Metabolic Activation of Nitroarenes by Human Aldo-Keto Reductases (AKR1C1-AKR1C3)

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Diesel engine exhaust (DEE) is listed as a Group 1 Carcinogen by the International Agency for Research on Cancer (IARC) and contributes to occupational and environmental causes of lung cancer. Nitrated-polycyclic aromatic hydrocarbons, or nitroarenes, are major constituents of DEE and are detected in ambient air pollution. Nitroarenes require metabolic activation to exert their mutagenic and tumorigenic effects. Metabolic activation of nitroarenes involves three successive two-electron reductions, leading to the formation of nitroso-, hydroxylamino-, and amine derivatives. The hydroxylamino-derivatives can give rise to DNA-adducts following sulfonation or acetylation. Identification of human enzymes involved in this process will be important for the assessment of individual susceptibilities. NADPH: Quinone Oxidoreductase (NQO1) is considered the primary nitroreductase in the metabolic activation of nitroarenes. However, AKR1C3 displays nitroreductase activity towards the cancer chemotherapeutic agent PR-104A and so we sought to determine whether AKR1C subfamily members could also contribute to toxification of nitroarenes. We have determined that AKR1C1-AKR1C3 catalyze the nitroreduction of 3-nitrobenzanthrone (3-NBA), a representative nitroarene, using discontinuous UV-HPLC assays. Evidence for the formation of the nitroso-, hydroxylamino-, and amine- products was obtained by UPLC-HRMS/MS. Specific activities for 3-aminobenzanthrone formation were compared with those for recombinant NQO1. Another representative nitroarene, 6-nitrochrysene (6-NC), has the unique characteristic that it can be activated by both monoxygenation and nitroreduction. Here we demonstrate that AKR1C1-AKR1C3 display dihydrodiol dehydrogenase and nitroreductase activity towards 6-nitrochrysene-1,2-dihydrodiol. Reaction products were characterized by LC-ion-trap mass spectrometry. The nitroreduction of diverse nitroarenes by AKR1C enzymes suggest that they may play a role in the activation of these diesel exhaust carcinogens. Notably both NQO1 and the AKR1C genes are highly induced by Nrf2-Keap1-ARE signaling, suggesting that the antioxidant response may not be entirely protective in the context of DEE exposures.

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