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## INVITED REVIEW

# ALCOHOL–HISTAMINE INTERACTIONS

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**Abstract** — Alcohol and histamine metabolic pathways in the body have the common enzymes aldehyde dehydrogenase and aldehyde oxidase. The metabolite of ethanol, acetaldehyde, can effectively compete with the metabolites of histamine, methylimidazole acetaldehyde, and imidazole acetaldehyde. At the periphery, alcohol and acetaldehyde liberate histamine from its store in mast cells and depress histamine elimination by inhibiting diamine oxidase, resulting in elevated histamine levels in tissues. Histamine mediates alcohol-induced gastric and intestinal damage and bronchial asthma as well as flushing in Orientals. On the other hand, alcohol provokes food-induced histaminosis and histamine intolerance, which is an epidemiological problem. There are many controversial reports concerning the effect of $H_2$ receptor antagonists on ethanol metabolism and the activity of alcohol dehydrogenase in the stomach. In addition, alcohol affects histamine levels in the brain by modulating histamine synthesis, release, and turnover. Histamine receptor antagonists can affect ethanol metabolism and change the sensitivity of animals to the hypnotic effects of alcohol. In contrast to other neurotransmitters, the involvement of the brain histamine system in the mechanisms of the central actions of alcohol and in the pathogenesis of alcoholism is poorly studied and understood.

## INTRODUCTION

To the authors' knowledge, the problem of alcohol–histamine interaction, surprisingly, has not been reviewed or discussed either in the literature or at international meetings. Most of the publications available on the problem are devoted to the safety of histamine receptor antagonists (antihistamines) as drugs widely used clinically for the treatment of allergy and stomach hypersecretion and ulcers (reviewed by Smallwood *et al.*, 1995). Only a few of such studies consider the problem in the context of biomedical research on alcoholism. Histamine is biologically a very active compound, which participates in intercellular signalling and is characterized as a neurotransmitter. There are several comprehensive reviews of various aspects of histamine function and histamine systems in the body (Schwartz *et al.*, 1991; Yamatodani *et al.*, 1991; Onodera *et al.*, 1994). The data available can be summarized briefly as follows. Since histamine cannot pass through the blood–brain barrier easily, the histamine in the body can be divided into two pools: peripheral and central. The main stores of histamine at the periphery are the mast cells, basophils, and enterochromaffin-like cells. In the brain, histamine is localized in histaminergic neurones; small amounts of histamine reside in mast cells and possibly in the endothelium of blood vessels. The cell bodies of histaminergic neurones are located in the hypothalamus only, but their processes reach all important parts of the brain. In the periphery, histamine produces contractile effects on smooth muscles, capillary dilatative action, and a stimulant effect on gastric secretion. Central histamine is involved in various physiological functions including the regulation of neuroendocrine and cardiovascular systems, sleep–wakefulness, thermoregulation, feeding, drinking, learning and memory, cerebral vascular regulation, analgesia, etc. The involvement of central histamine in a number of pathological

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states (motion sickness, epilepsy, Alzheimer's disease, morphine dependence) has also been suggested (see reviews by Schwartz *et al.*, 1991; Yamatodani *et al.*, 1991; Onodera *et al.*, 1994). Histamine acts through three types of receptors, $H_1$, $H_2$ (postsynaptic), and $H_3$ (presynaptic, mediating the autoinhibition of histamine synthesis and release). Histamine receptors are widely and heterogeneously distributed in the brain and peripheral tissues and belong to the G-protein coupled receptor superfamily (Schwartz *et al.*, 1991; Leurs *et al.*, 1995). Histamine is synthesized from L-histidine by the enzyme histidine decarboxylase. No high-affinity and selective uptake system for histamine has been found in the central nervous system (CNS). Histamine is removed by histamine-N-methyltransferase (HMT) by conversion to *tele*-methylhistamine, which is further metabolized to N-*tele*-methylimidazole-acetic acid by the sequential actions of type B monoamine oxidase and aldehyde dehydrogenase (ALDH). In peripheral tissues, about 30–40% of total histamine is oxidized by diamine oxidase (DAO, histaminase) and aldehyde oxidase to imidazolacetic acid, a full agonist of type A GABA receptors. In brain, this can take place when the HMT is inhibited (Prell *et al.*, 1997). Thus the histamine- and ethanol-metabolic pathways have common enzymes — ALDH and aldehyde oxidase. Therefore, the highly active ethanol metabolite, acetaldehyde, can interfere with histamine degradation by competition with N-*tele*-methylimidazole and imidazole acetaldehydes for these enzymes (Ambroziak and Pietruszko, 1987). This may form the metabolic basis for alcohol–histamine interactions in the body.

## EFFECTS OF ALCOHOL ON HISTAMINE LEVELS AND METABOLISM

The effect of acute ethanol administration on histamine levels in brain strongly depends on the dose of alcohol, the species of experimental animals, and the brain structure studied, with increases, decreases or no change all having been reported (Table 1). The chronic administration of ethanol to adult rats has been reported to increase (Nowak and

Table 1. Acute effects of ethanol on histamine level in brain

| Dose (g/kg, body wt) and method of ethanol administration | Animal species | Brain structure | Direction of change | Reference |
|---|---|---|---|---|
| 2, i.p. | Rat | Whole brain | ↑ | Rawat (1980) |
| 0.8–1.6, p.o. | Rat | Brain cortex | ↑ | Subramanian *et al.* |
| | | Thalamus | ↑ | (1980) |
| 0.175, i.p. | Mouse | Whole brain | ↑ | Papanicolaou |
| 1.755, i.p. | Mouse | Whole brain | ↓ | and Fennessy (1980) |
| 1, p.o. | Rat | Hypothalamus | ↑ | Prell *et al.* (1982) |
| | | Midbrain | ↑ | |
| 2, p.o. | Rat | Hypothalamus | ↓ | Prell *et al.* (1982) |
| | | Hypothalamus | = | |
| | | Midbrain | = | |
| | | Brain cortex | = | |
| 0.5–5, p.o. | Mouse | Hypothalamus | = | Itoh *et al.* (1985) |
| 5, i.p. | Guinea pig | Brain cortex | ↓ | Nowak and |
| | | Hypothalamus | ↓ | Maslinski (1984) |
| | | Rest of brain | ↓ | |

i.p., Intraperitoneally; p.o., *per os*.

Maslinski, 1984) or not to change (Fogel *et al.*, 1991) the level of histamine in the brain regions. Chronic alcohol consumption in neonatal rats suckling ethanol-feeding mothers increases brain histamine (Rawat, 1980). Maternal alcohol consumption in rats significantly increases the urinary excretion of histamine and decreases the content of the histamine precursor histidine in fetal tissues (Lin *et al.*, 1990). Maternal alcohol consumption either during gestation or during lactation does not result in a significant change in histidine decarboxylase activity in the fetal and neonatal whole brains (Rawat, 1980). However, the activity of the above enzyme has been reported to be increased after the administration of ethanol in hypothalamus, midbrain and brain cortex of adult rats (Prell *et al.*, 1982), but it has also been reported to be decreased in brain cortex and thalamus (Subramanian *et al.*, 1980). Almost all authors consider that following alcohol administration, the activity of histamine N-methyltransferase does not change in any brain region (Subramanian *et al.*, 1980; Prell and Mazurkiewicz-Kwilecki, 1981; Prell *et al.*, 1982). Ethanol increases the steady-state N-*tele*-methylhistamine levels in the mouse hypothalamus, probably by inhibiting the elimination of this metabolite from the brain (Itoh *et al.*, 1985). Ethanol selectively inhibits the activity of the B-form of monoamine oxidase in membranes obtained from human platelet and brain (Tabakoff *et al.*, 1985). Acute and chronic administration of ethanol inhibits the activity of diamine oxidase (DAO) in rat tissues (Desiderio *et al.*, 1987; Sessa *et al.*, 1987; Sessa and Perin, 1992). This may be one of the reasons why alcohol provokes food-induced histaminosis and histamine intolerance (Sattler *et al.*, 1988; Jarisch and Wantke, 1996). Normally, histamine from food is metabolized rapidly in the gastrointestinal tract by DAO and is thus not absorbed into the circulation. Oral histamine administration to pigs pretreated with a DAO inhibitor leads to a marked increase of histamine level in plasma and associated clinical responses: flush, hypotension, increased heart rate (Sattler *et al.*, 1988).

The biochemical data indicate that alcohol can affect histamine content and metabolism both at the periphery and in the brain, but there are no morphological observations of the central histamine system in animals or humans (alcoholic patients), either in the adult or developing brain.

## HISTAMINE-RECEPTOR LIGANDS IN THE REGULATION OF ALCOHOL METABOLISM

The data available on the role of histamine in the regulation of alcohol metabolism are restricted to the effects of histamine $H_2$ receptor antagonists on the first-pass ethanol metabolism. Since histamine stimulates gastric acid secretion through the $H_2$ receptors, antagonists of these receptors are widely used for treatment of gastric hypersecretion and ulcers. The data have been analysed in the context of safety of acid-suppressing drugs. In some studies of animals and humans, treatment with histamine $H_2$ receptor antagonists increased (12–18%) the peak blood-ethanol concentration and increased (8–15%) the area under the blood-alcohol concentration curve, probably because of the inhibition of the alcohol dehydrogenase (δ-ADH) in the stomach (see review by Gugler, 1994; Kawashima *et al.*, 1996). However, in numerous other studies, little or no effect on alcohol metabolism was observed (see reviews of Gugler, 1994 and Smallwood *et al.*, 1995). The reasons for the conflicting evidence concerning the effects of $H_2$ receptor antagonists on ethanol kinetics can be explained by differences in timing of alcohol ingestion, dose, relationship to food intake and the varying ethnic backgrounds of subjects in the different studies (Baraona *et al.*, 1994; Smallwood *et al.*, 1995). The absence of δ-ADH isoenzyme has been demonstrated in the stomach of normal Orientals and this may be directly related to the diminished first-pass metabolism of ethanol in gastric mucosa and the absence of an effect of antihistamines in these subjects (Baraona *et al.*, 1994; Kawashima *et al.*, 1996). In addition, $H_2$ histamine receptor antagonists do not influence the ethanol concentration–time curve when ethanol is ingested on an empty stomach (Clemmensen *et al.*, 1997). However, in this case, the first-pass metabolism itself may be very low due to the insufficient period for ethanol absorption and elimination in the stomach as a result of its quick transition to the duodenum.

There are limited data on the involvement of histamine in regulation of alcohol metabolism in the other organs: the histamine $H_2$ receptor antagonist cimetidine (3 mM) inhibits rat liver ALDH, but not ADH *in vitro* (Messiha, 1989). The effect of histamine $H_1$ receptor antagonists (clemastin

and promethazine) on ethanol metabolism has been studied (Zimatkin *et al.*, 1997). These antagonists decrease the concentrations of ethanol in the brain (measured from 1–6 h following ethanol administration). In addition, promethazine decreases blood ethanol and acetaldehyde levels at the later elimination period (4–6 h) (Zimatkin *et al.*, 1997).

## HISTAMINE MEDIATION OF THE PERIPHERAL EFFECTS OF ALCOHOL

The involvement of histamine in ethanol-induced injury of the stomach and intestine, bronchial asthma, and flushing are considered here. The alcohol-induced damage of the gastrointestinal mucosa is well known and has been reviewed by MacMath (1990). It has been reported that administration of $H_2$ receptor antagonists to rats corrected ethanol-induced damage of mucosa promptly (Hernandez-Munoz and Montiel-Ruiz, 1996). Exposure of the intestinal mucosa to ethanol solution induced histamine release from the intestinal mast cells and a dramatic jejunal protein loss, reflecting microvascular injury; histamine $H_1$ and $H_2$ receptor antagonists partly prevented this phenomenon (Dinda *et al.*, 1988, 1996). R-α-methylhistamine, a selective agonist of histamine $H_3$ receptors (autoinhibition of histamine synthesis and release) dose-dependently inhibited ethanol-induced gastric lesions (Morini *et al.*, 1995). These results indicate the important role of local histamine in the mediation of the damaging effects of alcohol on the gastrointestinal mucosa.

Many Japanese patients have asthma episodes or exacerbation of asthma after alcohol consumption. This phenomenon is not seen in Caucasians and is specific to Asians and probably attributable to known ethnic differences in alcohol metabolism. Inhalation of acetaldehyde, but not ethanol, in guinea pigs causes bronchoconstriction in a dose-dependent manner, which is prevented by pretreatment with the histamine $H_1$ receptor antagonist diphenhydramine (Myou *et al.*, 1994, 1995). It was found recently that blood acetaldehyde and histamine levels were significantly higher in patients who were responsive to alcohol in this way, than in non-responsive subjects with asthma (Shimoda *et al.*, 1996). It seems that the metabolite of ethanol, acetaldehyde, is a major factor in alcohol-induced asthma, causing bronchoconstriction indirectly through endogenously released histamine in asthmatic subjects. No tachyphylaxis was, however, found following inhalation of histamine (Myou *et al.*, 1995).

It is well known that Orientals (Mongoloid ancestry) have a genetic predisposition to the adverse reaction to alcohol, which is manifested as alcohol-induced flushing. It includes a cutaneous flush, decrease in blood pressure, increase in skin temperature and pulse rate and subjective symptoms such as dizziness, sleepiness, anxiety, headache, weakness, and nausea (Wolff, 1972; Seto *et al.*, 1978). Acetaldehyde is known to be the mediator of the Oriental flush and its accumulation following ethanol administration is due to a specific genetic deficiency of low $K_m$ mitochondrial ALDH (Goedde *et al.*, 1985; Chan, 1986). The ingestion of alcohol in the presence of the ALDH inhibitor, disulfiram, results in a reaction similar to the flushing reaction in Orientals (Zeiner *et al.*, 1979). There are some data supporting the idea that histamine can mediate the acetaldehyde-induced flushing reaction. Elevated plasma histamine levels following the administration of histamine correlate well with clinical symptoms resembling the alcohol-induced flushing in Orientals. Combined antihistamines also block the alcohol-induced flushing associated with metastatic gastric carcinoma (Roberts *et al.*, 1979). Alcohol-induced flushing in Orientals, including cutaneous flush, increase in skin temperature and oxygen tension, and systolic hypotension, is significantly blocked by a combination of $H_1$ and $H_2$ receptor antagonists (Tan *et al.*, 1979, 1982; Pardo and Hall, 1981; Miller *et al.*, 1987). These authors suggested that blocking of both the central and peripheral histamine receptors is necessary to abolish alcohol-induced flushing. Miller *et al.* (1987) suggested that histamine interactions may be an important genetic factor in the basic mechanisms of tolerance that ultimately contribute to the risk of the development of alcoholism. However, this hypothesis should be confirmed by studies concerning the genetic specificities of the peripheral histamine system, including the amount and properties of mast cells, histamine metabolizing enzymes, binding proteins, and receptors.

## HISTAMINE-RECEPTOR LIGANDS IN MODULATION OF CENTRAL ETHANOL EFFECTS AND ALCOHOL-RELATED BEHAVIOUR

The older, first generation, $H_1$ histamine receptor antagonists in therapeutic doses can cross the blood–brain barrier. They produce sedation in 10–25% of cases and potentiate some known ethanol effects on visual motor co-ordination, driving, mental, and cognitive performance (Simons, 1994). The novel, second-generation, $H_1$ antagonists do not cross the blood–brain barrier. They do not induce sedation and the other previously mentioned central disturbances and do not potentiate ethanol effects (reviewed by Meltzer, 1991; Patat *et al.*, 1995; Smallwood *et al.*, 1995). This indicates that the interaction of antihistamines and alcohol takes place in the CNS.

It was found that a single administration of the centrally acting histamine $H_1$ receptor antagonists clemastin and promethazine to rats 2 h before administration of a test dose of ethanol (3.5 g/kg, i.p.) significantly affected locomotor activity in open-field testing the following day. The double administration of the preparations (12 and 2 h before the test dose of ethanol) significantly increases the duration of alcohol-induced sleep. Ethanol and acetaldehyde measurements have shown that the animals pre-treated with $H_1$ antagonists woke at lower levels of ethanol in the blood and, particularly, in the brain (Zimatkin *et al.*, 1997). These results suggest that the $H_1$ antagonists increase the sensitivity of animals to the hypnotic action of alcohol. In contrast, the histamine $H_2$ receptor antagonist cimetidine decreased ethanol-mediated narcosis in mice (Messiha, 1989). In addition, it has been found that cimetidine did not alter voluntary alcohol consumption in rats, whereas the histamine $H_2$ receptor agonist, histagol, decreased it and pretreatment with cimetidine eliminated the effect of histagol (Messiha, 1989). In rats with portocaval anastomosis, both the level of histamine in the brain and voluntary alcohol consumption increase dramatically (Fogel *et al.*, 1991); however, these two phenomena may not be directly related.

## GENERAL CONCLUSIONS AND COMMENTS

The data available indicate a significant effect of ethanol on histamine metabolism in the periphery and in the brain as well as the involvement of histamine in the regulation of alcohol metabolism and the mediation of its actions in the periphery. However, in contrast to other neurotransmitters, the involvement of the brain neuronal histaminergic system in the mechanisms of the central actions of alcohol and alcoholism pathogenesis is poorly studied and understood. The possibility that the histamine system in animals differs in respect to alcohol-related behaviour between inbred animals or genetically selected animals has not been studied. No data on the effects of alcohol on the morphology of the brain histamine system in adult animals and in human alcoholics or in the development of the system can be found in literature. The possibilities of modulation of alcohol-related behaviour and alcohol metabolism by histamine receptor ligands require further detailed investigation.

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