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ORAL CAVITY CANCER: EFFECTS OF THE ALCOHOL CONSUMPTION

KARCINOM USNE DUPLJE: EFEKTI KONZUMACIJE ALKOHOLA

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Ključne reči
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Abstract

It is not easy to establish the connection between oral cavity cancer and alcohol consumption due to the confluence of risk factors within the same person (i.e., alcohol and tobacco) and the lack of data that could be verified by the clinician. From an epidemiological point of view, the consumption of alcoholic beverages has been found to be associated with an increased risk of upper gastrointestinal tract cancer development. The exact pathogenic mechanism responsible for this increased risk is not known yet, since ethanol per se was not confirmed to be carcinogenic. So far, different hypotheses have been proposed, explaining how ethanol, by oral or systemic route, can act as a risk factor for the development of oral cancer. Therefore, since it is difficult to establish a direct cause-effect relation between these two entities the aim of this study is to summarise potential pathogenic mechanisms which are divided to local and systemic.

INTRODUCTION

Ethyl alcohol or ethanol, whose chemical formula is CH_3CH_2OH, is the essential active component of alcoholic beverages [1, 2, 3]. Its production consists of two procedures: fermentation or decomposition of sugars contained in various fruits, and distillation, which involves purification of the fermented drink [4].

After the consumption of an alcoholic drink, the ethanol contained within is mainly absorbed in the small intestine, and to a lesser extent in the large intestine and the stomach, reaching the liver by portal entry, where majority of it is metabolised [5]. Ethanol is metabolised in two stages: the first stage consists of the transformation of ethanol to acetaldehyde, which can be achieved in three ways - by alcohol dehydrogenase (ADH), by hepatic microsomal system (MEOS), and by catalase enzyme. The second stage is characterised by the oxidation of the previously obtained acetaldehyde into acetate by aldehyde dehydrogenase enzyme (ALDH) [5]. The consumption of alcoholic beverages has repercussions in practically whole body, manifesting itself throughout all organs and systems of the body: nervous [4-6], cardiovascular [5-8], digestive [5-8], sexual [5,6] or at the level of the medulla osea [5,6]. In the oral cavity it is characterised by the appearance of a series of clinical signs and symptoms triggered by either the direct effect of alcohol in the organism or by the consequence of poor personal hygiene. In this manner, significant cases of caries [6,9], calculus [6,9], sialosis [10-15], bruxism [6,9], leukoplakia [16-22] and erythroplasia [23-25] are found in chronic alcoholics. With regards to lichen planus, ethanol could be implicated in its potential transformation process to malignancy [26-29].

RELATION BETWEEN ALCOHOL AND ORAL CANCER

From an epidemiological viewpoint, chronic consumption of alcoholic beverages is associated with an increased risk of the upper gastrointestinal tract cancer [30-43]. The pathogenic mechanism of the promoting effect of alcohol is not clear yet despite existence of multiple explanations [30]. It turns out to be difficult to establish a direct cause-effect

relation between these two entities due to the frequent association of alcohol consumption with other risk bearing habits, such as cigarette smoking, as well as the lack of objective data provided by patients regarding the amount of alcohol ingested.

Carcinogenic effect of alcohol has not been verified [30, 44], but various hypotheses have been proposed in order to clarify possible role of ethanol as a risk factor, locally or systemically, in the development of oral cancer.

LOCAL EFFECTS OF ALCOHOL

The local process is the most studied, since the mouth is the external part of the body that first comes in contact with alcohol. At that point the components of the beverages are encountered in their maximum concentration. This is followed by a various transformation processes mediated by the enzyme systems of the body.

INCREASE OF PERMEABILITY

Alcohol is capable of producing an alteration in morphology of the oral mucosa characterized by an epithelial atrophy [14, 34, 38, 45], which leads to increased susceptibility of this tissue to the effects of the other carcinogenic chemicals. In this manner, it was suggested that ethanol is capable of increasing the penetration of carcinogens through the oral mucosa [16, 38, 46], due to both their increased solubility [16, 38], and increased permeability of the oral mucosa [5, 38, 47, 48]. This increase can be caused by the dissolvent effect of ethanol which eliminates the lipid component of the oral cavity barrier. This barrier constitutes of the derived lipids of the membrane that surrounds the granules of the epithelial spinous layer [37]. On the other side, according to other authors [49, 47], the increase in permeability could be the consequence of the reorganization of the elements constituting the cell membrane, as observed in samples of lingual tissues of recent human cadavers. Thus,, ethanol is capable of increasing the penetration of molecules of high molecular weight without producing any type of variation in its lipid component.

ACTION OF ACETALDEHYDE

The increase of the oral mucosa permeability on its own could not be the major risk for developing oral cancer in alcoholics. This has extended the search for other mechanisms associated with the consumption of ethanol. Since ethanol by itself has not been proven to be carcinogenic [44], the role of its first metabolite, acetaldehyde, has been postulated as a potential risk factor implicated in the effects of the alcoholic drinks. The International Agency for Research on Cancer (IARC) has established that sufficient evidence exists to identify acetaldehyde as carcinogenic in animals, being possibly carcinogenic to humans [50, 51]. Various studies have been focused in identifying the harmful effects of acetaldehyde. It was revealed that in short term cell cultures it causes mutations and other damages to the DNA, *in vitro* it forms compounds with the DNA while *in vivo* it initiates the transformation of rat kidney cells and inhibits the repair of DNA. It appears to be a nasal tract carcinogen when inhaled by rodents in a laboratory. It has been shown that acetaldehyde interferes with the synthesis and reparation of DNA, which consequently leads to the development of tumors. Also, it has been demonstrated that it induces interchanges in sister chromatids, produces specific gene mutations, inhibits the O6-methylguanitransferase, enzyme responsible for repairing the damage caused by alkylating agents. Acetaldehyde unites with the cellular proteins and DNA provoking morphological and cellular injuries. It was detected that its components are neo-antigens that determine the production of antibodies, stimulating the immune system and inducing a cytotoxic immune response and it is also capable of *in vitro* folic acid destruction [30, 34, 52-54].

Thus, due to the important role that acetaldehyde seems to play in the development of the oral cancer, it is considered as a major risk whenever its accumulation is detected, either due to an increase of its production or to a decrease in its elimination.

Oral Metabolism of Acetaldehyde:

Similar to what occurs in the liver, ethanol in the oral cavity is oxidised to acetaldehyde by the oral microflora and the cells of the oral mucosa in the same way as by cytochrome P4502E1. In the next step acetaldehyde is oxidised by ALDH, which transforms it into acetate, hampering the toxic activity of the first metabolite [5]. Therefore, the accumulation of acetaldehyde can be due to the increased activity of ADH in the oral microflora or in the cells of the oral mucosa, increased activity of the cytochrome P4502E1 or decreased activity of the ADLH.

ROLE OF THE ADH IN THE ORAL MICROFLORA

Homann [30-33] studied the role of the oral microflora in the oxidation of ethanol and detected the production of considerable amounts of acetaldehyde during the social consumption of alcohol. This author has demonstrated that in subjects with predominantly aerobic flora (Streptococcus salivarius, Streptococcus viridans hemolytic Corynebacterium sp., Stomatococcus sp. fungi) the production of salivary acetaldehyde is high. It appears that ethanol increases the bacterial production of acetaldehyde in a dose-dependent manner, and from the levels of intake greater than 40 grams of ethanol a day [30, 34]. Homann [33] also has found a correlation between the poor oral hygiene and a bacterial overgrowth in alcoholics, which is reflected in a significant salivary acetaldehyde levels in these subjects. This explains the increased risk for oral cancer in alcoholic patients with poor oral health [34, 55].

The acetaldehyde dissolved in the saliva is being distributed throughout the upper gastrointestinal tract [30] where it is acting on the covering mucosa. Effects of acetaldehyde are facilitated either by its increased permeability, permitting the passage to other carcinogens as well, or by penetration into the epithelial cells that is followed by DNA damage. In order to clarify the effects of acetaldehyde on the oral mucosa Homann [31] analysed its effects in a group of rats during the eight-month period by means of biopsies. He did not detect any type of dysplastic, neither microscopic nor macroscopic cancerous lesions, only increased epithelial proliferation in the experimental group of rats. Nevertheless, hyperproliferation state might represent the first step in the development of the oral cancer. Namely, cells in continuous state of replication carry a risk of accumulating major errors that can give rise to the appearance of mutations. Additionally, cells in this phase are more susceptible to the action of other carcinogens that can cross their membranes and generate irreversible damage [30].

ROLE OF ADH OF THE ORAL MUCOSA

Thanks to its small molecular size, ethanol is capable of passing through cellular membranes by simple diffusion [5]. Once ethanol enters into the oral epithelial cells ADH transforms it into acetaldehyde, which is then accumulated in cytosol and exhibits its harmful effects on the epithelial DNA [37, 38]. ADH present in the cells of the oral mucosa has a high affinity constant (Km), which implies that enzyme will have small contribution to the metabolism of ethanol (the greater the value of the affinity constant the lesser is the affinity of ADH for ethanol and therefore lesser transformation to acetaldehyde) [30]. The human ADH gene complex is localised on the long arm of chromosome 4. It consists of at least five different genes, ADH_1, ADH_2, ADH_1, ADH_3 is polymorphous in Caucasians (Arg ^{271}Gln and Ile^{349}Val) for which ADH_3 (Arg^{271}) and ADH^2 are spoken of [56]. There is a possible connection between the polymorphism of ADH isoenzymes and individual differences in alcohol-oxidizing capacity. Namely, according to the studies done in 1986 [57], isoenzymes that are coded by the allele ADH^1 metabolise ethanol to acetaldehyde two to three times faster than those that are coded by the allele ADH_3^2. This implies a major accumulation of acetaldehyde, supporting the hypothesis that homozygous subjects for the allele ADH_3^{1-1} posses a major risk of cancer induced by alcohol. In 1997, in Puerto Rico and [58] in France simultaneously [52], was discovered that subjects with the genotype ADH have a greater risk of oral cancer than ADH_3^2. More recent studies performed in 2000 [59], 2001 [60] and 2001 [56] did not show increased risk of oropharyngeal cancer in drinkers with ADH genotype. This disagreement between studies indicates a need for an assessment of the importance of the ADH_3 in the metabolism of ethanol. Namely, it is shown that this is not the main metabolic pathway [60] and that differences in the genetic risks for ADH_3 alleles are significant only in cases of chronic exposures to elevated amounts of ethanol [60].

Cytochrome P450

Cytochrome P4502E1 is found in the smooth endoplasmic reticulum and participates in the oxidation of ethanol when ethanol levels exceed 50-80 mg/dl [5]. Various studies suggest that the variant alleles c2 and c are associated with an increase in enzymatic activity of cytochrome P4502E1 [48, 61], which leads to a significant accumulation of acetaldehyde within the epithelial cells of the oral cavity, increasing the risk for the development of oral cancer. On the other hand, the cytochrome P4502E1 is capable of inducing the development of oral cancer in an indirect manner by activating pro-carcinogens and increasing the production of free radicals [34]. These effects have mostly been studied in relation to colon cancer. However, future researches that apply this knowledge to the oral cavity field are needed.

ALDH Activity

Accumulation of acetaldehyde in the oral cavity cells can also be a consequence of its decreased elimination. Acetaldehyde is transformed to acetate by aldehyde dehydrogenase enzyme [5, 50], so any alteration in the levels of this enzyme would lead to increased accumulation of acetaldehyde.

Different isoforms of the ALDH exhibit different kinetic characteristics, so genetic polymorphism affects ALDH in the same way as alcohol dehydrogenase. ALDH is a tetrameric protein located within the mitochondria. There are two isoenzymes: ALDHI and ALDHII [34,50]. The ALDHII is coded by the locus ALDH 2 of chromosome 12. It has been noted that 40% of American Indians and 50% of Orientals have a modified isoenzyme with a different activity (change of lysine 487 to glutamine). On the other side, subjects with the allele ALDH2*2 have inactive enzyme which makes them incapable to metabolise acetaldehyde so it gets accumulated inside of the cell.

ALTERATION IN RETINOID METABOLISM

Although the role of acetaldehyde in the development of oral cancer seems to be quite clear, a new route of investigation has been proposed to explore the role of retinoids in the development of precancerous lesions. Chronic consumption of ethanol is associated with decreased levels of retinoids in the oral cavity (34%). Vitamin A and its synthetic derivatives, collectively named retinoids, are small molecules involved in different biological functions [34, 63,64]. Any alteration in metabolism and activation of retinoids will result in increased susceptibility of the oral mucosa to other carcinogens [63]. In line with this, relationship between vitamin A deficiency and a high incidence of cancer and increased susceptibility to chemical carcinogens was demonstrated in experimental animals [63].

Retinol (vitamin A) is converted to retinoic acid (an active binding protein) that binds to nuclear receptor proteins that are capable of transcribing and regulating hundreds of genes [65]. Ethanol is a competitive inhibitor of retinol metabolism, since the same enzyme (ADH) is in charge of catalyzing two reactions that result in accumulation of retinol, at the expense of the retinoic acid [34, 56]. At the same time, the first metabolite of ethanol, acetaldehyde, is also capable of inhibiting the generation of retinoic acid [64]. Also, ethanol apparently causes a deficiency of retinoic acid in the liver due to the increased catabolism mediated by the cytochrome P4502E1 which is induced by ethanol [64].

With low levels of retinoic acid there is a lack of control in epithelial growth, which could initiate the development of malignant lesions. Currently, retinoids are being used in the treatment of cancerous and precancerous lesions with partial and total remissions of leukoplakia demonstrated in 40-60% of the patients in systemic vitamin A treatment, although their topical use seem to have a limited effect [63].

SYSTEMIC EFFECT

Knowing the effects that ethanol manifests on the distant organs different theories have been proposed in order to explain the relationship between the consumption of alcoholic drinks and the development of oral cancer. The most important consequences of alcohol consumption are manifested on the liver, since it is the main organ responsible for metabolism of ingested alcohol. Ethanol redirects liver functions towards its own transformation reducing the metabolism of other substances, which then stay longer in the blood and act as a possible carcinogen.

HEPATIC MATER

When ethanol levels increase in the liver all liver functions are centered on metabolic transformation of ethanol, which in return alters metabolism of the other substances. This means that the detoxification of certain compounds [37, 46, 66] and the activation [66] of others, with potential carcinogenic activity, will be impeded. Alcohol impairs the absorption of the nutrients by occupying and impairing metabolic processes [67]. Alcoholics often eat poorly, limiting their supply of essential nutrients [6] and have high tendency to vomit [5], which affects both energy supply and structure maintenance. Nutritional deficiency can be directly associated with a prevalence for oral cancer [67], and general body weakness, which presents a major risk for development of any pathology [37, 66]. The suppression of the immune system associated with the chronic consumption of ethanol contributes to the aggravation of this situation.

SALIVARY GLANDS AFFECTION

Ethanol affects salivary glands by altering them morphologically and functionally. These changes include degeneration of autonomic innervation, fatty infiltration and salivary gland hypertrophy with a painless, symmetric and bilateral increase of the parotid glands size, and reduced salivary flow that leads to the accumulation of carcinogens on the surface of the oral mucosa and increases the risk for oral cancer [11, 14, 37, 38, 68-72].

However, it is difficult to establish a direct relationship between the systemic alterations associated with the consumption of alcoholic drinks and the development of cancer in local tissues, such as the oral cavity. From epidemiological point of view there is evidence of such connection and future thorough studies are needed to clarify this.

ALCOHOL AND TOBACCO

Alcohol and tobacco are considered as two principal risk factors for the development of oral cancer [38, 71-76]. The independent role of each one of them seems to be clear. However, their combined effect, since they are commonly consumed together nowadays, is topic of many debates [38, 79]. In attempt to shed light on this problem, three models have been proposed by different authors: Additive, which predicts that combined effect is simple sum of their individual effects; Exponential, which proposes that combined effect is multiplication of individual effects and [66] and Synergic or Intermediate. The majority of the authors agree that combined effect should be higher than what additive model proposes so potential mechanisms are examined within the synergistic model.

According to the one of the proposed mechanisms, ethanol increases permeability of the oral mucosa cells [78, 79] facilitating the passage of the carcinogenic derivatives of tobacco (e.g., N-Nitrosonornicotine) into the cell, causing damages to the DNA. On the other hand, it would be difficult to determine the potential of ethanol to alter the hepatic metabolism of certain substances when it is simultaneously consumed with tobacco, although there are data that confirm this connection. However, the exact mechanisms through which ethanol exerts its effect in the oral cavity are not yet known.

Some studies confirmed that ethanol increases the permeability of the oral mucosa cells, but this is not sufficient to explain the development of the oral cancer. Acetaldehyde, the first metabolite of ethanol, has been identified as carcinogenic in animals. Therefore, any increase in its concentration, caused either by increase of its production or decrease in its elimination, will affect the oral mucosa. This is suggesting that ADH can influence the oral bacteria in subjects with poor oral hygiene by switching them to aerobic flora. There is a significant role of certain genetic susceptibility to oral cancer related to the consumption of ethanol in addition to the environmental factors (oral hygiene). .This susceptibility is a consequence of the presence of genetic polymorphisms of enzymes involved in the metabolism of both ethanol and acetaldehyde. Subjects with „susceptible alleles" possess functional alterations that are causing acetaldehyde accumulation. Available studies assessing this issue are either contradictory, as in the case of the ADH in the epithelial cells, or scanty, when referring to the polymorphisms of cytochrome P4502E1 or ALDH.

Bearing in mind the significance of retinoids in the regulation of epithelium growth and differentiation, impairment of their normal activity caused by competitive inhibition during the ethanol transformation represents a new field that should be thoroughly investigated.

However, despite the major effects that ethanol exhibits at systemic level, especially in the liver which has the central role in its metabolism, there is insufficient data regarding the relationship between systemic effect of ethanol and influence on the development of oral cancer.

Finally, it should be emphasized that the vast majority of authors agree that combined effect of alcohol and tobacco represents higher risk of development of oral cancer, compared to simple sum of their individual effects.

Sažetak

Vezu između karcinoma usne duplje i konzumacije alkohola nije lako ustanoviti i zbog velikog broja faktora rizika kod svake pojedine osobe (na primer alcohol i duvan), kao i zbog nedostatka podataka koje kliničar može da proveri. Iz ugla gledanja epidemiologa, konzumiranje alkoholonih pića je u vezi sa povećanim rizikom od karcinoma gornjeg gastrointestinalnog trakta. Zbog toga još uvek nije poznat tačan patofiziološki mehanizam koji uzrokuje povećanje rizika, jer nije potvrđeno da je etanol sam po sebi kancerogen. Predložene su razne hipoteze koje pokušavaju da objasne kako etanol, oralnim unosom ili sistemskim putem, može da bude factor rizika za obolevanje od karcinoma usne duplje. Uspostavljanje direktne uzročno-posledične veze između ova dva entiteta je teško, zbog toga u ovom radu sumiramo potencijalne patološke mehanizme deleći ih na lokalne i sistemske.

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