S-III-3

8-HYDROXYGUANINE; A MEDIATOR OF OXIDATIVE STRESS-INDUCED CYTOTOXICITY AND A DETECTOR OF GENE-SPECIFIC OXIDATIVE DAMAGE

Jin-Won Hyun, Jinhee Choi, Ja-Eun Kim, and Myung-Hee Chung

Department of Pharmacology, Seoul National University College of Medicine
Yongon-dong 28, Chongno-gu, Seoul 100-799, Korea

8-Hydroxyguanine(oh^{8}Gua), an oxidative DNA adduct is a most easily and abundantly formed base modification. What we have known about oh^{8}Gua so far is that this DNA adduct mediates the mutagenesis and it is used as a useful marker of oxidative DNA damage. We found additional evidence and here present them: 1) oh^{8}Gua in DNA can trigger cell death by inducing cell cycle arrest and apoptosis and 2) it can be used to assess the oxidative damage of each individual gene. The first evidence was obtained by the establishment of a method to make a specific increase of oh^{8}Gua in DNA. This specific increase was done by culturing KG-1, a leukemic cell line with loss of OGG1(a DNA repair enzyme for oh^{8}Gua) activity due to a mutation. The KG-1 with the resulting high level of oh8Gua in DNA showed severe distress symptoms which were cell cycle arrest at G1 phase, apoptosis(caspase-dependent) and cell death. The increase of oh8Gua level in KG-1 DNA appears to be due to the increase of polymerase beta activity. The second evidence was obtained by the amount difference in PCR products for a targeted gene when the PCR was performed before and after genomic DNA obtained from cells subjected to oxidative stress was treated with OGG1. Using this method, we found that genes of p53, receptor of IGF and receptor of TGF were preferentially attacked by oxygen radicals. From these findings, it is concluded that in addition to the mutagenesis, oh^{8}Gua in cellular DNA can affect cell functions. This action of oh^{8}Gua may serve as another mechanism for oxygen radicals to impair cell functions very severely and thus, provide a new mechanistic background through which antioxidants can give benefits to cells. And also, we are able to assess the DNA damage of individual genes and accordingly, can evaluate actions of antioxidants at a level of a specific targeted gene, not at the level of total DNA damage used so far.