Tadalafil alleviates cisplatin-induced reproductive toxicity through the activation of the Nrf2/HO-1 pathway and the inhibition of oxidative stress and apoptosis in male rats

Basel A Abdel-Wahab, Saad Ahmed Alkahtani, Ehab AM Elagab

Abstract:

Male reproductive toxicity is a well-known adverse effect of cisplatin (CIS), an important antineoplastic agent used to control several types of cancers. Tadalafil (TDF), is a long-acting phosphodiesterase-5 (PDE5) inhibitor commonly used as treatment for erectile dysfunction. The aim of this work was to study the possible protective effect of TDF against CIS-induced testicular toxicity in rats and the possible involvement of Nrf2/HO-1 pathway, which demonstrates antioxidant and inflammatory activities utilizing zinc protoporphyrin-IX (ZnPP) as HO-1 inhibitor. Results revealed that TDF attenuated the CIS-induced disturbances in sperm count and activities, normalized the serum testosterone level, improved the CIS-induced changes in epididymal and testicular weights and restored the normal structure of testicular tissues. In addition, TDF upregulated the gene expression levels of Nrf2 and HO-1 and the activity of HO-1 whereas, it reduced the CIS-induced changes in testicular oxidative stress markers and the levels of inflammatory mediators (TNF-α and iNOS). Furthermore, TDF antagonized the CIS-induced increase in testicular gene expression of apoptotic markers caspase-3 and Bax, and the decrease in Bcl-2. However, ZnPP co-administration significantly attenuated all TDF-mediated improvements in CIS-induced testicular toxicity, biochemical changes, and apoptosis. In conclusion, TDF exerts a protective effect against CIS-induced reproductive toxicity in males, through different mechanisms, besides its inhibitory action to PDE5, possibly mediated by the upregulation of Nrf2/HO-1, along with its antioxidant, anti-inflammatory, and anti-apoptotic effects. Hence, the use of TDF represents a promising therapeutic approach to protect the male reproductive system from the harmful toxic effects of CIS.

Keywords:

Cisplatin-induced testicular toxicity Tadalafil Nrf2/HO-1 Heme oxygenase-1 Zinc protoporphyrin Oxidative stress Apoptosis

Published In:

Reproductive Toxicology, 96, 165-174