

## HIV-1 protease inhibitor induced oxidative stress in pancreatic B-cells: thymoquinone protection

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Researchers at the Tulane University School of Medicine, New Orleans, Louisiana have discovered that the HIV-1 protease inhibitors (PIs), such as nelfinavir included in highly active antiretroviral therapy (HAART) regimen for the treatment of HIV-1 patients, induce deleterious effects on insulin secretion mediated through the oxidative stress pathway.

They report a significant decrease in the levels of the antioxidants, cytosolic superoxide dismutase (Cu/Zn SOD) and glutathione, whereas mitochondrial SOD levels remained unaffected in pancreatic beta-cells (INS-1 cells) exposed to nelfinavir. However, the mitochondrial uncoupling protein (UCP2) levels were up-regulated during nelfinavir induced oxidative stress and directly affected the ATP levels in these cells.

A significant decrease in <u>ATP production</u> was also observed which may account for the decrease in glucose stimulated <u>insulin secretion</u> upon nelfinavir treatment. This study appears in the April 2009 issue of *Experimental Biology and Medicine*. Although <u>insulin resistance</u> has been clinically observed in HIV-1 patients receiving HAART regimen, the molecular mechanisms of this <u>metabolic abnormality</u> have not been delineated.

The research team led by Dr. Krishna C. Agrawal, Regents Professor and Chairman included Surabhi Chandra, a graduate student and another



faculty member, Dr. Debasis Mondal in the Department of Pharmacology. These investigators successfully tested the hypothesis that nelfinavir induced oxidative stress was responsible for the <u>deleterious effects</u> of the HIV-1 protease inhibitor on insulin production by pancreatic beta-cells and they further investigated the therapeutic strategies to ameliorate the insulin dysregulation at this level. Since the hypoglycemic effects of Nigella sativa oil have been investigated in the past, the investigators postulated that nelfinavir induced oxidative stress may be ameliorated by the administration of the active ingredient of this oil, thymoquinone.

Furthermore, it was envisioned that since thymoguinone shares a structural homology with ubiquinone (mitochondrial component) it is likely that it may act as a mitochondrial antioxidant. Indeed pretreatment of pancreatic beta-cells with thymoquinone caused a reversal of nelfinavir induced deleterious effects. Thymoquinone decreased the production of reactive oxygen species, increased the Cu/Zn SOD and glutathione levels, suppressed the UCP-2 protein levels and restored nelfinavir induced decrease in insulin secretion to normal levels in these cells. Dr. Agrawal commented, "An important finding of this study is that the dysregulation of insulin production in pancreatic beta-cells is due to generation of reactive oxygen species induced by nelfinavir, an HIV-1 protease inhibitor". Furthermore, Dr. Agrawal said, "thymoquinone, an antioxidant provided a significant protection to pancreatic beta-cells from the toxic effects of nelfinavir and therefore these findings clearly suggest a potential role for the use of black seed oil or thymoquione as a protective agent against HIV-1 protease inhibitor induced deleterious effects on pancreatic beta-cells".

Source: Society for Experimental Biology and Medicine



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