Polyamines Stimulate the Formation of Mutagenic 1,N^2-Propano-Deoxyguanosine Adducts from Acetaldehyde

Alcoholic beverage consumption is associated with an increased risk of upper gastrointestinal cancer and other types of cancer. Researchers looking for the potential biochemical basis for this link have focused on acetaldehyde, a suspected carcinogen formed as the body metabolizes alcohol. Acetaldehyde (AA), the first metabolite of ethanol, can form several DNA adducts including Cr-PdG (α-methyl-γ-hydroxy-1,N^2-propano-2'-deoxyguanosin). Cr-PdG is responsible for the mutagenic effects of the environmental pollutant, crotonaldehyde (CrA). However, the concentrations of AA used previously to generate Cr-PdG in DNA are far higher than would be found in vivo. In this work, we tested the hypothesis that polyamines could facilitate the formation of Cr-PdG from biologically relevant AA concentrations.

J. A. Theruvathu (NIH), P. Jaruga (Div. 831), R. G. Nath (NIH), M. Dizdaroglu (Div. 831), and P. J. Brooks (NIH)

Polyamines are small, highly basic molecules that are present in low concentrations in mammalian cells. We found that Cr-PdG is formed by reacting deoxyguanosine with micromolar concentrations of acetaldehyde (AA) in the presence of spermidine, but not with either AA or spermidine alone. A method was developed at NIST for the measurement of two diastereomers of Cr-PdG using both liquid chromatography-mass spectrometry and gas chromatography-mass spectrometry with isotope-dilution. We found that in the presence of 5 mmol/L spermidine, AA concentrations of 100 μmol/L and above resulted in the formation of Cr-PdG in genomic DNA. These AA levels are within the range that occurs in human saliva after alcoholic beverage consumption. Finally, we showed that spermidine directly catalyzes the conversion of AA to CrA via an aldol condensation mechanism.

Based on this research we propose that acetaldehyde derived from ethanol metabolism is converted to crotonaldehyde by polyamines in dividing cells, and the resulting crotonaldehyde gives rise to the formation of α-methyl-γ-hydroxy-1,N^2-propano-2'-deoxyguanosin, which is responsible for the carcinogenicity of alcoholic beverage consumption.

Previous studies had shown acetaldehyde could be converted to mutagenic Cr-PdG, but those studies used very high acetaldehyde concentrations. The present work demonstrated that these reactions can take place with acetaldehyde concentrations that have been measured in human saliva during alcohol consumption. These findings have significant implications for researchers seeking to understand how genes affect the risk for cancer. Many studies have shown that certain genetic variants that affect alcohol and acetaldehyde metabolism can also affect individual susceptibility to alcohol-related gastrointestinal cancer. This work may serve as a roadmap for future studies to investigate other genetic factors, particularly those that influence DNA repair pathways, in relation to alcohol consumption and cancer. We plan to further develop our methods of measurement and to investigate the genetic factors and DNA repair mechanisms in relation to alcohol consumption and upper gastrointestinal cancer with our NIH collaborators.

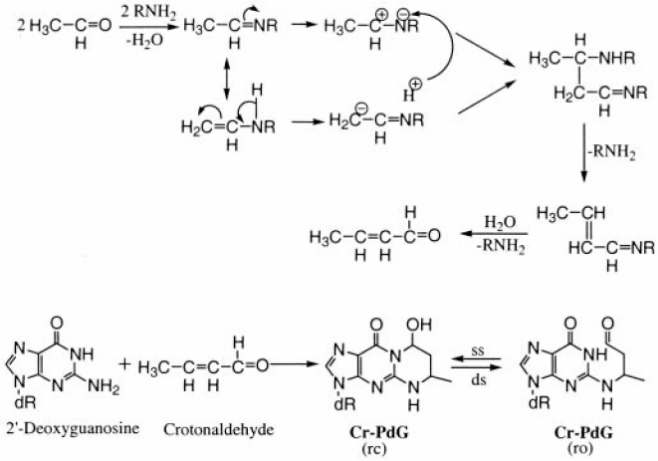

Illustration of the mechanisms of AA-derived DNA adduct formation and the proposed relationship of the Cr-PdG adducts to the known cytogenetic effects of acetaldehyde. The ring-opened (ro) and ring-closed (rc) forms of the Cr-PdG adducts are shown. Other abbreviations: ss, single-stranded DNA; ds, double-stranded DNA.

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