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Acetaldehyde production capacity of salivary microflora in alcoholics during early recovery

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ABSTRACT

This study investigated whether a relationship exists between the acetaldehyde production capacity of salivary microflora (sAPC) in recovering alcoholics, and craving, and/or resumption of drinking within 12 weeks after embarking on an abstinence-based treatment program. Serial sAPC measurements were determined by gas chromatography on spontaneous saliva samples of 30 male alcoholics on days 2, 4, 11, and 18 during a 21-day in-patient treatment program. Craving was measured simultaneously with the Penn Alcohol Craving Scale. Outcome over 12 weeks was assessed by telephone interviews. There was no significant change in sAPC values from day 2 to day 18, while craving scores decreased markedly between day 2 to day 4. Sixteen participants remained abstinent for the full 12 weeks. Statistically significant differences were found between the sAPC values of the group that remained abstinent and the group that resumed drinking within 12 weeks. The highest sAPC value measured on day 2 had a strong predictive value for maintained abstinence at 12 weeks for beer-only drinkers or drinkers consuming less than 320 g of alcohol per week. The study is the first investigation into a potential relationship between the acetaldehyde production capacity of salivary microflora and early resumption of drinking in recovering alcoholics. The findings suggest that such a relationship indeed exists for beer-only drinkers, possibly linked to lower alcohol intake, and that it is unrelated to withdrawal craving. sAPC is proposed as a candidate biomarker with diagnostic and/or prognostic potential.

Introduction

Relapse after successful detoxification is so common that it is regarded by many as an integral element of the condition of alcohol dependence (Breese, Sinha, & Heilig, 2011; Enoch & Goldman, 2002; Leshner, 1997; McLellan, Lewis, O'Brien, & Kleber, 2000; Vengeliene, Bilbao, Molander, & Spanagel, 2008). Though this viewpoint is disputed from a public health point of view (Cunningham & McCambridge, 2012), relapse remains a major challenge for alcohol-dependent persons seeking treatment. In this study, we investigated the possibility that salivary microbial production of acetaldehyde might play a role in the resumption of drinking after detoxification.

Acetaldehyde, a major product of alcohol metabolism, is a highly reactive substance that has been shown to play a role in the development of alcohol dependence (Amit, Brown, & Rockman, 1977; Aragon, Abitbol, & Amit, 1986; Brown, Amit, & Smith, 1980; Deng & Deitrich, 2008; Myers, Ng, Marzuki, Myers, & Singer, 1984; Ortiz, Griffiths, & Littleton, 1974; Quertemont, 2004). The microflora in the gut also acts as a source of acetaldehyde (Guarner & Malagelada, 2003; Son, Kremer, & Hines, 2010). The potential role of microbial acetaldehyde in the development of alcohol dependence has, however, not been investigated to our knowledge.

Acetaldehyde formation and breakdown

Acetaldehyde is formed during the metabolism of ingested alcohol via various metabolic pathways in different organs, but

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mainly through the oxidation of alcohol by alcohol dehydrogenase (ADH) in the gastric mucosa and liver (Quertemont, 2004). Tobacco smoking also contributes to acetaldehyde formation (Homann, Jousimies-Somer, Jokelainen, Heine, & Salaspuro, 1997; Salaspuro & Salaspuro, 2004). In turn, acetaldehyde is broken down to carboxylic acids via acetaldehyde dehydrogenase (ALDH).

Gastro-intestinal microflora is a secondary source of acetaldehyde

The composition of the resident microflora population in the gastro-intestinal tract is unique to a particular individual (Guarner & Malagelada, 2003). The population is relatively stable, yet can be disrupted by, for example, infections, antibiotics, and heavy alcohol use. Some Gram−positive bacteria (Kurkivuori et al., 2007) and yeasts (Tillonen, Homann, Rautio, Jousimies-Somer, & Salaspuro, 1997) produce alcohol from ingested carbohydrates via aldehyde dehydrogenase (ADH). Other organisms will break down acetaldehyde. The composition of the microflora population thus determines the results of exposure to alcohol, but the microflora population is also affected by exposure to alcohol. The variation in capacity of commensal microbial populations to produce and break down acetaldehyde may lead to accumulation of acetaldehyde in some individuals. Homann et al. (2000) demonstrated that the acetaldehyde production capacity of salivary microflora (sAPC) varies considerably between individuals and is elevated in heavy drinkers and smokers in a dose-dependent fashion.

Acetaldehyde in saliva originates almost exclusively from microbial activity, provided that ALDH-2 function is intact (Väkeväinen, Tillonen, Agarwal, Srivastava, & Salaspuro, 2000). Yokoyama et al. (2008) showed that salivary acetaldehyde levels can be influenced by ALDH-2 genotype, but this only applies when alcohol is present (Helminen, Väkeväinen, & Salaspuro, 2013). Wang, Nakajima, Kawamoto, and Honma (2002) found that drinking alcohol or smoking does not affect ALDH function.

Role of acetaldehyde in development of alcohol dependence

Genetic studies provided strong evidence in support of a role for acetaldehyde in the development of alcoholism. These studies linked the differential risk for developing alcohol dependence in different ethnic groups to polymorphisms in the genes coding for ADH and ALDH (Agarwal, Eckey, Harada, & Goedde, 1984; Ducci & Goldman, 2008; Edenberg, 2007; Foroud, Edenberg, & Crabbe, 2010), protecting against the development of alcohol dependence through its effects on acetaldehyde levels (Chen et al., 1999).

ALDH function is particularly crucial to contain acetaldehyde levels. Polymorphisms of the isoform ALDH-2 were found to be high in Asian populations (Agarwal, Harada, & Goedde, 1981; Goedde et al., 1984; Novoradovsky et al., 1995; Thomasson et al., 1991), causing poor ALDH function. This results in the development of a syndrome reminiscent of the disulfiram reaction (Harada, Agarwal, & Goedde, 1981), when the affected individual consumes alcohol. Such individuals therefore tend to avoid alcohol and are less likely to develop alcoholism. Isse et al. (2002) demonstrated reduced alcohol intake in a transgenic mouse model of poor ALDH function.

The protective effect of such a genetic predisposition is, however, incomplete. Muramatsu, Higuchi, Murayama, Matsushita, and Hayashida (1996) postulated that a second factor must play a role that causes persons with low ALDH function to become dependent, proposing a role for the gene coding for the D4 receptor. The contribution of the dopamine-opioid system, among other neurotransmitter systems in the development, reinstatement, and maintenance of dependence, has been repeatedly demonstrated (Bonci, Bernardi, Grillner, & Mercuri, 2003; Di Chiara & Imperato, 1988; Vengeliene et al., 2008; Verheul, van den Brink, & Geerlings, 1999; Volpicelli, 1987). Foddai, Dosia, Spiga, and Diana (2004) demonstrated that central administration of acetaldehyde increases dopaminergic neurotransmission. A recent study by Clarke, Adermark, Chau, Söderpalm, and Ericson (2014), however, showed that alcohol itself causes the increase in dopamine neurotransmission and not acetaldehyde. Still, acetaldehyde influences dopaminergic neurotransmission and thus reward function by diverting dopamine breakdown to form tetrahydroisoquinolines (Collins, Ung-Chhun, Cheng, & Pronger, 1990; Davis & Walsh, 1970; Duncan & Deitrich, 1980; Myers, 1989; Myers et al., 1985). These opioid agonists are substitutes for enkephalins and play an important part in mediating the effect of alcohol on the reward area (Lucchi, Bosio, Spano, & Trabucchi, 1982; Melis, Carboni, Caboni, & Acquas, 2015). According to Volpicelli (1987), drinking occurs during the aftermath of intense adversity when endorphins are depleted. Chronic exposure to alcohol may also cause reduced enkephalin levels. These changes may in turn affect dopaminergic function, driving craving and so maintaining continued alcohol intake (Addolorato, Leggio, Abenavoli, Gasbarini, & Alcoholism Treatment Study Group, 2005; Naoi, Maruyama, & Nagy, 2004).

Effects of acetaldehyde on alcohol ingestion

Acetaldehyde has been shown to have both reinforcing (Amit & Smith, 1985; Myers & Veale, 1996; Quintanilla & Tampier, 2003a) and aversive effects (Myers et al., 1984; Quintanilla, Callejas, & Tampier, 2002; Quintanilla & Tampier, 2003b) on alcohol ingestion in animal models. Several examples of the clinical expression of this bi-directional role played by acetaldehyde in the initiation and maintenance of alcohol dependence exist. Acetaldehyde dehydrogenase inhibitors cause the accumulation of acetaldehyde, resulting in aversion to alcohol drinking (Koppaka et al., 2012). However, in Lesch Type I alcoholism, intense craving elicited by small amounts of alcohol and a strong kindling effect with recurrent withdrawals co-exists with a genetically determined increased tendency to maintain high levels of acetaldehyde (Kogoj et al., 2010). Additionally, there is Quertemont and Didone (2006) report of some rare cases of a paradoxical reaction to the alcohol−disulfiram interaction, where the patient enjoys the reaction.

Acetaldehyde during abstinence

Several authors documented a drop in blood acetaldehyde levels during abstinence, accompanied by an increase in ALDH function (Di Padova, Worner, & Lieber, 1987; Jenkins, Cakebread, & Palmer, 1984; Lin, Potter, & Mezey, 1984).

Yokoyama et al. (2007) demonstrated that sAPC values drop in unison with microbial counts after 3 weeks of abstinence.

We hypothesized that higher production of acetaldehyde by the salivary microflora may cause earlier resumption of drinking by increasing craving. Alternatively, higher salivary acetaldehyde production capacity might have an aversive effect and prevent or delay resumption of drinking. The aim of our study was to determine whether there is a relationship between sAPC and resumption of drinking within 12 weeks of initiation of a 21-day abstinence-based treatment program. Specific objectives were to determine whether sAPC values in alcoholics change during early abstinence; if so; whether such changes are associated with the experience of craving, and whether sAPC values could predict early resumption of drinking. For the purpose of our study, we viewed the recovery period of alcoholics as a state of heightened vulnerability for commencement of drinking and thus a natural model for our investigation.