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Review

DNA adduction and mutagenic properties of acrylamide

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Abstract

This review article summarizes our current knowledge on DNA damaging and mutagenic properties of acrylamide. Direct and indirect modes of interaction of acrylamide with DNA are discussed, and the resulting alkylating DNA adducts are highlighted. Emphasis is placed on glycidamide-DNA adducts generated via epoxidation of acrylamide presumably by cytochrome P4502E1. Dosimetry and mapping of acrylamide-induced DNA adducts in vitro and/or in vivo are described. Mutagenic potency and specificity of acrylamide in relation to its respective DNA adducts are discussed. Prospective views are provided on the potential applications of acrylamide-induced DNA adduct dosimetry/mapping and mutation frequency/spectrometry for biomonitoring purposes.

Keywords: Acrylamide; *cII* transgene; DNA adducts; Glycidamide; Mutations; *p53* gene

Contents

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1. Introduction

The recent discovery of acrylamide, a known rodent carcinogen [1], in a wide range of foods consumed by humans has raised public health concerns [2]. The unknown mechanism of acrylamide carcinogenicity has, however, deterred finding of a possible link between acrylamide exposure and human cancers. The underlying mechanism of acrylamide carcinogenicity can be resolved by investigating a multi-stage continuum that starts with exposure to acrylamide and ends with tumorigenesis. Of significance in this continuum are acrylamide-induced DNA adduction and mutagenesis. Formation of DNA adducts is a key element in the multi-stage process of carcinogenesis [3]. DNA adducts refractory to repair and/or inefficiently reparable may cause mispairing during DNA replication, thereby giving rise to mutations. Specific mutations in crucial genes encoding proteins for cell-cycle control and growth, i.e., oncogenes and tumor suppressor genes, might trigger tumorigenesis. Currently, DNA adduct dosimetry/mapping in combination with mutation frequency/spectrometry analyses are widely used to explore the etiology of cancers in which mutagenic carcinogens are implicated [4,5]. The prime examples are human skin and lung cancers for which solar ultraviolet radiation and tobacco-derived polycyclic aromatic hydrocarbons, respectively, are identified as the likely causative agents. The respective agents form DNA adducts at specific locations along the *p53* gene, which coincide with the sites of mutation hotspots in this tumor suppressor gene in skin and lung cancers, respectively. Also, the mutation spectra experimentally induced by these agents, i.e., C to T or CC to TT transitions at dipyrimidine sites and G to T transversions at methylated CpG dinucleotides, closely resemble those established for *p53* mutations in skin- and lung cancers, respectively [5,6]. In this review article, we survey the current knowledge on acrylamide biological properties of significance for carcinogenesis. We focus on acrylamide-DNA adduction and mutagenicity, and summarize the available data on acrylamide DNA adduct dosimetry/mapping and mutation frequency/spectrometry.

2. Acrylamide reactivity

Acrylamide is reactive in three different ways. Firstly, it can undergo radical-mediated polymerization [7]. This process is best attained anaerobically [7,8]. Secondly, as an α,β-unsaturated carbonyl compound, acrylamide can function as a 'Michael acceptor' and undergo addition to thiol, hydroxyl or amino groups [7]. The thiol addition largely represents a detoxification pathway by yielding primarily

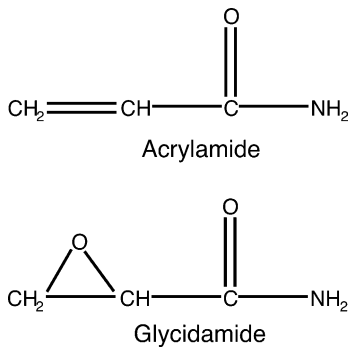

Fig. 1. Chemical structures of acrylamide and glycidamide.