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ALDH2-deficiency as genetic epidemiologic and biochemical model for the carcinogenicity of acetaldehyde

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ABSTRACT

Humans are cumulatively exposed to acetaldehyde from various sources including alcoholic beverages, tobacco smoke, foods and beverages. The genetic-epidemiologic and biochemical evidence in ALDH2-deficient humans provides strong evidence for the causal relationship between acetaldehyde-exposure due to alcohol consumption and cancer of the upper digestive tract. The risk assessment has so far relied on thresholds based on animal toxicology with lower one-sided confidence limit of the benchmark dose values (BMDL) typically ranging between 11 and 63 mg/kg bodyweight (bw)/day dependent on species and endpoint. The animal data is problematic for regulatory toxicology for various reasons (lack in study quality, problems in animal models and appropriateness of endpoints - especially cancer - for transfer to humans). In this study, data from genetic epidemiologic and biochemical studies are reviewed. The increase in the daily exposure dose to acetaldehyde in alcohol-consuming ALDH2-deficients vs. ALDH2-actives was about twofold. The acetaldehyde increase due to ALDH2 inactivity was calculated to be 6.7 μg/kg bw/day for heavy drinkers, which is associated with odds ratios of up to 7 for head and neck as well as oesophageal cancer. Previous animal toxicology based risk assessments may have underestimated the risk of acetaldehyde. Risk assessments of acetaldehyde need to be revised using this updated evidence.

1. Introduction

Acetaldehyde (ethanal) is a compound to which humans are regularly exposed from multiple sources such as foods, beverages, cigarettes and the environment (Cavalcante et al., 2005; Feron et al., 1991; Homann et al., 1997; Lachenmeier et al., 2009b; Lachenmeier and Sohnius, 2008; Nazaroff and Singer, 2004; Salaspuro, 2009a, 2009b; Uebelacker and Lachenmeier, 2011). Highest exposure results from consumption of alcoholic beverages and is localized to mucosal surfaces of the upper digestive tract. This is due to the fact that after alcohol intake some ethanol is metabolized locally by oral microbes and mucosal cells to acetaldehyde. Because of the inefficient ability of mucosa and microbes to eliminate acetaldehyde, the compound accumulates in the saliva and gastric juice (Homann et al., 1997, 2001; Kurkivuori et al., 2007; Lachenmeier and Monakhova, 2011; Linderborg et al., 2011; Salaspuro, 2003; Salaspuro and Salaspuro, 2004; Väkeväinen et al., 2000, 2001a, 2001b, 2002). Furthermore, acetaldehyde is found in high concentrations in some spirits, but it is also regularly present in wine and beer (Boffetta et al., 2011; Lachenmeier and Sohnius, 2008; Linderborg et al., 2008; Paiano et al., 2014).

A point mutation in *ALDH2*-gene resulting in deficient activity of the main acetaldehyde metabolizing mitochondrial enzyme (ALDH2) provides conclusive evidence for the causal relationship between local acetaldehyde exposure and upper digestive tract cancer. When drinking alcohol, the upper digestive tract mucosa of ALDH2-deficients is exposed via saliva to about 2 times and via gastric juice to 5–6 times higher acetaldehyde concentrations than in persons with active ALDH2-enzyme (Maejima et al., 2015; Väkeväinen et al., 2000, 2001b; Yokoyama et al., 2016; Yokoyama et al., 2008). Parallel to increased local acetaldehyde exposure, the risk of ALDH2-deficient alcohol drinkers for oral, pharyngeal, oesophageal and gastric cancer is many fold compared to alcohol drinking ALDH2-actives (Boccia et al., 2009; Matsuo et al., 2013; Tsai et al., 2014; Yang et al., 2010). Moreover, the difference in cancer risk between ALDH2-deficients and ALDH2-actives increases with increasing alcohol consumption. Thus, ALDH2-

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deficiency provides a unique human cancer model for local acetaldehyde exposure in the upper digestive tract. Based on new gene-epidemiological and gene–biochemical evidence, the International Agency for Research on Cancer (IARC) has reclassified acetaldehyde associated with the consumption of alcoholic beverages as a Group 1 human carcinogen (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2012; Secretan et al., 2009).

For the risk assessment of acetaldehyde, no human data has been available so far, so that toxicological thresholds based on animal experiments have been suggested (Lachenmeier et al., 2009b). Some risk assessment bodies such as the German Federal Institute for Risk Assessment (BfR, 2010) or the MAK Commission (2013) have questioned the use of the available animal data for oral exposure, while other bodies such as the SCCS (2012) used them to provide quantitative risk estimates and suggest risk management actions such as implementation of limits in consumer products such as cosmetics.

ALDH2-deficiency provides an entirely new human model for the quantitative estimation of increased acetaldehyde exposure via saliva in the upper digestive tract of alcohol drinking ALDH2-deficients compared to ALDH2-actives. Point mutation in *ALDH2* gene has “randomized” millions of alcohol drinkers to abnormally high acetaldehyde exposure via saliva for decades thus providing a natural model. Therefore, the intention of this article was to review the human data that has become available from genetic epidemiological and biochemical research during the last decade and discuss its relevance for risk assessment.

2. Methods

Data on genetic epidemiological and genetic biochemical studies regarding the connection between aldehyde dehydrogenase 2 (*ALDH2*)-polymorphism, alcohol consumption, upper digestive tract cancer and salivary acetaldehyde concentrations in the presence of ethanol were obtained by a computer-assisted literature search. Searches were carried out in the PubMed database (U.S. National Library of Medicine, Bethesda, MD). We specifically aimed to identify studies that specified several dose groups of alcohol intake and compared ALDH2 active with ALDH2 deficient individuals, and hence might provide evidence of a clear dose-response effect.

3. Results

Three studies were identified that reported about the frequency of the *ALDH2* polymorphism among oesophageal cancer and head and neck cancer cases and controls according to two variant *ALDH2* genotypes [*1*2(deficient) and *1*1(active)] with similar levels of alcohol intake thus providing dose-response data (Table 1): one meta-analysis and one study on head and neck cancer (Boccia et al., 2009; Tsai et al., 2014) and one meta-analysis on oesophageal cancer (Yang et al., 2010). The data were dichotomized according to the drinking status of the original studies.

For the estimation of local acetaldehyde exposure via saliva in different levels of alcohol intake five studies reporting *in vivo* salivary acetaldehyde levels in ALDH2 deficients vs. ALDH2 actives after alcohol intake were identified (Maejima et al., 2015; Väkeväinen et al., 2000, 2001b; Yokoyama et al., 2016; Yokoyama et al., 2008). The main characteristics of these studies are presented in Table 2.

Mean blood and salivary acetaldehyde levels of ALDH2 actives and deficients after alcohol intake were averaged from the data presented in each study. In Table 3, salivary acetaldehyde levels represent sampling time points when ethanol had been evenly distributed to the whole-body water including saliva after alcohol intake. In three studies the areas under the curve (AUCs) of acetaldehyde exposure via saliva during the follow up ranging from 2 to 4 h was either reported or could be calculated. Thereafter differences in salivary acetaldehyde exposure of ALDH2 actives and deficients were calculated. The average difference was estimated to be 2.0fold at the sampling time point (5 studies) and according to AUCs 2.2fold (3 studies) for the deficients vs the actives (Table 3). The average of 2.1fold was selected for further calculations in Tables 4 and 5.

For the estimation of exposure of the upper digestive tract mucosa to acetaldehyde in μg/kg bodyweight (bw)/day, median unstimulated saliva flow rate was assumed to be 0.5 ml/min (Fenoll-Palomares et al., 2004). Mean alcohol consumption of moderate drinkers was assumed to be 3 drinks/day corresponding to about 4.5 h exposure via saliva (141 ml saliva) to acetaldehyde (Table 4). The mean alcohol consumption of heavy drinkers and corresponding exposure to salivary acetaldehyde was assumed to be 7 drinks (330 ml saliva) per day (Table 4). The additional acetaldehyde exposure for ALDH2 deficient compared to ALDH2 active persons was determined by multiplying the exposure of ALDH2 actives by 2.1 as indicated in Table 3.

Table 5 compares the acetaldehyde daily dose increase with the odds ratios for the cancer types. It can be deduced that for heavy drinkers odds ratios ranging from 4 to 7 are associated with acetaldehyde dose increases of 6.7 μg/kg bw/day.

Finally, Table 6 summarizes toxicological thresholds for acetaldehyde from various literature sources. It can be seen that thresholds based on animal experiments are generally above 10 mg/kg bw/day. Thresholds based on human epidemiological data are not yet available and the study data shown in Tables 5 and 6 did not allow for a dose-response-modelling as none of the study provided absolute or extra risk data. Nevertheless, the very low acetaldehyde doses (6.7 μg/kg bw/day) associated with significantly increased odds ratios for cancer, provide plausibility that the human threshold could lie considerably lower than 0.1 mg/kg bw/day.

4. Discussion

ALDH2-deficiency resulting from a single point mutation in *ALDH2*-gene is a health risk that passes in frequency familiar hypercholesterolemia (FH). The incidence of FH is 1:500 but that of ALDH2-deficiency 1:13. *ALDH2*-gene mutation took place in South China over 2000 years ago, and today its carrier frequency is close to 600 million people of East-Asian descent (Brooks et al., 2009; Li et al., 2009; Luo et al., 2009). Deficient activity of ALDH2-enzyme results in decreased ability to detoxify acetaldehyde locally formed from ethanol and thus provides a unique human model for increased exposure of upper digestive tract mucosa to acetaldehyde via saliva after drinking of alcohol (Helminen et al., 2013; Maejima et al., 2015; Väkeväinen et al., 2000, 2001b; Yokoyama et al., 2016; Yokoyama et al., 2008). With increased exposure to salivary acetaldehyde, oral, pharyngeal and oesophageal cancer risks of alcohol drinking ALDH2 deficients are many folds compared to ALDH2 active drinkers, and the higher their alcohol consumption has been (Boccia et al., 2009; Tsai et al., 2014; Yang et al., 2010).

Acetaldehyde is a cytotoxic, genotoxic and mutagenic compound and carcinogenic in experimental animals (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2012; Seitz and Stickel, 2010). In conjunction with the consumption of alcoholic beverages, acetaldehyde has been reclassified as carcinogenic to humans (Group 1) (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2012; Secretan et al., 2009). The new classification concerns both the acetaldehyde formed from ethanol by local microbial and mucosal oxidation as well as when present in alcoholic beverages.