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Research report

Central histaminergic transmission modulates the ethanol induced anxiolysis in mice

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HIGHLIGHTS

- Biphasic role of endogenous histamine in the ethanol induced anxiolysis is proposed.
- Low dose of histamine attenuates while high dose enhances the ethanol induced anxiolysis.
- Histamine H_1 receptor stimulation counteracts the ethanol induced anxiolysis.
- Histamine H_2 receptor stimulation potentiates the ethanol induced anxiolysis.

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ABSTRACT

Intrigued by the report demonstrating an increase in brain histamine levels by ethanol administration and central histamine transmission to affect the anxiety related behaviors, the present study examined the permissive role of central histaminergic transmission in the acute anxiolytic-like effect of the ethanol on elevated plus maze (EPM) in mice. Results demonstrated that prior administration of the agents that are known to enhance the brain histamine transmission, i.e. low dose of histamine (0.1 μg/mouse, i.c.v.) or histamine precursor, L-histidine (500, 1000 mg/kg, i.p.) or low dose of histamine releasing agent (H_3 receptor inverse agonist), thioperamide (2 μg/mouse) attenuated the acute anitanxiety-like effect of ethanol (2 g/kg, i.p, 8% w/v) in mice on EPM. However, pre-treatment with the H_1 receptor antagonist, cetirizine (0.1 μg/mouse, i.c.v.) or H_2 receptor antagonist, ranitidine (50 μg/mouse, i.c.v.) failed to affect the attenuating effect of low dose of histamine on ethanol induced anxiolysis. On the other hand, only H_1 receptor antagonist, cetirizine (0.1 μg/mouse, i.c.v.) was able to partially reverse the attenuation of ethanol induced anxiolysis by L-histidine (1000 mg/kg, i.p.). Surprisingly, in mice pre-treated with the higher dose of histamine (50 μg/mouse, i.c.v.) or thioperamide (10 μg/mouse, i.c.v.), the ethanol (2 g/kg, i.p.) induced antianxiety-like effect was further enhanced on EPM. Furthermore, this potentiating effect of high dose of histamine on the ethanol (2 g/kg, i.p.) was exacerbated on pre-treatment with the H_1 receptor antagonist, cetirizine, while H_2 receptor antagonist, ranitidine completely reversed this action of high dose of histamine on ethanol. Supportive to these results, i.c.v. pre-treatment with H_1 receptor agonist, FMPH (2, 6.5 μg/mouse, i.c.v.) attenuated while H_2 receptor agonist, amthamine (0.1, 0.5 μg/mouse, i.c.v.) enhanced the ethanol induced anxiolysis in mice. Thus, it is reasonable to contemplate that central histaminergic transmission functions to negatively modulate the acute ethanol-induced anxiolysis probably via stimulation of postsynaptic H_1 receptor and histamine might contribute to the anxiolytic action of ethanol via H_2 receptor activation.

1. Introduction

The acute anxiolytic effects of ethanol have been well established by the plethora of reports [1–3] and its chronic consumption precipitate withdrawal associated neuroadaptive changes that may lead to a gradual increase in anxiety measures [4–6]. These behavioral effects of the ethanol have been considered to be important for the relapse and subsequent increase in voluntary ethanol consump-

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tion in animals [7,8] and humans [9,10]. Apart from animal reports demonstrating an important and complex relationship between stress, anxiety, and alcohol use disorders (AUD) [3,11], clinical studies have also documented a significant degree of relation between anxiety disorders and alcohol abuse [12,13]. Moreover, ethanol dependence is often considered as a chronic, relapsing disease [14] and there is evidence that stress and anxiety may promote relapse and negatively influence treatment prognosis [15,16]. Previous findings have reported several mechanisms that can modulate the ethanol induced effects on anxiety for example, GABAergic neurosteroids by stimulation of α-aminobutyric acid receptor type A ($GABA_A$) participating in the ethanol induced anxiolysis [1] and neuropeptide like GnRH attenuates the ethanol withdrawal induced anxiety [17], while *n*-methyl-D-aspartate (NMDA) or 5-hydroxy tryptamine $(5\text{-HT})_3$ receptor have been reported to regulate the ethanol induced other behvioral effects [18–20]. Recently, the central histaminergic transmission has attracted lots of attention in the ethanol induced effects, but the exact role of such interaction in the acute ethanol induced anxiety related effects is still a matter of investigation.

Converging evidence indicates that central histaminergic transmission also modulates the anxiety related behaviors, reporting both anxiolytic [21,22] and anxiogenic profile of histamine or histamine precursor using different paradigms, which alter with the dose and site of administration [23,24]. Moreover, it was demonstrated that histamine turnover in the rodent brain increases on exposure to stressful conditions and was found to be reduced with treatment of anxiolytic drugs like diazepam or buspirone [25–27]. In addition, destruction of the rat tuberomamillary nucleus (TMN) reduces anxiety-related defensive behaviors in the EPM, a widely used animal model of anxiety [28]. In contrast, recently it was reported that animals maintained on a diet, deficient in histamine precursor, L-histidine, exhibited higher levels of anxiety [29] supporting the anxiolytic action of endogenous histamine. Therefore, all these reports are pointing towards a possible participation of endogenous histamine in the modulation of anxiety related behaviors. However, there is a paucity of reports suggesting the role of endogenous histamine in the ethanol induced anxiety related behavioral effects.

Interestingly, several arrays of research findings have shown an altered brain histamine concentration on ethanol treatment/consumption [30–33], which might be an important modulator to regulate the alcohol reward and reinforcements. Corroborative findings are available to support this, for examples, H_3 receptor inverse agonist/antagonists, which increase the synthesis and release of histamine, reduce alcohol consumption in rats [34]. On the other hand, R-α-methylhistamine, an H_3 receptor agonist, increases ethanol intake [34]. Moreover, potentiation of CNS depressant effects of ethanol by antihistaminic agents is a common clinical observation [35]. Further, It has also been reported that ethanol enhances the stimulatory effect of histamine on cyclic AMP formation in the cerebral cortex of mice treated chronically [36] and those of rats experiencing withdrawal [37]. Interestingly, acute ethanol treatment has been demonstrated to elevate the content of histamine in a time-dependent manner in the rat or mice whole brain [30], while chronic ethanol administration in increasing doses (up to 6 g/kg) is reported to decrease the rat hypothalamic histamine levels [38], which was in contrast to an earlier report demonstrating an elevation in the same brain region [39]. Moreover, ethanol induces dose and time dependent changes in brain histamine turnover and in HD (histidine decarboxylase) activity in the hypothalamus [40]. Recently, it was demonstrated that brain histamine might also modulate the ataxic and sedative effects of ethanol and could therefore interfere with the expression of ethanol-induced behaviors [41]. Above all, a pharmacokinetic interaction of ethanol and histamine at a metabolic level has also been demonstrated, due to competition for the common enzymes, i.e. aldehyde dehydrogenase and aldehyde oxidase [42].

Thus, intrigued by the reports indicating an increase in brain histamine levels on ethanol administration, ability of histamine to affect anxiety measure and modulation of ethanol induced effects by histamine, we hypothesized that increase in histaminergic transmission by ethanol administration might play a cardinal modulatory role in the ethanol induced anxiolytic effect. In order to ratify our hypothesis the present investigation was undertaken to evaluate the role of the central histaminergic transmission in the acute ethanol induced anxiety related behaviors in male Swiss mice on elevated plus maze (EPM). In order to address the above hypothesis, present study evaluated the effects of the agents that are known to enhance the central histaminergic transmission i.e. histamine, histamine precursor, L-histidine and histamine neuronal releasing agent, H_3 receptor inverse agonist on acute ethanol induced anxiolysis. In addition, the literature was also found to be silent on the role of histamine via H_1 and H_2 receptor in the acute ethanol induced behvioral effects on anxiety. Therefore, to address the involvement of H_1 or H_2 receptor in the histamine induced effects on ethanol anxiolysis, protocols were also designed using H_1 or H_2 receptor agonists and antagonists in combination with ethanol.

2. Material and methods

2.1. Subjects

All procedures were carried out under strict compliance with ethical principles and guidelines of the Committee for the Purpose of Control and Supervision of Experimental Animals, Ministry of Environment and Forests, Government of India, New Delhi. All the protocols were performed on adult male Swiss albino mice (age 10–12 weeks and weighing 20–25 g at the beginning of experiments), which were procured from a stock originally from a breeder Shree Farms, Bhandara, India. All the animals were allowed to acclimatize to the institute animal house facility for two weeks before being tested and were maintained on a 12:12-h light/dark cycle (lights on at 06:00 h) in a temperature-controlled ($24 \pm 2\,^{\circ}C$) and humidity-controlled environment ($65 \pm 5\%$). Animals were group housed ($n = 6$) except surgically cannulated mice, which were housed individually with free access to rodent chow (Trimurti Feeds, Nagpur, India) and water *ad libitum* except during the experiments. All the behavioral assessments were conducted during the light cycle between 09:00 and 14:00 h to minimize diurnal fluctuations induced changes in behaviors. Animals were brought to the experimental room 12 h prior to the start of the experiments to minimize novel environment-induced behavioral changes. Each experimental group had a separate set of animals, and an individual animal was tested once only to avoid 'one-trial tolerance' to the anxiolytic efficiency of drugs including ethanol in EPM test [43].

2.2. Drugs and solutions

Histamine dihydrochloride, histamine precursor, L-histidine dihydrochloride, histamine H_1 selective receptor agonist, 2-(3-trifluoromethylphenyl)histamine (FMPH) (2138-fold more selective to H_1 than on H_2-receptors) [44], H_2 selective receptor agonist, amthamine [45] and histamine releasing agent H_3 receptor antagnonist/inverse agonist, thioperamide maleate [46,47] were procured from Sigma-Aldrich, USA, while H_1 receptor antagonist, cetirizine hydrochloride (In binding studies, the affinity of cetirizine is at least 500 times in favour of histamine H_1 receptors vs. histamine H_2 or H_3 receptors) [48,49] and the selective H_2 receptor antagonist, ranitidine hydrochloride [50,51] were generously gifted