

Oxidative DNA damage by 1-hydroxyphenazine, virulence factor of *Pseudomonas aeruginosa*: Towards a Molecular understanding of the bacterial virulence factor 1-hydroxyphenazine

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ABSTRACT

1-Hydroxyphenazine is a secondary metabolite and virulence factor of *Pseudomonas aeruginosa*. This organism colonizes the airways of the patients of cystic fibrosis and causes progressive destruction of the airways. It is suggested that 1-hydroxyphenazine plays an important role in such tissue damage but mechanisms underlying the biological properties of 1-hydroxyphenazine are not well studied. We report chemical properties of 1-hydroxyphenazine which might help to explain its biological activities.

The work presented here provides first evidence that 1-hydroxyphenazine in presence of one electron reducing enzyme NADPH:cytochrome P450 reductase undergoes redox cycling by reaction with molecular oxygen and produces reactive oxygen species (ROS) for example, superoxide radical, hydrogen peroxide and hydroxyl radical and generation of ROS cause oxidative stress inside the cell. In addition to this, we show that 1-hydroxyphenazine oxidizes into cytotoxic *N*-oxides by reaction with hydrogen peroxide, oxygen and peroxyntirite and these *N*-oxides of 1-hydroxyphenazine also generate ROS in presence of NADPH:cytochrome P450 reductase via redox-cycling mechanism. Generation of ROS by both 1-hydroxyphenazine and its *N*-oxides might be the one of the causes of cytotoxicity of lung airways of cystic fibrosis patients. We used plasmid based DNA damage assay as a tool to elucidate the chemistry of oxidative stress caused by both 1-hydroxyphenazines and *N*-oxides of 1-hydroxyphenazine.