S077

VIOLENCE AND ALCOHOL: POTENTIAL ROLES OF PRE-EXISTING ANTISOCIAL PERSONALITY AND BEHAVIOR DISORDERS

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Aims: The association of alcohol and violence has been explained most frequently by causal models whereby increases in aggression would be attributable to the immediate effects, or expected effects, of this substance. While support for this hypothesis has been found in experimental research and community-based surveys, an important question concerns the degree of circularity that is present in this association. This communication addresses the prospective risk posed by pre-existing antisocial personality and behavior disorders in the likelihood of subsequent regular alcohol use, abuse and dependence.
Method: Data come from a nationally-representative sample of the US population that was followed prospectively over a 10-year period. A total of 5,001 respondents completed face-to-face diagnostic interviews at both baseline and follow-up.
Results: Aggregate analyses demonstrated that individuals with any disruptive behavior disorder at baseline were at increased risk (OR = 2.8) of developing alcohol dependence over the subsequent decade. Conditional analyses by stage of use demonstrated no association of these disorders with the onset of regular alcohol use. However, individuals were more likely to progress from regular drinking to abuse if they were previously diagnosed with Intermittent Explosive Disorder (OR = 1.8), ADHD (OR = 2.4), or Antisocial Personality Disorder (OR = 1.8), as well as to progress from abuse to dependence if they had Intermittent Explosive Disorder (OR = 3.6) or Oppositional Defiant Disorder (OR = 3.2).
Conclusions: The association observed between alcohol and violence may be more heavily concentrated in individuals already prone to aggression or to dysfunctional expression of anger. These prospective findings have implications for aiding the precision of prevention and treatment strategies targeting the reduction in violence associated with alcohol abuse and dependence.

Alcohol and hepatocarcinogenesis

Organizer/Chair: Helmut K. SEITZ

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THE ROLE OF ACETALDEHYDE-DNA ADDUCTS IN ALCOHOL MEDIATED CARCINOGENESIS

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Epidemiologic studies have demonstrated that ethanol drinking increases the risk of several types of cancer, including cancers of the upper aerodigestive tract, colorectum, liver, and female breast. In terms of mechanism, there is compelling evidence for a role for acetaldehyde in alcohol-related esophageal cancer, based on studies of ALDH2-deficient individuals. With regard to the other cancers, multiple mechanisms may be involved (Seitz HK, Stickel F. *Nat Rev Cancer* 2007;7(8):599-612).
One possible mechanism for at least some types of alcohol-related cancer involves DNA damage from acetaldehyde. Acetaldehyde can react directly with DNA to form a variety of different types of DNA adducts and some of these adducts can interconvert to form DNA interstrand crosslinks (ICLs) and DNA-protein crosslinks (Brooks, Theruvathu. *Alcohol* 2005;35(3):187-93). The Fanconi-anemia-breast cancer susceptibility (FA-BRCA) DNA damage response network is the major cellular mechanism that protects against DNA ICLs (see Wang W. *Nat Rev Genet* 2007;8(10):735-48). We have recently reported (Marietta et al. *Mutat Res* 2009;664:77-83) that exposure of human cells to exogenous acetaldehyde activates the FA-BRCA DNA damage response network, as indicated by ubiquitination of the FANCD2 protein, and phosphorylation of BRCA1. These results are consistent with the hypothesis that acetaldehyde causes replication-blocking DNA damage, such as ICLs.
Exposure of cells to exogenous acetaldehyde is a relevant model for alcohol related esophageal and colon cancer, since high levels of acetaldehdye can be produced from ethanol metabolism by microorganisms resident in the oral cavity and colon. For liver and breast cancer however, the relevant issue is whether acetaldehyde generated from intracellular ethanol metabolism can cause DNA damage. Therefore, in addition to discussing acetaldehyde-DNA adducts and our previous work, I will also present the results of our ongoing studies which are aimed at determining whether the intracellualr metabolism of ethanol into acetaldehyde causes DNA damage, and activates the FA-BRCA DNA damage response network. I will also discuss the implications of these findings for alcohol-related hepatocarcinogenesis.

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OXIDATIVE STRESS MAJOR MECHANISMS IN ALCOHOL MEDIATED HEPATOCARCINOGENESIS

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Increased generation of reactive oxygen species (ROS) plays a central role in the pathology of alcoholic liver disease (ALD) and primary liver cancer. The failure of previous therapeutic `antioxidative´ approaches is mainly due to the complex (patho) physiological role of ROS in the progression of ALD. Thus, ROS are not sole cellular toxins but essential metabolic intermediates and important cellular and intercellular signaling molecules. Direct oxidative damage of the DNA is a key step in ALD progression. Induction of the microsomal p450 2E1 dependent system by ethanol is an important factor. Cyp2E1 directly causes lipid peroxidation and formation of etheno DNA adducts. Another factor is the generation of key ROS such as H_2O_2 by various mechanisms such as inflammatory cells. While H_2O_2 per se is little reactive, it becomes very toxic in association with iron leading to the generation of the highly reactive hydroxyl radicals (Fenton chemistry). Since more than 50% of patients with ALD show pathological iron deposits in their livers, this mechanism seems to be critical for hepatic carcinogenesis. The exact molecular mechanisms of the pathological iron overload are not completely understood but involve the suppression of the systemic iron regulating peptide hepcidin. A better understanding of such molecular mechanisms will help to develop novel targeted therapeutic strategies and to identify patients at early disease states that are at high risk for ALD progression.

S080

ALCOHOL EPIGENETICS AND CANCER

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Chronic alcohol consumption is associated with the evolution of certain cancers including those in the upper gastrointestinal tract, liver, colorectum and female breast. Gene expression and tumorigenesis are regulated – among other mechanisms – by epigenetic modulators such as methylation, histone acetylation and proteasome activity. Importantly, chronic alcohol may affect these processes and causes demethylation, histone hyperacetylation and proteasome inhibition. Interference of alcohol with either of these complexes has important implications on gene expression, protein function, and host defense mechanisms. Importantly, therapeutic intervention with potent pharmaceuticals that reconstitute methylation, deacetylase histones, and protect the proteasome are under experimental and clinical investigation which offers novel perspectives for treatment and prevention, particularly, of alcohol-related cancers.