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Key role of local acetaldehyde in upper GI tract carcinogenesis

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ABSTRACT

Ethanol is neither genotoxic nor mutagenic. Its first metabolite acetaldehyde, however, is a powerful local carcinogen. Point mutation in *ALDH2* gene proves the causal relationship between acetaldehyde and upper digestive tract cancer in humans. Salivary acetaldehyde concentration and exposure time are the two major and quantifiable factors regulating the degree of local acetaldehyde exposure in the ideal target organ, oropharynx. Instant microbial acetaldehyde formation from alcohol represents >70% of total ethanol associated acetaldehyde exposure in the mouth. In the oropharynx and achlorhydric stomach acetaldehyde is not metabolized to safe products, instead in the presence of alcohol it accumulates in saliva and gastric juice in mutagenic concentrations. A common denominator in alcohol, tobacco and food associated upper digestive tract carcinogenesis is acetaldehyde. Epidemiological studies on upper GI tract cancer are biased, since they miss information on acetaldehyde exposure derived from alcohol and acetaldehyde present in 'non-alcoholic' beverages and food.

The worldwide annual incidence of upper GI tract cancers is close to 2 million and age standardized rate represents one fourth of all cancers [1]. The poor prognosis of these cancers underlines the importance of preventive measures. A key to cancer prevention is the identification of specific carcinogenic compounds, recognition of risk groups and early detection of precancerous conditions. Alcohol and tobacco are major risk factors for oral, pharyngeal and oesophageal cancer with a synergistic effect on their incidence [2,3]. They are also independent risk factors for stomach cancer [4,5]. A common carcinogenic denominator in alcohol, tobacco and food associated upper GI tract cancer is acetaldehyde, which in the presence of ethanol accumulates in the saliva and gastric juice. Acetaldehyde is also the most abundant carcinogen of tobacco smoke, which dissolves into saliva during smoking [6,7].

The ethanol molecule is neither genotoxic nor mutagenic [8,9]. Acetaldehyde is a group 1 carcinogen to humans, when associated with the consumption of alcoholic beverages [10]. Group 1 classification concerns acetaldehyde formed from ethanol by microbial and mucosal oxidation and when present in alcoholic beverages.

Acetaldehyde formation from ethanol starts instantly in saliva after the sipping of alcohol and continues for as long as ethanol is present in blood [11,12]. Solid genetic epidemiologic and biochemical evidence based on a point mutation in the *ALDH2* gene proves the causal relationship between local acetaldehyde exposure and upper GI tract cancer and provides a unique human model for the quantitative assessment of the carcinogenicity of acetaldehyde in man [13].

Exposure of upper GI tract mucosa to carcinogenic acetaldehyde is cumulative and can be markedly reduced both at population and individual level. Knowing the key factors regulating local acetaldehyde concentration in the upper digestive tract is thus of essential importance for health care workers, regulatory authorities, food and tobacco industry and not least consumers.

1. Acetaldehyde

1.1. Main characteristics

Acetaldehyde is a small molecule with orange aroma and low

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boiling point. It is soluble in water and lipids and passes therefore easily through the cell membranes. Acetaldehyde is widely present in our everyday environment. Its characteristics are described in Table 1. With regards to upper GI tract cancer, most important is the local *in vivo* oxidation of ethanol to acetaldehyde in reactions catalyzed by microbial alcohol dehydrogenase (ADH) enzymes [11,12]. This results in salivary and gastric juice acetaldehyde concentrations, which may exceed markedly its mutagenic level (40–100 μM, 1.8–4.4 mg/l) and recommended upper limit (5 mg/l) for cosmetic products [14,15]. Acetaldehyde is also a key metabolite in the alcoholic fermentation pathway from glucose to ethanol. Therefore, acetaldehyde is present in mutagenic concentrations in many alcoholic beverages and foodstuffs produced or preserved by fermentation (Table 2) [16–18]. Potentially risky acetaldehyde levels may exist also in some fruits and the substance may be added to certain foods as a flavouring compound [18].

1.2. Genotoxicity, mutagenicity and carcinogenicity

Acetaldehyde is genotoxic, mutagenic and carcinogenic *in vitro* and *in vivo* [9,10]. It causes DNA-protein crosslinks, DNA strand breaks, DNA adducts, sister chromatid exchanges, chromosomal aberrations, and micronuclei in eukaryotic cells. Although many of these effects have been produced in rather high acetaldehyde concentrations, there is strong evidence for the generation of specific mutagenic DNA adducts and induction of micronuclei in mammalian cells also at acetaldehyde concentrations realistically achievable from alcoholic beverage consumption [9,10,19].

Oral ingestion of alcohol produces dose dependent mutagenic acetaldehyde-DNA damage in the oral cavity of humans within 2–4 h (Fig. 1) [19]. In the alcohol sipping model used in that study salivary acetaldehyde can be assumed to have been about 150 μM (6.6 mg/l) for the first 40 min (Fig. 1) [11,20]. This profound instant effect of alcohol on salivary acetaldehyde is most obviously due to the dose dependent *in vitro* and *in vivo* capacity of oral microbes to produce acetaldehyde in increasing ethanol concentrations [11,20–22]. Within the following 30 min alcohol is distributed evenly to the body water including saliva resulting in rapid decrease in salivary acetaldehyde concentration to mean 20–30 μM for as long as alcohol stays in the blood (Fig. 1) [12]. These findings suggest that the *in vivo* mutagenic effect of acetaldehyde on human oral cells is exponential as indicated also by earlier *in vitro* findings on acetaldehyde-DNA adducts [23]. The formation of mutagenic acetaldehyde-DNA adducts in oral mucosa caused by local acetaldehyde formation from ethanol has been confirmed in rhesus monkeys exposed to alcohol over their lifetimes [24].

Table 1
Acetaldehyde (ethanal).

- CH3 - CHO, orange aroma, boiling point 20.2^OC, soluble in water and lipids
- Widely present in our everyday environment
  - Microbial formation from ethanol
  - Key metabolite in alcoholic fermentation
  - Most abundant carcinogenic compound of tobacco smoke
- Forms carcinogenic acetaldehyde-DNA adducts
- Genotoxic, mutagenic and carcinogenic even in physiologically relevant concentrations
- Common denominator for all known risk factors of upper GI tract cancer
- Causal relationship between acetaldehyde and upper GI tract cancer is based on a single mutation in *ALDH2* gene resulting in a profound effect on local acetaldehyde exposure after alcohol drinking

Table 2
Acetaldehyde concentrations (mg/l) in some widely used alcoholic beverages, foodstuffs and fruits [16–18]. Mutagenic concentration: 40–100 μM (1.8 – 4 mg/l).

Beverage/foodstuffs	n	Ranges (mg/l)
Beer (Germany)	364	0–1435
Beer (Italy)	12	3.6–15.1
Wine (Europe)	213	0–211
Wine (Italy)	60	18–477
Grappa (Italy)	13	23–1850
Calvados	27	9–67
Yogurt (Germany)[a]	23	2.4–17.4
Fruit juice[a]	4	0.8–19.1
Apples[a]	8	0.3–2.4
Bananas[a]	8	1.9–18.3

[a] If not containing any ethanol, the local exposure time of upper GI tract to acetaldehyde can be assumed to be considerably lower than that of ethanol containing beverages and food.

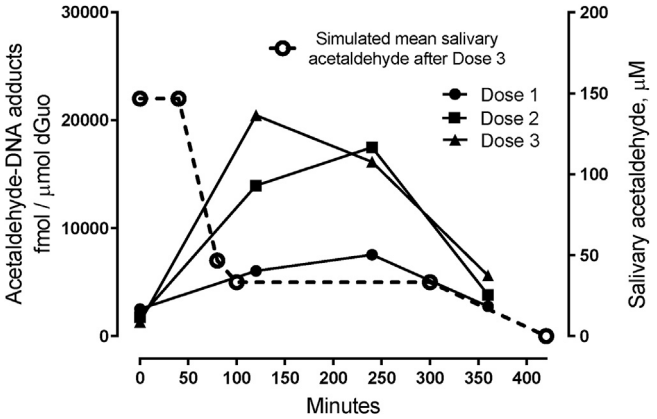

Fig. 1. Mutagenic acetaldehyde-DNA adducts in mouthwash samples of healthy human volunteers after ingestion of alcohol in relation to simulated salivary acetaldehyde levels. Adapted from Refs. [11,12,19,20]. Alcohol doses 1, 2 and 3 were aimed to reach 0.3, 0.5 and 0.7‰ blood alcohol levels, respectively. In alcohol sipping model used (Dose 3: diluted vodka at 5 min intervals), salivary acetaldehyde concentration can be assumed to have been about 150 μM for the first 40 min (max. 260 μM). Within the following 30 min there is a rapid decrease in salivary acetaldehyde to 20–30 μM for 350 min. Left y-axis: N^2-ethylidene-dGuo (fmol/μmol dGuo). Right y-axis: salivary acetaldehyde (μM).

In cultured human buccal epithelial cells, mutagenic acetaldehyde-DNA adducts are formed *in vitro* in a dose-dependent manner at acetaldehyde concentrations that are relatively nontoxic to the cells [25]. Furthermore, aldehyde dehydrogenase 2 (ALDH2)-deficient alcoholics have significantly higher blood levels of acetaldehyde-DNA adducts than ALDH2-actives [26,27]. Alcohol treated ALDH2-deficient mice show increased acetaldehyde-DNA adduct levels in the liver, stomach and oesophagus [28–30]. Another mutagenic acetaldehyde-DNA adduct (1,N^2-propanodeoxyguanosine) increases exponentially in 100–500 μM acetaldehyde concentrations in the presence of physiological polyamine concentrations [23]. Polyamine synthesis is tightly related to cellular proliferation, with the highest levels being found in rapidly dividing cells, which is characteristic for the regenerating oral and oesophageal mucosa [31].

According to the International Agency for Research on Cancer (IARC) acetaldehyde is carcinogenic in experimental animals [10]. Inhaled acetaldehyde produces nasal carcinomas in rats and laryngeal carcinomas in hamsters [32,33]. Life time administration of acetaldehyde in drinking-water to rats resulted in increased