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REACTION OF GUANOSINE WITH GLUCOSE UNDER OXIDATIVE CONDITIONS

Wolfgang Seidel and Monika Pischetsrieder*

Institut für Pharmazie und Lebensmittelchemie der Universität München, Sophienstr. 10, 80333 München (Germany)

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Abstract: Incubation of glucose with guanosine under oxidative conditions at 37 °C or 70 °C leads to the formation of a main product, which can be detected by HPLC/DAD. The compound was isolated and identified as N^2-carboxymethyl-guanosine (CMG). To confirm the structure, CMG was also synthesized from glyoxal and guanosine.

INTRODUCTION

Formation of covalent adducts between potentially genotoxic substances and DNA is considered as a crucial step for development of genetic disorders.[1] It was found that there is relatively high correlation between the capability of a compound to form DNA adducts and its cancerogenic potency.[2] Therefore considerable efforts have been made to identify DNA modifications which are formed from potentially mutagenic and cancerogenic substances. Particularly guanosine residues are modified, e.g. by the attack of electrophils to the 2-NH_2-group.[3,4] More recently it was shown that guanosine can react also with carbohydrates such as glucose, ribose, or ascorbic acid resulting in the formation of covalently bound adducts. Several products have been isolated and identified as N^2-(glucosyl)-guanosine,[5] N^2-(1-carboxy-3,4,5-trihydroxypentyl)-guanosine (CTPG),[6,7] N^2-carboxyethyl-guanosine (CEG),[8,9] N^2-(1-carboxy-3,4-dihydroxybutyl)-guanosine,[10] N^2-(1-carboxy-3-hydroxypropyl)-guanosine,[11] or the analogous derivatives of guanine or 2-deoxyguanosine. In the presence of primary amines such as lysine or propylamine the DNA-sugar interaction is accelerated[12] and crosslink products between guanosine and the amine are formed.[10]

e-mail: pischets@pharmchem.uni-muenchen.de
fax: ++49-89-5902-447

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There is evidence that the reaction of sugars with DNA (DNA glycation) causes increased mutation rates in bacteria cells[13] and mammalian cells.[14] Furthermore it was suggested that nonenzymatic glycation of DNA contributes to age-related increase in DNA mutations[15] and diabetes-associated teratogenesis.[16]

Genomic DNA, on the other hand is subjected to extensive oxidative stress resulting in approximately 10^4-10^5 base modifications per cell and day.[17] Since it is known that the presence of oxygen generally favours glycation,[18,19] we have investigated the reaction of guanosine with glucose under oxidative conditions and isolated and identified a major product which is formed.

RESULTS AND DISCUSSION

Guanosine was incubated with glucose at 37 °C in the presence of oxygen[20] and the reaction mixture was analyzed by HPLC with diode array detection.[21a] As a control the mixture was treated in the same way, but under anaerobic conditions.[22] Glucose turned out to be more active as glycating agent in the presence of oxygen than without. 6.7 % of the guanosine was converted into glycated derivates after 3 weeks under oxidative conditions, whereas under anaerobic conditions only 4.0 % of the educt was modified. Oxidation products of guanosine, particularly 8-hydroxy-guanosine could not be detected under the conditions applied here.

The main product which is formed from glucose and guanosine under oxidative conditions has the typical UV-absorbance curve of N^2-alkylated guanosine,[8] but it has not been described in literature so far. Under more stringent conditions, such as heating at 70 °C or boiling under reflux the same compound is formed, but in higher yields after shorter reaction time.

Scheme 1