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Slow loss of deoxyribose from the N7deoxyguanosine adducts of estradiol-3,4-quinone and hexestrol-3′,4′-quinone. Implications for mutagenic activity

Muhammad Saeed, Muhammad Zahid, Sandra J. Gunselman, Eleanor Rogan, Ercole Cavalieri*

Eppley Institute for Research in Cancer and Allied Diseases, University of Nebraska Medical Center, 986805 Nebraska Medical Center, Omaha, NE 68198-6805, USA

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Abstract

A variety of evidence has been obtained that estrogens are weak tumor initiators. A major step in the multi-stage process leading to tumor initiation involves metabolic formation of 4-catechol estrogens from estradiol (E_2) and/or estrone and further oxidation of the catechol estrogens to the corresponding catechol estrogen quinones. The electrophilic catechol quinones react with DNA mostly at the N-3 of adenine (Ade) and N-7 of guanine (Gua) by 1,4-Michael addition to form depurinating adducts. The N3Ade adducts depurinate instantaneously, whereas the N7Gua adducts depurinate with a half-life of several hours. Only the apurinic sites generated in the DNA by the rapidly depurinating N3Ade adducts appear to produce mutations by error-prone repair. Analogously to the catechol estrogen-3,4-quinones, the synthetic nonsteroidal estrogen hexestrol-3′,4′-quinone (HES-3′,4′-Q) reacts with DNA at the N-3 of Ade and N-7 of Gua to form depurinating adducts. We report here an additional similarity between the natural estrogen E_2 and the synthetic estrogen HES, namely, the slow loss of deoxyribose from the N7deoxyguanosine (N7dG) adducts formed by reaction of E_2-3,4-Q or HES-3′,4′-Q with dG. The half-life of the loss of deoxyribose from the N7dG adducts to form the corresponding 4-OHE_2-1-N7Gua and 3′-OH-HES-6′-N7Gua is 6 or 8 h, respectively. The slow cleavage of this glycosyl bond in DNA seems to limit the ability of these adducts to induce mutations.

Keywords: Steroidal and nonsteroidal estrogens; Catechol quinones; 1,4-Michael addition; Depurinating DNA adducts

1. Introduction

The natural and synthetic estrogens have been found to be carcinogenic in animal model studies [1–5]. The nonsteroidal synthetic estrogen diethylstilbestrol has also been shown to be carcinogenic in humans [6]. Estrogens are considered to be weak tumor initiators [7–9]. One pathway in the metabolism of estrogens leading to tumor initiation includes formation of 4-catechol estrogens from estradiol (E_2) and/or estrone. These catechol estrogens are further oxidized to the corresponding catechol estrogen quinones. The catechol quinones react with DNA at the N-3 of adenine (Ade) and N-7 of guanine (Gua) to form depurinating adducts [8–11]. These adducts are lost from DNA by destabilization of the glycosyl bond. The apurinic sites generated in the DNA can produce mutations by error-prone repair [11,12].

A similar metabolic activation has been found for the synthetic estrogen hexestrol (HES). The major metabolite of HES is its catechol [3,13], which can be oxidized to the catechol quinone. The HES-3′,4′-quinone (HES-3′,4′-Q) reacts with DNA at the N-3 of Ade and N-7 of Gua to form depurinating adducts analogous to the adducts formed by cat-

Abbreviations: Ade, adenine; dG, 2′-deoxyguanosine; DMF, *N*,*N*-dimethylformamide; E_2, estradiol; E_2-3,4-Q, estradiol-3,4-quinone; Gua, guanine; HES, hexestrol; HES-3′,4′-Q, hexestrol-3′,4′-quinone; MS/MS, tandem mass spectrometry; 4-OHE_2, 4-hydroxyestradiol; 3′-OH-HES, 3′-hydroxyhexestrol; TFA, trifluoroacetic acid

* Corresponding author. Tel.: +1 402 559 7237; fax: +1 402 559 8068.
E-mail address: ecavalie@unmc.edu (E. Cavalieri).

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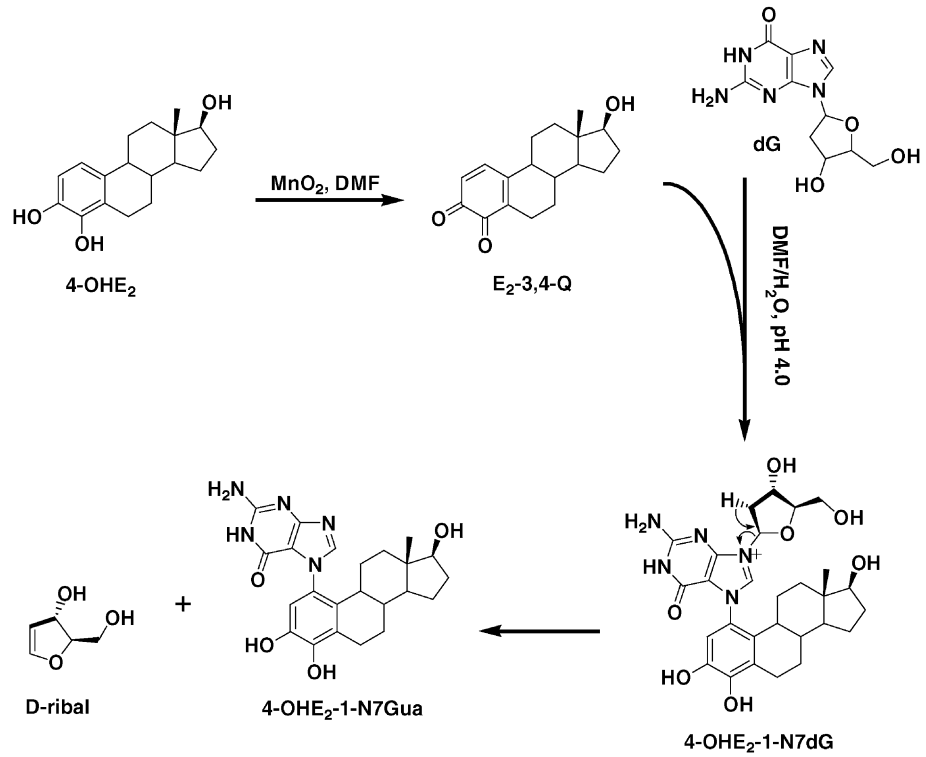

Fig. 1. Reaction scheme for the oxidation of 4-OHE_2 to E_2-3,4-Q and its reaction with dG to form 4-OHE_2-1-N7dG, followed by loss of deoxyribose to yield 4-OHE_2-1-N7Gua.

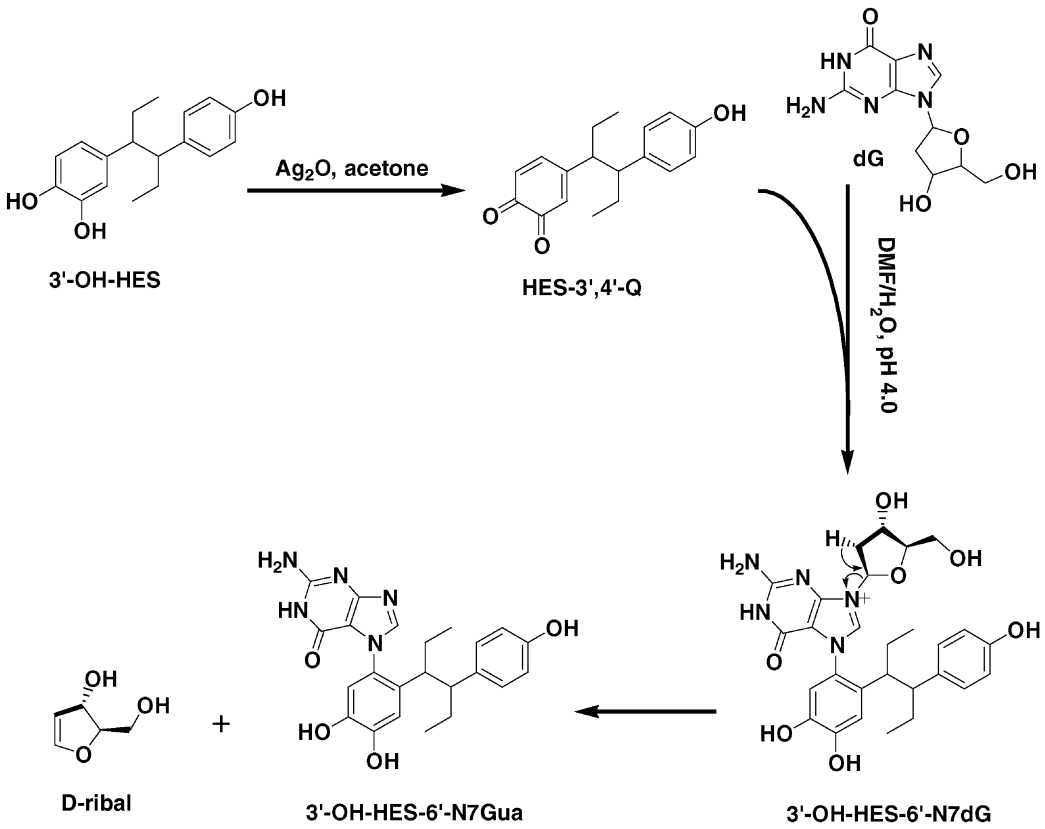

Fig. 2. Reaction scheme for the oxidation of 3′-OH-HES to HES-3′,4′-Q and its reaction with dG to form 3′-OH-HES-6′-N7dG, followed by loss of deoxyribose to yield 3′-OH-HES-6′-N7Gua.