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Simultaneous analysis of six aldehyde-DNA adducts in salivary DNA of nonsmokers and smokers using stable isotope dilution liquid chromatography electrospray ionization-tandem mass spectrometry

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ABSTRACT

A stable method, using isotope dilution liquid chromatography-tandem mass spectrometry (LC–MS/MS), to simultaneously determine six aldehyde-DNA adducts was developed and applied to the analysis of human salivary DNA samples. The detection limit of these six DNA adducts was in the range of 0.006–0.014 ng/mL and that of the quantification limit was 0.017–0.026 ng/mL. The intra-day and inter-day precision of all aldehyde-DNA adducts was < 10%. The analysis was completed within 25 min. Additionally, a noninvasive technique was used to collect the DNA samples from human saliva. The new method was successfully applied for the analysis of salivary DNA of nonsmokers and smokers. Five aldehyde-DNA adducts were detected in both smoker and nonsmoker salivary DNA, while α-Acr-dG was not detected in all the samples. Among these detected DNA adducts, no significant differences were found between smoker and nonsmoker ($p > 0.05$). This may due to the individual detoxifying differences or environmental and endogenous exposure. Our study provides a rapid and selective method to simultaneously detect six aldehyde-DNA adducts and to assess potential DNA damage induced by aldehydes,

1. Introduction

Cigarette smoke contains more than 7000 chemicals, including carcinogenic and toxic aldehydes such as formaldehyde, acetaldehyde, acrolein, and crotonaldehyde [1,2]. The International Agency for Research on Cancer (IARC) classifies formaldehyde and acetaldehyde as category 1 and category 2B carcinogens, respectively, while acrolein and crotonaldehyde are category 3 [3]; when acetaldehyde associates with alcohol, it is a Group 1 carcinogen. The World Health Organization (WHO) Framework Convention on Tobacco Control (FCTC) lists formaldehyde, acetaldehyde, and acrolein as priority control pollutants in cigarette smoke. Formaldehyde, acetaldehyde, acrolein, and crotonaldehyde in cigarette smoke are included in the Canadian government and the Hoffman lists because of their toxicity [4,5]. The concentrations of these aldehydes in mainstream smoke are relatively high, up to μg/cig level. Reactive aldehyde groups can directly attack nucleophiles, such as guanine, adenine, cytosine, and thymine in nucleic acid, to produce DNA adducts. The common aldehyde-DNA adducts of these four aldehydes are listed in Table 1. DNA adducts play an important role in the initiation stage of multistage carcinogenesis. The resulting aldehyde-DNA adducts, if not repaired before DNA replication, may cause genetic instability and mutation, and lead to the eventual development of cancer [6].

Cigarette smoke is a potentially important source of exposure to these aldehydes. A recent study by Wang et al. showed clear differences in the amounts of HOMe-dA in the leukocytes of smokers and those of nonsmokers [16]; Hecht et al. found that the level of ethylidene-dG in the DNA of human leukocytes was significantly decreased by 28% upon quitting smoking [17]; Raghu et al. showed that acrolein-DNA adducts and 8,5′-cyclo-2′-deoxyguanosine (CdG) can be used as potential biomarkers for smoking-induced DNA damage in human oral tissues [18]. Thus, the detection of these aldehyde-DNA adducts (Table 1) can provide potential biomarkers for better risk assessment of the damage related to smoking tobacco. Among these aldehyde-DNA adducts, HOMe-dA, HOMe-dG, and ethylidene-dG are unstable in their nucleotide states and need to be reduced to their alkyl forms [N^6-methyl-deoxyadenosine

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Table 1
Common aldehyde-DNA adducts and abbreviations of the four aldehydes.

Aldehyde	DNA adducts	Abbreviations	Reference
Formaldehyde	N^6-hydroxymethyl-deoxyadenosine	HOMe-dA	[7,8]
	N^2-hydroxymethyl-deoxyguanosine	HOMe-dG	
Acetaldehyde	N^2-ethylidene-deoxyguanosine	Ethylidene-dG	[9–11]
	1,N^2-propano-2′-deoxyguanosine	CdG	
Acrolein	6-hydroxy-1,N^2-propano 2′-deoxyguanosine	α-Acr-dG	[12,13]
	8-hydroxy-1,N^2-propano 2′-deoxyguanosine	γ-Acr-dG	
Crotonaldehyde	8,5′-cyclo-2′-deoxyguanosine	CdG	[14,15]

(Me-dA), N^2-methyl-deoxyguanosine (Me-dG), and N^2-ethyl-deoxyguanosine (Et-dG)] by $NaBH_3CN$ for the purposes of quantitation [19,20]. The chemical structures of these aldehyde-DNA adducts, and the related target analytes, are listed in Fig. 1.

Because of the low content of DNA adducts in vivo, and the limited availability of clinical DNA samples, highly accurate, sensitive, specific, and quantitative analytical approaches are needed to examine the roles of DNA adducts in tumorigenesis and evaluation of cancer risk. Penn et al. used the sensitive ^{32}P-postlabeling/high pressure liquid chromatography (HPLC) to detect acrolein-DNA adducts, derived from acrolein inhalation, in the aortic DNA of cockerels; that study shows that acrolein-DNA adducts were five times higher in the exposed group than in the control group immediately after exposure to acrolein [21]. Greenspan et al. developed a high-throughput and in-situ method, using a monoclonal antibody, for quantifying acrolein-DNA adducts in human oral cells by immunohistochemical detection [22]. However, the ^{32}P-postlabeling-based technology is a laborious multi-step procedure with poor labeling efficiency; additionally, the antibody, used in the immunohistochemical step, is difficult to obtain.

Recent advancements in liquid chromatography (LC) interfaces and mass spectrometry (MS) ionization technologies have rendered the LC–MS-based method suitable for analyzing the polar DNA adducts directly. Chen et al. employed the LC–MS/MS technology to simultaneously quantify multiple exocyclic DNA adducts in a multi-reaction monitoring (MRM) mode [23]. Because LC–MS/MS methodology can directly analyze polar DNA adducts without derivatization, and shows high separation efficiency, specificity, and structural characterization, it has become one of the most efficient methods for the detection of DNA adducts [13]. Using stable isotopomers as the internal standard, which corrects for the errors and matrix effect, MS-based assays can accurately quantify the DNA adducts present at low abundance in vivo [24,23].

The objective of this study was to establish an assay for the simultaneous analysis of six aldehyde-DNA adducts, in order to compare the levels of trace amounts of DNA adducts between smokers and nonsmokers in a single experiment. In this study, a highly sensitive, accurate, and specific analytical method, based on stable isotope dilution liquid chromatography-electron spray ionization-tandem mass spectrometry (LC-ESI/MS/MS), was developed for the simultaneous

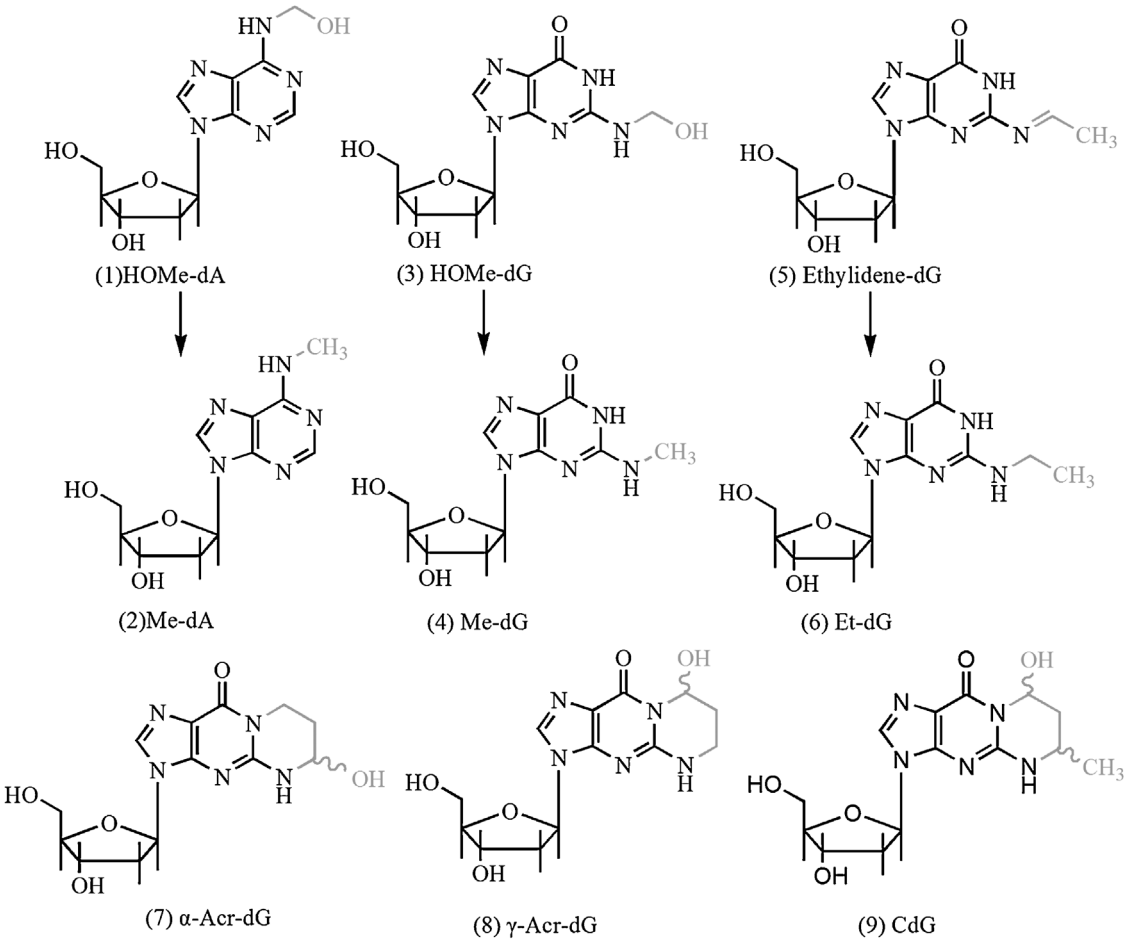

Fig. 1. Structures of the DNA adducts derived from four aldehydes and their stable forms; (4–9) are the target analytes.

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