to ATP) and inhibition of cellular uptake by ENT-1 blockade [45]. This overactivity of the adenosine system may result in different excitatory mechanisms by alteration of the balance between adenosine A1 (inhibitory) and A2A (excitatory) receptors, consequently affecting other neurotransmitters involved in anxiety [45]. As mentioned above, A1R are widespread in the brain, with the highest expression in the hippocampus, cerebral and cerebellar cortex, and thalamic nuclei [46]. Additionally, A1R are moderately expressed in the caudate-putamen and *nucleus accumbens*, acting presynaptically and postsynaptically [14]. In turn, A2AR have the highest density in basal ganglia and are also present in the extended amygdala and hypothalamus that are involved in the modulation of anxiety and stress [47][48].

The exploration of anxiety-like behavior (elevated plus maze and open field test) at several time points after withdrawal of ethanol intake following an intraperitoneal administration of an acute ethanol dose (4 g/kg) revealed a more pronounced alteration of anxiety between 12–18 h [49]; the acute administration of an A1R agonist (CCPA: 0.05, 0.125, and 0.25 intraperitoneally) reduced of anxiogenic-like behavior in the elevated plus-maze, whereas the administration of the selective A2AR agonist (DPMA) had no effect. Conversely, the selective A1R antagonist 8-cyclopentyl-1,3-dipropylxanthine (DPCPX) triggered anxiety. These findings were also reported by another group [50] using the A1R agonist R-N6-phenylisopropyladenosine (R-PIA) and the A2AR agonist 2-p-(2-carboxethyl) phenylethyl-amino-5′-N-ethylcarboxamidoadenosine (CGS 21680). Other studies also suggest the direct involvement of adenosine on anxiety, since A1R knockout mice displayed increased anxiety and an aggressive profile [51][52]. These results indicate that A1R may be involved in anxiety-like behavior and emerges as a promising pharmacological target to attenuate anxiety conditions [53].

A2AR knockout mice also display alterations of anxiety-like behaviors, and ADORA2A polymorphisms are associated with social behavior and exploratory activity, eliciting anxiety-like behavior with the involvement of the anterior cingulate cortex and amygdala [54][55][56][57]. Accordingly, the genetic deletion of neuronal A2AR prevents stress-induced anxiety [58], whereas the overexpression of A2AR leads to an anxiogenic profile [59]. This also implies a role of A2AR in the control of anxiety [60][61].

The researchers hypothesize that ethanol exposure induces hyperexcitability of the adenosinergic system in the adolescent brain, eliciting two fundamental alterations: (i) disruption of brain maturation, promoting unbalance of adenosine A1/A2A receptors, inducing anxiety behavior, and (ii) modifying adenosine-dependent neurotransmitter levels and the activity of neurocircuits involved in anxiety.

The impact of ethanol intake on the density and expression of adenosine receptors has resulted in somewhat conflicting results. Thus, chronic heavy intermittent ethanol vapor exposure followed by withdrawal (blood ethanol concentration 162.1–217.9 mg/dL) for 64 h, followed by 8 h of withdrawal or not, causes an overexpression of A1R in the cerebral cortex, with no changes of A2AR density in the striatum [62]. In contrast to these findings in adult rodents, the intake of ethanol in adolescent mice triggers a persistent reduction of brain A1R density during withdrawal [63]. A reduction of A1R expression and density in the cerebral cortex and cerebellum of the offspring of dams exposed to ethanol was also observed [64]. Notably, there is a positive correlation between A2AR affinity and the A2AR/A1R affinity ratio but a negative correlation between A1R affinity and the potency (ED50) of adenosine agonists to accentuate ethanol-induced motor incoordination [65]. In general, noxious situations trigger a downregulation of A1R and an upregulation of A2AR [11][59].

These adaptive changes are expected to contribute to an increase in excitatory glutamatergic synaptic transmission [66][67], mainly by a reduction of A1R density, impairing inhibitory control in synapses, as reported in experimental and clinical studies [68][69]. In particular, both glutamatergic N-methyl-D-aspartate (NMDA) receptors and voltage-sensitive calcium channels are controlled by the tonic activation of A1R [70][71], as well as by A2AR [72], implying that ethanol can imbalance the control of synaptic plasticity as well as of neurodegeneration that is critically dependent on NMDA receptors and voltage-sensitive calcium channels [73].

Apart from this imbalanced adenosine modulation of plasticity that is critical for the development of additive behaviors, adenosine modulation of reward circuitry is also altered [24][60][74]. Reward circuitry activation by glutamatergic inputs from the cortex, as well as dopaminergic inputs from the ventral tegmental area with projections to medium spiny neuron striatum, through heterodimers of A2A-D2 and A2A-mGlu5 receptors, may be probable pathophysiological mechanisms induced by ethanol abuse since this substance increases adenosine levels causing hyperactivation of A2AR, with consequent increased release of dopamine and glutamate [24][75][76]. Consequently, neural excitotoxicity, changes in homeostatic regulation by oxidative stress, abuse risk, and several behavioral alterations, such as anxiety, occur [27].

Adenosine receptors, in particular A2AR, control the activity of the hypothalamus–pituitary–adrenal (HPA) axis [77]. In particular, adenosine modulates different circuits of the pituitary gland [78]. In the intermediate region, the blockade of A2AR reduces proopiomelanocortin and alfa-MSH levels, reducing the activation of the HPA axis [79]. Conversely, the inhibition of A2AR in the anterior lobe of the pituitary hyperactivates the HPA axis, increasing proopiomelanocortin, adrenocorticotropic hormone, and consequently blood corticosterone levels [79], which characterizes the anxiety-related profile. However, further investigations focused on ethanol-induced anxiety versus adenosinergic modulation of the HPA axis during adolescence should be undertake.

In summary, the knowledge of the balance between adenosine receptors (A1 and A2A) in the adolescent brain and the control of neurotransmitters in different neurocircuits is a significative step toward elucidating the hypothesis. Such well-outlined mechanisms may support critical strategies for neuroprotection or treatment of anxiety induced by ethanol consumption in adolescents by pharmacological or genetic manipulations targeting adenosine receptors.

3. Ethanol versus Adenosine Effects on Depression

Depression is an affective disorder characterized by the presence of mood dysregulation typified by a depressed mood (dysphoria) and reduced ability to have pleasure (anhedonia). Depressed patients may also present cognitive impairment and somatic symptoms, leading to significant distress or impairment in general body system functioning [80][81][82]. Depressive disorders can be triggered by several etiologies, including drug abuse, such as opioids, sedatives, stimulants, and hallucinogens, whereas depressive symptoms can appear during or shortly after intoxication or discontinuation of the drug of abuse [80][83][84][85].

Epidemiological studies have consistently concluded that alcohol intake in a binge pattern, mainly in late adolescence, elevates the risk of developing depressive symptoms in young women between 20 to 30 years of age, when the consumption occurs frequently, approximately 16% [86]. Moreover, drinking habits are often associated with depressive symptoms and suicide in young individuals, with circa 11.5% showing depressive behavioral and 2.8% suicidal ideation [87]. Ethanol is a CNS depressant which triggers depressive symptoms by different molecular targets. According to Alasmari et al. [88], ethanol consumption elicits modifications in dopamine, glutamate, and GABA neurotransmitter release. It is noteworthy that significant dopaminergic reductions in the reward system or in neurotransmitter recruitment play a role in the progression of negative reinforcement, resulting in psychoneuroimmunological neuroadaptations related to neuroinflammation and emotional disruption [88][89][90][91]. It has also been reported that ethanol exposure reduces brain-derived neurotrophic factor (BDNF) in the hippocampus [92][93][94]. Such alterations are more harmful during adolescence since, during brain maturation, an unbalance of neuromodulatory mediators affects limbic circuitry, impairing the development of neurocircuitry in the prefrontal cortex, leading to increased limbic reactivity and consequently changes in affective control [95][96].

In addition, adolescent subjects present elevated amygdala activity and decreased fear extinction, mediated by changes in prefrontal cortex–amygdala connectivity [97]. Furthermore, the adolescent brain is particularly sensitive to repeated ethanol exposure. Thus, ethanol neurotoxicity associated with enhanced emotional reactivity and poor effective control displays augmented risk of emergence and exacerbation of emotional dysregulation, such as depression [2][96][98].

An interesting study indicated a relationship between adenosine and the pathophysiology of alcoholism and depression [99]. Inhibitory mechanisms of adenosine in the CNS, which modulate excitability, neurotransmitter release, and ion channel function regulation, play a role in mood changes in alcohol-exposed patients [14][100][101]. In cell culture assays, ethanol acute exposure increases adenosine levels and contributes to intoxicating and/or rewarding effects [102][103]. High levels of adenosine hyperactivate A2AR signaling, which develops desensitization across prolonged ethanol exposure [104]. Another fundamental neuroadaptation consists of the reduction of the plasma membrane nucleoside transporter ENT-1, which results in reduced extracellular and synaptic adenosine levels [60][104]. Despite these findings, few studies have addressed the impact of alcohol exposure during adolescence on the adenosine modulation system.

Scarce studies have demonstrated that repeated ethanol administration (2.0 g/kg) in adolescent mice increased the binding activity of cAMP response element-binding protein (CREB) in the prefrontal cortex and hippocampus [105]. It is well-defined that elevation of CREB expression in the dorsomedial striatum, olfactory bulb, and GABAergic neurons of caudate-putamen, *nucleus accumbens*, and tuberculum olfactory, also occurs upon recruitment of A2AR and is likely associated with negative behavioral changes (i.e., anxiety-like and depressive-like phenotype) induced by heavy ethanol consumption in mice [59][106].

Taken together, the available evidence is suggestive of the involvement of the adenosine modulation system in the depressive-like profile induced by ethanol exposure during adolescence, namely through CREB overexpression resulting from the overactivation of A2AR. It is noteworthy that A2AR hyperactivation directly influences A2A/D2 heterodimerization, as already mentioned above when discussing anxiety [107][108]. Accordingly, functional interrelationships related to mesocortical and mesolimbic pathways of A2A/D2 receptor interactions that are impaired by ethanol administrations may result in emotional, motivational, rewarding, and addiction behavior disruption and learning dysfunction, which reinforces the putative role of the adenosine modulation system in several neuropathologies, such as anxiety, drug addiction, schizophrenia, and depression [59][109].

To support this link between A2AR modulation and depressive-like behavior through the influence of dopamine levels, Coelho et al. [59] investigated the impact of A2AR overexpression in cortical areas for dopamine-related behavior. These authors found that the hyperactivity of the A2AR pathway induces a depressive-like phenotype [59][110][111]. Furthermore, Kaster et al. [58] reported that the chronic caffeine administration or selective adenosine A2AR antagonism or genetic deletion of adenosine A2AR is able to prevent or revert mood and memory dysfunction, as well as neurochemical and synaptic deficits induced by chronic stress.

In summary, acute and/or chronic ethanol exposure during adolescence disturbs the homeostasis of the adenosine modulation system in the brain, contributing to hazardous symptoms related to depression. In addition, overexpression of A2A/D2 receptors in mesocorticolimbic areas, preferably in the forebrain, has been associated with depression behavior, which may explain the depressive signs seen in aging and chronic stress [59].

4. Ethanol versus Adenosine Effects on Cognition

Cognitive functioning depends on multiple integrated processes occurring in distinct areas of the CNS. For instance, the acquisition of declarative (or spatial) memories begins in the hippocampus, through synaptic changes, since damages to this structure compromise recent memory, while remote memories remain intact. This fact suggests that cognitive storage occurs in other structures, such as the neocortex, which has been widely pointed out as an important storage location [112][113][114]. In turn, the targeting/selection of memories that will become long-lasting is regulated by environmental factors and emotionality, among other factors, and this modulation is operated by structures such as the prefrontal cortex amongst others [113][115].

Classically, the neurotransmitters glutamate and acetylcholine play a fundamental role in memory processing [116][117]. Nonetheless, other signaling systems robustly regulate memory acquisition, including the adenosine

modulation system. Imbalances in the adenosine system affect several CNS functions, including cognition, whereas overactivation of adenosinergic receptors, especially the A1R and A2AR subtypes, elicit memory impairment [108]. Although it is complex to define the exact contribution of the different adenosine receptors to the control of cognition since their responses differ upon homeostatic or pathological conditions [118][119][120], a prominent role of A2AR seems evident: this is best heralded by the observation that the pharmacological overactivation of A2AR [121] or the overexpression of A2AR in forebrain neurons [122] or the opto-stimulation of the A2AR transducing system [123] are each sufficient to cause a disruption of spatial reference memory performance.

In keeping with the hypothesis of a parallel an opposite deregulation of the A1R/A2AR imbalance upon repeated ethanol intake, the researchers propose that cognitive deficits may also be dependent on A1R/A2AR activity. Thus, overactivation of A1R inhibits the release of glutamate and acetylcholine, impairing cognition processes, such as memory acquisition and consolidation mediated by the hippocampus [116][117]. The overactivity of A1R may lead to cognitive impairment. Accordingly, acute treatment with micromolar doses of A1 receptor agonists induced deficits in memory acquisition and retention, whereas the administration of selective A1 receptor antagonists reversed these negative effects [124].

Therefore, substances that promote an increase or imbalance in adenosine receptor activity may produce mnemonic impairments, especially in critical periods of development/remodeling of the CNS [125]. Epidemiological data reveal that ethanol consumption, especially in a binge pattern, usually starts during adolescence [125][126][127][128], and neural circuits in the immature brain are vulnerable to several factors that modulate brain function [128].

Accordingly, the researchers reported that the cumulative four cycles of binge drinking paradigm (3 g/kg/day) during adolescence impairs short-term memory in object recognition tasks in the immediate ethanol withdrawal period [39]. In agreement with this, other binge drinking studies during adolescence also found mnemonic disruption by applying diverse cognitive tests [8][129][130][131], highlighting the potentially hazardous effects of binge-like consumption on distinct types of memory.

Numerous pathophysiological mechanisms have been attributed to mnemonic abnormalities. Oxidative stress, deficits of neurotrophin levels, glutamatergic hyperactivity, and reduction of neuronal viability and survival have been considered as possible causes of memory impairments induced by adolescent alcohol binge drinking [8][129][130][131][132]. Although all these previously described mechanisms induce mnemonic disturbances, the probable involvement of the adenosine system should also be considered. Indeed, it was reported that the acetate originating from ethanol metabolism could be incorporated into acetyl-coenzyme A, supporting the production of cAMP and adenosine, thus bolstering adenosinergic signaling [133]. In addition, alcohol consumption also inhibits adenosine reuptake, which increases the extracellular levels of adenosine and, consequently, its actions [60]. These effects likely depend on the pattern of alcohol exposure. Acutely, alcohol increases adenosine levels, which leads particularly to sedation and cognitive impairment [124]. Chronic exposure seems to trigger a reduction of ENT-1 expression and an influx of adenosine, as mentioned above [102][133]. Both responses impair the balance of influx/efflux of adenosine, thus reducing its regulatory activity, a reduction further aggravated by the early heterologous desensitization of A1R and A2AR. Microdialysis studies detected a four-fold increase in adenosine

levels in the brain parenchyma following ethanol exposure, which, among other responses, contributes to its sedative/hypnotic properties, in addition to inducing cognitive disorders [124]. In fact, animal and human studies confirm the potential of ethanol to display memory impairment related to adenosine overactivity. Obviously, these toxicological events can also occur in adolescents and adult individuals. Studies in zebrafish exploring the long-term consequences of early ethanol exposure in distinct embryonic stages indicated the emergence of a mnemonic impairment, which was reversed by acute administration of an ecto-5'-nucleotidase inhibitor (an enzyme that converts extracellular AMP into adenosine) [134]. This emphasizes the influence of the adenosine system on persistent cognitive deficits induced by ethanol exposure during neurodevelopment [134].

However, there are some peculiarities related to maturing processes during adolescence, which might elicit different results. For example, both increased expression of adenosine receptors and downregulation of their reuptake seem to be associated with continuous consumption, accompanied by multiple episodes of withdrawal [29] [102]. This fact is of relevance since the binge drinking, frequently performed by teenagers, is characterized by an intermittent consumption, which provides favorable conditions for the occurrence of these mechanisms [126][128]. Unfortunately, few approaches have assessed the relationship of this pattern of alcohol intake with adaptations of the adenosine system affecting memory processing, especially during adolescence, which await further investigations to unravel novel therapeutic strategies.

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