

Abstract 7

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Reaction oxygen species production from smokeless tobacco

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A number of well-known xenobiotics exert their pharmacologic effects via the generation of reactive oxygen species (ROS), oxygen-containing molecules that have a higher reactivity than ground state molecular oxygen. One ROS species, superoxide ($O_2^{\cdot-}$), can react with the nitric oxide ($\cdot NO$) free radical to form the powerful biological nitrosating agent, peroxynitrite ($ONOO^-$). Unchecked, ROS and $ONOO^-$ may damage vital cellular macromolecules, including DNA. To protect against this damage, cells have developed a compartmentalized system of antioxidant enzymes that control ROS levels, and by extension, $ONOO^-$ formation, at or near their sites of production. These include the superoxide dismutase (SOD), catalase and glutathione peroxidase (GPx) enzymes. We and others have shown that smokeless tobacco and some of its constituents including nicotine, nitrosonornicotine (NNN) and 4-(methyl-N-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK) have the capacity to induce or directly release ROS and $\cdot NO$ at levels that cause lipid peroxidation, protein tyrosine nitrosation and DNA single strand breaks in cells and tissue explants. Moreover, incubation of these experimental systems with recombinant antioxidant enzymes, or gene transfer of antioxidant enzymes protects cells against this damage. Understanding the mechanisms of smokeless tobacco damage to oral cells and tissues could provide the basis for the development of novel strategies that could prevent, or potentially reverse epithelial changes in the oral mucosa from smokeless tobacco. This work was supported by grants from the Alberta Heritage Foundation for Medical Research and the Canadian Institutes for Health Research.