The protective action of melatonin on indomethacin-induced gastric and testicular oxidative stress in rats.

Reactive oxygen species and lipid peroxidation play a role in the pathogenesis induced by the nonsteroidal anti-inflammatory drug indomethacin. Melatonin (MLT) protection against indomethacin-induced oxidative tissue injury was investigated in gastric mucosa and testis of rats. MLT was administered intragastrically (i.g.) 30 min before the administration to fasted rats of 20 mg indomethacin/kg rat given i.g.. The area of gastric lesion as well as thiobarbituric acid substances (TBARS) and lactate dehydrogenase (LDH) activity were found to be significantly increased 4 h after administration of indomethacin in rat gastric mucosa and testis indicating acute oxidative injury. MLT pretreatment reduced gastric lesion area to 80% of the indomethacin-treated rats and reduced the rise in TBARS concentration. MLT treatment reduced the LDH activity increase in testis but not in gastric mucosa. In indomethacin-treated rats, both the cytosolic Cu,Zn superoxide dismutase (Cu,Zn-SOD) and mitochondrial Mn-SOD activities were significantly diminished in gastric mucosa as well as the total SOD activity in testis. In addition, glutathione (GSH) content in both tissues was markedly decreased following indomethacin treatment. Pretreatment with MLT significantly ameliorated both the inhibition of SOD activity and the decreased GSH content in both tissues. Thus, these results show the effective antiperoxidative and preventative actions of MLT against indomethacin-induced gastric mucosal damage and testicular oxidative injury and we propose that this action might be relevant for its use with other free radical generating drugs.

Melatonin controls oxidative stress and modulates iron, ferritin, and transferrin levels in adriamycin treated rats

Aim

Chemotherapy with adriamycin (ADR) is limited by its iron-mediated pro-oxidant toxicity. Because melatonin (MLT) is a broad spectrum antioxidant, we investigated the ability of MLT to control iron, its binding proteins, and the oxidative damage induced by ADR.

Main methods
ADR was given as a single i.p. dose of 10 mg kg\(^{-1}\) body weight into male rats. MLT at a dose of 15 mg kg\(^{-1}\) was injected daily for 5 days before ADR treatment followed by another injection for 5 days. Biochemical methods were used for this investigation.

**Key findings**

ADR injection caused elevations in plasma creatine kinase isoenzyme, lactate dehydrogenase, and aminotransferases, iron, ferritin, and transferrin. These changes were associated with increases in lipid peroxidation and protein oxidation as well as decreases in glutathione (GSH) levels and glutathione-S-transferase (GST) activity, while glutathione peroxidase (GSH-Px), and catalase (CAT) activity were elevated in the heart and liver of ADR treated rats. In the MLT + ADR group, the cardiac and hepatic function parameters and the levels of iron, transferrin, and ferritin in plasma were normalized to control levels. The rats that were subjected to MLT + ADR had normalized CAT and GSH-Px activity and decreased TBARS and protein carbonyl levels compared to the group only treated with ADR. GST activity and GSH concentration in the heart and liver were normalized when MLT accompanied ADR treatment.

**Significance**

MLT ameliorated oxidative stress by controlling iron, and binding protein levels in ADR treated rats demonstrating the usefulness of adriamycin in cancer chemotherapy and allowing a better management of iron levels.

### 3- Role of melatonin in ameliorating lead induced haematotoxicity

Owing to the risks of heavy metals-induced severe haematopoietic disorders, it is important to investigate these chemicals for their haematotoxicity and the possible ways to ameliorate their toxicity. The effects of melatonin on lead-induced haematotoxicity have, therefore, been examined in rat blood and bone marrow. When adult male rats were injected intramuscularly with lead acetate (10 mg kg\(^{-1}\)) daily for 7 days, the erythrocytic count, haematocrit value and haemoglobin content were significantly decreased. The counts of platelets, total leucocytes and lymphocytes in the peripheral blood were also significantly lower in lead-treated rats than in control animals. The total granulocyte count was significantly elevated in the peripheral blood of the same lead-treated rats. Significant decreases in polychromatic and pyknotic erythroid series as well as lymphocytes in bone marrow of the lead-intoxicated rats were also demonstrated. Meanwhile, the neutrophiles were increased in the same treated rats. The erythropoietin level was significantly decreased and the lead concentration was increased in the plasma of the lead-treated rats compared with the control rats. Bone marrow examination of the rats treated with lead for 7 days showed erythroid hyperplasia with a sign of dyserythropoiesis and demonstrated ringed sideroblasts in varying proportions. Daily pretreatment with melatonin (30 mg kg\(^{-1}\)) intragastrically, concurrently with lead injection for 7 days significantly prevented the changes recorded in the peripheral blood parameters. The changes observed in the bone marrow polychromatic erythroid, lymphocytes and the neutrophiles were significantly ameliorated by coadministration of melatonin and lead.
compared with lead-treated rats, while the pyknotic erythroid series was still significantly low. The levels of erythropoietin and lead in plasma were not changed in melatonin + lead-treated group compared with lead only treated rats. In addition, melatonin administration ameliorated the decrease in erythroid cell count in bone marrow. Less dyserythropoiesis and megaloblastic changes were observed in bone marrow film when melatonin was concurrently administered with lead. In the same animals, iron staining of the bone marrow cells showed absence of ringed sideroblasts. In conclusion, the present results indicate that melatonin has the ability to protect the haematopoietic cells from the damaging effects of exposure to lead. This protection might be attributed to the antioxidative power of melatonin.

4-

**L-Arginine ameliorates oxidative stress in alloxan-induced experimental diabetes mellitus.**

Oxidative stress occurs in diabetic patients and experimental models of diabetes. The ability of L-arginine to ameliorate the oxidative stress and metabolic changes after treatment with alloxan was investigated in rats. Adult male rats were injected intraperitoneally with 100 mg kg\(^{-1}\) of alloxan to produce experimental oxidative stress characteristic of diabetes mellitus. Hyperglycaemia and hypercholesterolaemia were observed in serum after 7 days of alloxan treatment. This was associated with a depression of glutathione (GSH) concentration as well as superoxide dismutase (SOD) and catalase (CAT) activities in the liver and brain. In addition, the thiobarbituric acid-reactive substances (TBARS) were significantly elevated, indicating increased lipid peroxidation and oxidative stress in the same tissues. Administration of 100 mg kg\(^{-1}\) L-arginine for 7 days either before or after alloxan injection significantly ameliorated the oxidative stress evidenced by a lower TBARS and a higher level of the endogenous GSH concentration and SOD and CAT activities than alloxan-treated rats. These effects were paralleled by marked protection and partial prophylaxis against alloxan-induced hyperglycaemia and cholesterolama. Thus, these results showed that exogenously administered L-arginine might improve the clinical manifestation of diabetes mellitus and decrease the oxidative stress in the liver and brain. In addition, the study supports the beneficial effect of L-arginine, which might be attributed to its direct, NO-dependent antioxidant capacity and/or NO-independent pathways. Copyright 2004 © John Wiley &
Attenuation of the acute adriamycin-induced cardiac and hepatic oxidative toxicity by N-(2-mercaptopropionyl) glycine in rats

The protective effect of the synthetic aminothiol, N-(2-mercaptopropionyl) glycine (MPG) on adriamycin (ADR) induced acute cardiac and hepatic oxidative toxicity was evaluated in rats. ADR toxicity, induced by a single intraperitoneal injection (15 mg/kg), was indicated by an elevation in the level of serum glutamic pyruvic transaminase (GPT), glutamic oxaloacetic transaminase (GOT), creatine kinase isoenzyme (CK-MB), and lactic dehydrogenase (LDH). ADR produced significant elevation in thiobarbituric acid reactive substances (TBARS), indicating lipid peroxidation, and significantly inhibited the activity of superoxide dismutase (SOD) in heart and liver tissues. In contrast, a single injection of ADR did not affect the cardiac or hepatic glutathione (GSH) content and cardiac catalase (CAT) activity but elevated hepatic CAT. Pretreatment with MPG, (2.5 mg/kg) intragastrically, significantly reduced TBARS concentration in both heart and liver and ameliorated the inhibition of cardiac and hepatic SOD activity. In addition, MPG significantly decreased the serum level of GOT, GPT, CK-MB, and LDH of ADR treated rats. These results suggest that MPG exhibited antioxidative potentials that may protect heart and liver against ADR-induced acute oxidative toxicity. This protective effect might be mediated, at least in part, by the high redox potential of sulfhydryl groups that limit the activity of free radicals generated by ADR.

Potential protective role of angiotensin-converting enzyme inhibitors captopril and enalapril against adriamycin-induced acute cardiac and hepatic toxicity in rats

Captopril and enalaprilâ€”angiotensin-converting enzyme (ACE) inhibitorsâ€”were evaluated for their antioxidative protective action against adriamycin-induced cardiac and hepatic toxicity. Rats were treated with either captopril (10 mg kg?1) or enalapril (2 mg kg?1) intragastrically (i.g.) daily for 7 days before single intraperitoneal (i.p.) injection with adriamycin (15 mg kg?1). The animals were killed 30 h after adriamycin
administration. Adriamycin produced significant elevation in thiobarbituric acid reactive substances (TBARS), which is an indicator of lipid peroxidation, and significantly inhibited the activity of superoxide dismutase (SOD) in heart and liver tissues, with a significant rise in the serum levels of glutamic pyruvic transaminase (GPT), glutamic oxaloacetic transaminase (GOT), creatine kinase isoenzyme (CK-MB) and lactic dehydrogenase (LDH), indicating acute cardiac toxicity. A single injection of adriamycin did not affect the cardiac or hepatic glutathione (GSH) content or cardiac catalase (CAT) activity, but hepatic CAT activity was elevated. Pretreatment with ACE inhibitors significantly reduced the TBARS concentration in both heart and liver and ameliorated the inhibition of cardiac and hepatic SOD activity. In addition, the ACE inhibitors significantly improved the serum levels of GOT, GPT, CK-MB and LDH in adriamycin-treated rats. Thus, these results suggest that captopril and enalapril possess antioxidative potential that may protect the heart against adriamycin-induced acute oxidative toxicity. This protective effect might be mediated, at least in part, by the limitation of culprit free radicals and the amelioration of oxidative stress. Copyright © 2001 John Wiley & Sons, Ltd.

Protection by metal complexes with SOD-mimetic activity against oxidative gastric injury induced by indomethacin and ethanol in rats

We have investigated the protective effect of oral administration of copper and manganese complexes with superoxide dismutase (SOD)-mimetic activity against oxidative gastric mucosal injury induced by the non-steroidal antiinflammatory drug indomethacin with ethanol in the rat. The total area of the gastric lesions and lipid peroxidation were significantly increased 1 h after oral administration of indomethacin (15 mg/kg) and ethanol, indicating an acute oxidative injury. The activities of SOD, catalase (CAT), glutathione-S-transferase (GST) and glutathione content were significantly decreased in the gastric mucosa by indomethacin plus ethanol. Manganese or copper complexes showed SOD-mimetic activity. Pretreatment with these complexes protected against gastric mucosal lesions and decreased lipid peroxides, as well as attenuating the decrease in the activities of SOD, CAT and GST in gastric mucosa. These findings suggest that active oxygen species and lipid peroxidation play an important role in the pathogenesis of gastric mucosal injury induced by indomethacin. In addition, we have shown that Mn and Cu complexes have gastroprotective properties against ulceration induced by indomethacin plus ethanol. The present results suggest that appropriate copper or manganese complex supplementation may potentially provide prophylaxis or therapy for some pathologies associated with excessive free radical production and inhibited SOD.
8- **Role of selenium against lead toxicity in male rats**

Male albino rats were intramuscularly administered a single dose of lead acetate (100 lmol/kg b.wt). Another group of rats were injected with sodium selenite (10 lmol/kg b.wt) before lead intoxication. After 3 and 24 hours, lead treatment resulted in significant increases in acid and alkaline phosphatases, GOT and GPT, total proteins, and cholesterol in serum. The total triglycerides in serum was decreased after 24 hours of intoxication. Lead treatment also produced significant elevation of lipid peroxidation in liver and kidney. The antioxidant capacity of hepatic and renal cells in terms of the activities of superoxide dismutase, glutathione reductase, and glutathione content was diminished. It appears from these results that lead may exert its toxic effect via peroxidative damage to renal and hepatic cell membranes after 24 hours. Selenium administration prior to lead injection produced pronounced prophylactic action against lead effects, and it is observed that selenium enhances the endogenous antioxidant capacity of the cells by increasing the activities of the superoxide dismutase and glutathione reductase and the glutathione content. As a result, the lipid peroxidation was decreased in both liver and kidney.


9- **Alfa-Lipoic acid protects testosterone secretion pathway and sperm quality against 4-tert-octylphenol induced reproductive toxicity**

LA protected against OP induced oxidative injury in both the hypothalamus and epididymal sperm by augmenting the endogenous antioxidants, particularly GSH and GST. This led to the maintenance of steroidogenesis that in turn maintained regular germ cell proliferation and production of normal sperm count, motility and morphology. Furthermore, LA showed the potential to protect DNA and protein organization in sperm against OP-induced oxidative stress. It is anticipated that LA supplementation not only protects male fertility but also may assist normal fertilization and prevents the transfer of defective paternal DNA to the progeny.

10- **Current Topics in Ionizing Radiation Research**
Radiations exist ubiquitously in the environment since the Earth’s creation in soil, water and plants. Radiation exposure is a concern in the health industry and other occupations in the world. Apart from diagnostic, therapeutic and industrial purposes, humans also are exposed to ionizing radiations during air and space travel and exploration, background radiation, nuclear accidents, and nuclear terror attacks. Elevated radiation levels have been detected following Chernobyl on April 1986 at Ukraine, and recently Fukushima Daiichi Nuclear Power Plants on March 2011 at Japan. This raised the need for finding out efficient and reliable radioprotectors especially when a whole nation is exposed at high or even low levels for a prolonged period. The fallout and radioactivity cause concern during the weeks and months after the accidents. In addition, radiations are commonly used in a number of medical and industrial situations; however, their pro-oxidative effects limit their applications. Therefore, it is essential to protect humans from ionizing radiations by efficient pharmacological intervention. A valid approach to halt normal tissue radiotoxicity is the use of radioprotectors that when present prior to radiation exposure protect normal tissues from radiation effects. This view has also been used as a successful preventative measure for possible nuclear/radiological situation. From a practical point of view radioprotectors should perfectly have several criteria that relate to the ability of the agent to improve the therapeutic outcome. Ionizing radiation causes oxidative damage to tissues within an extremely short period, and possible protection against it would require the rapid transfer of smart antioxidants to the sensitive sites in cells. At this point, melatonin (N-acetyl-5-methoxytryptamine; MW= 232), an innate antioxidant produced mainly by the pineal gland, seems unique among antioxidants because of its multiple properties and reactions which reviewed and documented in several publications and summarised herein. While ionizing radiation exposures, due to free radical generation, present an enormous challenge for biological and medical safety, melatonin is a potent radioprotector. In several investigations, melatonin has been recognized for successful amelioration of oxidative injury and illness due to direct and indirect effects of ionizing radiation and against oxidative stress in several experimental and clinical settings. Furthermore, numerous studies have established that melatonin is a highly efficient free radical scavenger, broad antioxidant and stimulator of several antioxidants in biological systems. Because of its unique characteristics; melatonin has effects not only at the cell level but also within subcellular organelles and structures. The antioxidant and prophylactic properties of melatonin allow the use of radiation during radiotherapy to get better therapeutic outcomes. Several published articles documented that melatonin’s anticancer and oncostatic effects make melatonin an excellent candidate and good choice to be used in routine radiotherapies, occupational settings where accidental exposure may occur, and space travel and following nuclear accidents. This article will review antioxidant features that put melatonin on top of potentially efficient pharmacological radioprotectors.