

- 1: [Clin Exp Pharmacol Physiol](#). 2007 Dec;34(12):1252-9.

## **REVERSAL OF CISPLATIN-INDUCED CARNITINE DEFICIENCY AND ENERGY STARVATION BY PROPIONYL-L-CARNITINE IN RAT KIDNEY TISSUES.**

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1. The present study examined whether propionyl-L-carnitine (PLC) could prevent the development of cisplatin (CDDP)-induced acute renal failure in rats. 2. Forty adult male Wistar albino rats were divided into four groups. Rats in the first group were injected daily with normal saline (2.5 mL/kg, i.p.) for 10 consecutive days, whereas the second group received PLC (250 mg/kg, i.p.) for 10 consecutive days. Animals in the third group were injected daily with normal saline for 5 consecutive days before and after a single dose of CDDP (7 mg/kg, i.p.). Rats in the fourth group received a combination of PLC (250 mg/kg, i.p.) for 5 consecutive days before and after a single dose of CDDP (7 mg/kg, i.p.). On Day 6 following CDDP treatment, animals were killed and serum and kidneys were isolated for analysis. 3. Injection of CDDP resulted in a significant increase in serum creatinine, blood urea nitrogen (BUN), thiobarbituric acid-reactive substances (TBARS) and total nitrate/nitrite (NO(x)), as well as a significant decrease in reduced glutathione (GSH), total carnitine, ATP and ATP/ADP in kidney tissues. 4. Administration of PLC significantly attenuated the nephrotoxic effects of CDDP, manifested as normalization of the CDDP-induced increase in serum creatinine, BUN, TBARS and NO(x) and the CDDP-induced decrease in total carnitine, GSH, ATP and ATP/ADP in kidney tissues. 5. Histopathological examination of kidney tissues from CDDP-treated rats showed severe nephrotoxicity, in which 50-75% of glomeruli and renal tubules exhibited massive degenerative changes. Interestingly, administration of PLC to CDDP-treated rats resulted in a significant improvement in glomeruli and renal tubules, in which less than 25% of glomeruli and renal tubules exhibited focal necrosis. 6. Data from the present study suggest that PLC prevents the development of CDDP-induced acute renal injury by a mechanism related, at least in part, to the ability of PLC to increase intracellular carnitine content, with a consequent improvement in mitochondrial oxidative phosphorylation and energy production, as well as its ability to decrease oxidative stress. This will open new perspectives for the use of PLC in the treatment of renal diseases associated with or secondary to carnitine deficiency.

- 2: [Clin Exp Pharmacol Physiol](#). 2007 May-Jun;34(5-6):399-405.

**Thymoquinone supplementation prevents the development of gentamicin-induced acute renal toxicity in rats.**

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1. The present study investigated the possible protective effects of thymoquinone (TQ), a compound derived from *Nigella sativa* with strong anti-oxidant properties, against gentamicin (GM)-induced nephrotoxicity. 2. A total of 40 adult male Wistar albino rats was divided into four groups. Rats in the first group were injected daily with normal saline (2.5 mL/kg, i.p.) for 8 consecutive days, whereas rats in the second group received TQ (50 mg/L in drinking water) for 8 consecutive days. Animals in the third group were injected daily with GM (80 mg/kg, i.p.) for 8 consecutive days, whereas animals in the fourth group received a combination of GM (80 mg/kg, i.p.) and TQ (50 mg/L in drinking water) for 8 consecutive days. 3. Gentamicin resulted in a significant increase in serum creatinine, blood urea nitrogen (BUN), thiobarbituric acid-reactive substances (TBARS) and total nitrate/nitrite (NO<sub>x</sub>) and a significant decrease in reduced glutathione (GSH), glutathione peroxidase (GPx), catalase (CAT) and ATP levels in kidney tissues. 4. Interestingly, TQ supplementation resulted in a complete reversal of the GM-induced increase in BUN, creatinine, TBARS and NO<sub>x</sub> and decrease in GSH, GPx, CAT and ATP to control values. Moreover, histopathological examination of kidney tissues confirmed the biochemical data, wherein TQ supplementation prevents GM-induced degenerative changes in kidney tissues. 5. Data from the present study suggest that TQ supplementation prevents the development of GM-induced acute renal failure by a mechanism related, at least in part, to its ability to decrease oxidative stress and to preserve the activity of the anti-oxidant enzymes, as well as its ability to prevent the energy decline in kidney tissues.

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- 3: [Clin Exp Pharmacol Physiol](#). 2006 Aug;33(8):725-33.

**Carnitine esters prevent oxidative stress damage and energy depletion following transient forebrain ischaemia in the rat hippocampus.**

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1. The present study investigated whether propionyl-L-carnitine (PLC) has neuroprotective effects, similar to those reported for acetyl-L-carnitine (AC), against transient forebrain ischaemia-induced neuronal damage and biochemical derangement in the rat hippocampal CA1 region. 2. In total, 105 adult male Wistar albino rats were divided into seven groups of 15 animals each. The first three groups were injected i.p. with normal saline, AC (300 mg/kg) or PLC (300 mg/kg) for 7 successive days. The next three groups were injected i.p. with the same doses of normal saline, AC or PLC immediately after the induction of 10 min forebrain ischaemia and i.p. injections were continued for 7 successive days. Rats in the seventh group were subjected to sham-operated ischaemia and injected with normal saline for 7 successive days. 3. Seven days after treatment, animals were killed and their brains isolated for histopathological examination and biochemical studies. 4. Forebrain ischaemia resulted in a significant decrease in the number of intact neurons (77%), ATP concentration (51%) and glutathione content (32%), whereas there was a significant increase in the production of thiobarbituric acid-reactive substances (TBARS; 71%) and total nitrate/nitrite (NOx; 260%) in hippocampal tissues. 5. Administration of either AC or PLC attenuated forebrain ischaemia-induced neuronal damage, manifested by a greater number of intact neurons, ATP and glutathione, as well as a decrease in TBARS and NOx in hippocampal tissues. 6. Results from the present study suggest, for the first time, that PLC attenuates forebrain ischaemia-induced neuronal injury, oxidative stress and energy depletion in the hippocampal CA1 region. Propionyl-L-carnitine has neuroprotective effects similar to AC and could have a potential use in the treatment of neurodegenerative diseases. 7. The results of the present study will open up new perspectives for the use of PLC in the treatment of neurodegenerative diseases associated with, or secondary to, myocardial ischaemia-reperfusion injury and chronic circulatory failure.

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- 4: [Pharmacol Res.](#) 2006 Mar;53(3):278-86. Epub 2006 Jan 24.

**Propionyl-L-carnitine prevents the progression of cisplatin-induced cardiomyopathy in a carnitine-depleted rat model.**

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This study has been initiated to investigate whether endogenous carnitine depletion and/or carnitine deficiency is a risk factor during development of cisplatin (CDDP)-induced cardiomyopathy and if so, whether carnitine supplementation by propionyl-L-carnitine (PLC) could offer protection against this toxicity. To achieve the ultimate goal of this study, a total of 60 adult male Wistar albino rats were divided into six groups. The first three groups were injected intraperitoneally with normal saline, PLC (500 mg kg<sup>-1</sup>), and d-carnitine (500 mg kg<sup>-1</sup>) respectively, for 10 successive days. The 4th, 5th, and 6th groups were injected intraperitoneally with the same doses of normal saline, PLC and D-carnitine, respectively, for 5 successive days before and after a single dose of CDDP (7 mg kg<sup>-1</sup>). On day 6 after CDDP treatment, animals were sacrificed, serum as well as hearts were isolated and analyzed. CDDP resulted in a significant increase in serum creatine phosphokinase isoenzyme (CK-MB) and lactate dehydrogenase (LDH), thiobarbituric acid reactive substances (TBARS) and total nitrate/nitrite (NO(x)) and a significant decrease in reduced glutathione (GSH), total carnitine, and adenosine triphosphate (ATP) content in cardiac tissues. In the carnitine-depleted rat model, CDDP induced dramatic increase in serum cardiomyopathy enzymatic indices, CK-MB and LDH, as well as progressive reduction in total carnitine and ATP content in cardiac tissue. Interestingly, PLC supplementation resulted in a complete reversal of the increase in cardiac enzymes, TBARS and NO(x), and the decrease in total carnitine, GSH and ATP, induced by CDDP, to the control values. Moreover, histopathological examination of cardiac tissues confirmed the biochemical data, where PLC prevents CDDP-induced cardiac degenerative changes while d-carnitine aggravated CDDP-induced cardiac tissue damage. In conclusion, data from this study suggest for the first time that carnitine deficiency and oxidative stress are risk factors and should be viewed as mechanisms during development of CDDP-related cardiomyopathy and that carnitine supplementation, using PLC, prevents the progression of CDDP-induced cardiotoxicity.

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- 5: [J Egypt Natl Canc Inst.](#) 2004 Dec;16(4):237-43.

**Acetyl-L-carnitine modulates bleomycin-induced oxidative stress and energy depletion in lung tissues.**

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**BACKGROUND AND PURPOSE:** The usefulness of Bleomycin (BLM) as an important antineoplastic drug is usually limited to the development of dose and time-dependent interstitial pneumonitis and pulmonary fibrosis. This study has been initiated to investigate the possible protective effects of acetyl-L-carnitine (AC) against BLM-induced lung toxicity at an early stage of its development.

**MATERIAL AND METHODS:** A total of 40 male Sprague-Dawley rats weighing from 200-250 g each, were divided into 4 groups of 10 animals each. The first group received a daily i.p. injection of normal saline (0.5 ml/200 gm body weight) for 5 consecutive days and served as a control. Animals in the second, third and fourth groups were daily injected intraperitoneally (i.p.) with BLM (15 mg/kg body weight), AC (250 mg/kg body weight) and AC (250 mg/kg) 2 hrs before BLM (15 mg/kg) each for 5 consecutive days,

**RESULTS:** Treatment of rats with BLM (15 mg/kg) resulted in a significant 3.4 and 2.9 folds increase in malondialdehyde (MDA) and nitric oxide (NO) production in lung tissue, respectively and a significant 39%, 35%, 54% and 44% decrease in reduced glutathione (GSH), superoxide dismutase (SOD), glutathione peroxidase (GSHPx) and adenosine triphosphate (ATP), respectively as compared to the control group. Treatment of rats with AC did not lead to any significant change in the mentioned biochemical parameters in the lung tissue. Administration of AC two hours before BLM attenuated BLM-induced increase in MDA and NO and the decrease in GSH, SOD, GSHPx and ATP in lung tissue.

**CONCLUSION:** The present data suggests that the protective effect of AC against BLM-induced acute lung injury could be, at least in part, due to its free radical scavenging properties with the consequent improvement in mitochondrial function and ATP production.

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- 6: [Pharmacol Res.](#) 2005 Apr;51(4):311-8.

**Probucol attenuates oxidative stress and energy decline in isoproterenol-induced heart failure in rat.**

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In the present study, we examined whether the powerful antioxidant probucol (a clinically used lipid-lowering drug) would attenuate the oxidative stress and energy starvation in experimental model of heart failure (HF) using isoproterenol. Rats were injected subcutaneously with isoproterenol (2.4 mg/kg) daily for 1 week, and then treated with probucol (61 mg/kg) daily for 2 weeks. Oxidative stress was assessed by measuring myocardial lipid peroxides level and antioxidant enzymes activities, glutathione peroxidase (GPx) and superoxide dismutase. In addition, cardiac metabolic damage was estimated by measuring myocardial ATP, ADP and AMP levels as well as ATP/ADP ratio. It was found that isoproterenol induced a significant increase in heart rate by approximately 30% as compared with the pre-value. These changes were significantly attenuated by post-treatment of rats with probucol. Also, isoproterenol induced several pathological changes including lymphocyte infiltration, myofibrillar hemorrhage and degeneration, and these changes were attenuated by probucol. In addition, animals treated with isoproterenol showed a significant increase in myocardial lipid peroxides level up to 163% and a significant decrease in myocardial GPx activity by 35% as compared with the control group. Probucol not only counteracted significantly the pronounced oxidative stress effect of isoproterenol but also it induced a significant increase in myocardial GPx as compared with the control group. The major new finding of the present study is that treatment with probucol induced a significant increase in myocardial ATP level (the source of energy) and ATP/ADP ratio. Moreover, there is a significant correlation between ATP/ADP ratio and myocardial probucol level. In conclusion, the cardioprotective effect of probucol in treatment of HF is a result of not only its antioxidant properties and an enhancement of endogenous antioxidant reserve (mainly GPx) but also an enhancement of myocardial energy state.

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- 7: [Chemotherapy](#). 2004 Oct;50(4):162-70. Epub 2004 Sep 3.

**Progression of cisplatin-induced nephrotoxicity in a carnitine-depleted rat model.**

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**BACKGROUND:** This study has been initiated to investigate whether endogenous carnitine depletion and/or carnitine deficiency is an additional risk factor and/or a mechanism in cisplatin-induced nephrotoxicity and to gain insights into the possibility of a mechanism-based protection by L-carnitine against this toxicity. **METHODS:** 60 male Sprague-Dawley rats were divided into six groups of 10 animals each and received one of the following treatments: The first three groups were injected intraperitoneally with normal saline, L-carnitine (500 mg/kg), and D-carnitine (750 mg/kg), respectively, for 10 successive days. The 4th, 5th, and 6th groups were injected intraperitoneally with the same doses of normal saline, L-carnitine and D-carnitine, respectively, for 5 successive days before and after a single dose of cisplatin (7 mg/kg). Six days after cisplatin treatment, the animals were sacrificed, and serum as well as kidneys were isolated and analyzed. **RESULTS:** A single dose of cisplatin resulted in a significant increase in blood urea nitrogen (BUN), serum creatinine, malondialdehyde (MDA) and nitric oxide (NO) and a significant decrease in total carnitine, reduced glutathione (GSH) and adenosine triphosphate (ATP) content in kidney tissues. Interestingly, L-carnitine supplementation attenuated cisplatin-induced nephrotoxicity manifested by normalizing the increase of serum creatinine, BUN, MDA and NO and the decrease in total carnitine, GSH and ATP content in kidney tissues. In the carnitine-depleted rat model, cisplatin induced a progressive increase in serum creatinine and BUN as well as a progressive reduction in total carnitine and ATP content in kidney tissue. Histopathological examination of kidney tissues confirmed the biochemical data, i.e. L-carnitine supplementation protected against cisplatin-induced kidney damage, whereas D-carnitine aggravated cisplatin-induced renal injury. **CONCLUSION:** Data from this study suggest that: (1) oxidative stress plays an important role in cisplatin-induced kidney damage; (2) carnitine deficiency should be viewed as an additional risk factor and/or a mechanism in cisplatin-induced renal dysfunction, and (3) L-carnitine supplementation attenuates cisplatin-induced renal dysfunction. Copyright (c) 2004 S. Karger AG, Basel.

- 8: [Cancer Chemother Pharmacol](#). 2003 Nov;52(5):411-6. Epub 2003 Jul 23.

**New aspects in probucol cardioprotection against doxorubicin-induced cardiotoxicity.**

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**PURPOSE:** Doxorubicin (DOX) is a broad-spectrum anticancer drug with dose-dependent cardiotoxicity. Probucol has been reported to completely prevent DOX-induced cardiomyopathy. The aim of the present study was to determine the possible effect of probucol pretreatment on the pharmacokinetics of DOX and its role in cardioprotection as well as the possible contribution of the lipid-lowering effect of probucol on the disposition of DOX in cardiac tissue. **METHODS:** Two groups of male albino rats were given either probucol (10 mg/kg, i.p.) or corn oil daily for 12 days followed by a single dose of DOX (15 mg/kg, i.p.). The concentration-time profile of DOX in plasma and its concentration in different tissues, and plasma and myocardial lipids were determined. **RESULTS:** A rapid and significant increase in plasma DOX clearance was observed in rats pretreated with probucol. Probucol induced a significant increase in DOX concentration in both liver and kidney tissues and a significant decrease in DOX concentration in the spleen. However, heart and lung DOX concentrations were not affected. Also, probucol pretreatment resulted in a significant reduction in cardiotoxicity indices including peak serum creatine kinase (CK) concentration and the area under the CK concentration-time curve. Moreover, probucol pretreatment not only counteracted significantly the decrease in the ATP/ADP ratio induced by DOX, but also induced a significant increase as compared with the control group. In addition, probucol significantly reduced plasma total cholesterol and low-density lipoprotein, but it did not induce any significant changes in myocardial lipids. **CONCLUSIONS:** The present study demonstrated, for the first time, that probucol pretreatment alters the pharmacokinetics of DOX. Besides its antioxidant properties, the cardioprotective effect of probucol may be related to its enhancing action on the ATP/ADP ratio.

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- 9: [Pharmacol Res.](#) 2003 Sep;48(3):285-90.

**Protective role of carnitine esters against alcohol-induced gastric lesions in rats.**

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We have investigated in the current study the possible protective effects of two carnitine esters known to have powerful anti-oxidant potential namely, propionyl L-carnitine (PLC) and acetyl L-carnitine (AC) against alcohol-induced gastric lesions in rats. Both drugs were administered as a single oral dose of 200 mg kg<sup>-1</sup> body weight 1h before alcohol intake. Both carnitine esters could protect the gastric mucosa against the injurious effect of absolute alcohol and promote ulcer healing as evidenced from the ulcer index (UI) values. Propionyl L-carnitine prevented alcohol-induced increase in thiobarbituric acid-reactive substances (TBARS), an index of lipid peroxidation. The propionyl carnitine ester also increased the gastric content of reduced glutathione (GSH), besides it increased the enzymatic activities of gastric superoxide dismutase (SOD) and glutathione-S-transferase (GST). Likewise, AC did protect against the ulcerating effect of alcohol and mitigate most of the biochemical adverse effects induced by alcohol in gastric mucosa, but to a lesser extent than PLC. Neither PLC nor AC did affect catalase activity in gastric tissue. Based on these observations, one could conclude that carnitine esters, particularly PLC could partly protect gastric mucosa from alcohol-induced acute mucosal injury, and these gastroprotective effects might be probably induced, at least partly, through anti-oxidant mechanisms.

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- 10: [Pharmacol Toxicol](#). 2001 Sep;89(3):140-4.

**Increased plasma endothelin-1 and cardiac nitric oxide during doxorubicin-induced cardiomyopathy.**

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The major limiting factor in long-term administration of doxorubicin is the development of cumulative dose-dependent cardiomyopathy and congestive heart failure. Although several mechanisms have been suggested to explain the exact cause of doxorubicin-induced cardiomyopathy, the role of the vascular endothelium-derived vasoactive mediators in the pathophysiology of this toxic effect is still unknown. Accordingly, the present study has been initiated to investigate whether the changes in plasma level of endothelin-1 and nitric oxide along with cardiac nitric oxide are associated with the development of doxorubicin-induced cardiomyopathy. Doxorubicin was injected with a single dose of 5 mg/kg and every other day with a dose of 5 mg/kg, intraperitoneally, to have four cumulative doses of, 10, 15, 20 and 25 mg/kg in five separate groups of male rats. An additional group receiving a single dose of 20 mg/kg and one receiving normal saline were also included in the study. Twenty-four hr after the last dose, the animals were sacrificed and the plasma levels of endothelin-1 and nitric oxide in addition to cardiac nitric oxide were determined. The results show that doxorubicin caused a statistically significant increase of 85%, 76% and 97% in plasma endothelin-1 at a cumulative dose levels of 10, 15 and 20 mg/kg, respectively. However, the level of plasma nitric oxide remained unchanged. Furthermore, doxorubicin treatment resulted in a significant dose-dependent increase in serum lactate dehydrogenase and creatine phosphokinase. In contrast, the increase in nitric oxide production in cardiac tissue by doxorubicin was not dose-dependent with the maximum increase (81%) at a cumulative dose of 10 mg/kg. It is worth mentioning that plasma endothelin-1 and cardiac nitric oxide were significantly increased at 24 hr after the single dose of 20 mg/kg doxorubicin. The increase of plasma endothelin-1 and cardiac nitric oxide with the cardiomyopathy enzymatic indices, may point to the conclusion that both endothelin-1 and cardiac nitric oxide are increased during the development of doxorubicin-induced cardiomyopathy.

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- 11: [Pharmacol Res.](#) 2001 Sep;44(3):235-42.

**L-carnitine prevents the progression of atherosclerotic lesions in hypercholesterolaemic rabbits.**

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This study has been initiated to investigate, in hypercholesterolaemic rabbits, whether L-carnitine deficiency could be an additional risk factor in atherosclerosis, and if so, whether L-carnitine supplementation could prevent the progression of atherosclerosis. Hypercholesterolaemia was induced by feeding rabbits 2% cholesterol-enriched diet for 28 days, whereas, carnitine deficiency was induced by daily i.p. administration of 250 mg kg<sup>-1</sup> of D-carnitine for 28 days. Histopathological examination of aorta and coronaries from hypercholesterolaemic rabbits revealed severe atherosclerotic lesions, intimal plaques and foam cell formation. Also, hypercholesterolaemic diet resulted in a significant 53 and 43% decrease in reduced glutathion (GSH) levels and a significant (1.87-fold) and (14.1-fold) increase in malonedialdhyde (MDA) levels in aorta and cardiac tissues, respectively. Daily administration of L-carnitine (250 mg kg<sup>-1</sup>) for 28 days, completely prevented the progression of atherosclerotic lesions induced by hpercholesterolaemia in both aorta and coronaries. Conversely, daily administration of D-carnitine (250 mg kg<sup>-1</sup>) for 28 days increased the progression of atherosclerotic lesions with the appearance of foam cells and apparent intimal plaques which are even larger than that seen in hypercholesterolaemic rabbits. Both L-carnitine and D-carnitine produced similar effects on the lipid profile, GSH and MDA which may point to the conclusion that: (1) L-carnitine prevents the progression of atherosclerotic lesions by another mechanism in addition to its antioxidant and lipid-lowering effects; (2) endogenous carnitine depletion and/or carnitine deficiency should be viewed as an additional risk factor in atherogenesis.

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□ 12: [Pharmacol Res.](#) 2001 Jun;43(6):513-20.

### **Propionyl-L-carnitine as protector against adriamycin-induced cardiomyopathy.**

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Propionyl-L-carnitine (PLC) is a naturally occurring compound that has been considered for the treatment of many forms of cardiomyopathies. In this study, the possible mechanisms whereby PLC could protect against adriamycin (ADR)-induced cardiomyopathy were carried out. Administration of ADR (3 mg kg<sup>-1</sup>) i.p., every other day over a period of 2 weeks) resulted in a significant two-fold increase in serum levels of creatine phosphokinase, lactate dehydrogenase and glutamic oxaloacetic transaminase, whereas daily administration of PLC (250 mg kg<sup>-1</sup>), i.p. for 2 weeks) induced non-significant change. Daily administration of PLC to ADR-treated rats resulted in complete reversal of ADR-induced increase in cardiac enzymes except lactate dehydrogenase which was only reversed by 66%. In cardiac tissue homogenate, ADR caused a significant 53% increase in malonaldehyde (MDA) and a significant 50% decrease in reduced glutathione (GSH) levels, whereas PLC induced a significant 33% decrease in MDA and a significant 41% increase in GSH levels. Daily administration of PLC to ADR-treated rats completely reversed the increase in MDA and the decrease in GSH induced by ADR to the normal levels. In rat heart mitochondria isolated 24 h after the last dose, ADR induced a significant 48% and 42% decrease in <sup>14</sup>C<sub>2</sub> released from the oxidation of [1-<sup>14</sup>C]palmitoyl-CoA and [1-<sup>14</sup>C]palmitoylcarnitine, respectively, whereas PLC resulted in a significant 66% and 54% increase in the oxidation of both substrates, respectively. Interestingly, administration of PLC to ADR-treated rats resulted in complete recovery of the ADR-induced decrease in the oxidation of both substrates. In addition, in rat heart mitochondria, the oxidation of [1-<sup>14</sup>C]pyruvate, [1-<sup>14</sup>C]pyruvate and [1-<sup>14</sup>C]octanoate were not affected by ADR and/or PLC treatment. Moreover, ADR caused severe histopathological lesions manifested as toxic myocarditis which is protected by PLC. Worth mentioning is that PLC had no effect on the antitumour activity of ADR in solid Ehrlich carcinoma. Results from this study suggest that: (1) in the heart, PLC therapy completely protects against ADR-induced inhibition of mitochondrial beta-oxidation of long-chain fatty acids; (2) PLC has and/or induces a powerful antioxidant defense mechanism against ADR-induced lipid peroxidation of cardiac membranes; and finally (3) PLC has no effect on the antitumour activity of ADR.

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□ 13: [Pharmacol Res.](#) 2001 Feb;43(2):185-91.

**Modulation of radiation-induced organs toxicity by cremophor-el in experimental animals.**

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Pharmacological and cytogenetic evaluations of the protective effects of polyethoxylated castor oil cremophor-EL (cremophor) against hepato, renal and bone marrow toxicity induced by gamma irradiation in normal rats were carried out. A single dose of irradiation (6 Gy) caused hepatic and renal damage manifested biochemically as an elevation in levels of serum alanine and aspartate aminotransferase as well as an increase in blood urea. Cremophor administration at a dose level of 50 microl kg<sup>-1</sup> intravenously 1 day before exposure to irradiation (6 Gy) protected the liver and kidney as indicated by the recovery of levels of hepatic aminotransferase, urea and lipid profiles to normal values. Gamma irradiation of male rats caused a decrease in reduced glutathione and an increase in the oxidized form in rat-liver homogenate. A highly significant increase in the incidence of micronucleated normochromatic erythrocytes and micronucleated polychromatic erythrocytes was observed after irradiation exposure. The induced genotoxicity in the bone marrow cells was corrected by pretreatment with cremophor. The findings of this study suggest that cremophor pretreatment can potentially be used clinically to prevent irradiation-induced hepato, renal and bone marrow toxicity without interference with its cytotoxic activity.

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- 14: [Pharmacol Res.](#) 2000 Feb;41(2):143-50.

**Propionyl-L-carnitine as potential protective agent against adriamycin-induced impairment of fatty acid beta-oxidation in isolated heart mitochondria.**

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Propionyl-L-carnitine (PLC), a natural short-chain derivative of L-carnitine, has been tested in this study as a potential protective agent against adriamycin (ADR)-induced cardiotoxicity in isolated rat heart myocytes and mitochondria. In cardiac myocytes, ADR (0.5 mM) caused a significant (70%) inhibition of palmitate oxidation, whereas, PLC (5 mM) induced a significant (49%) stimulation. Addition of PLC to ADR-incubated myocytes induced 79% reversal of ADR-induced inhibition of palmitate oxidation. In isolated rat heart mitochondria, ADR produced concentration-dependent inhibition of both palmitoyl-CoA and palmitoyl-carnitine oxidation, while PLC caused a more than 2.5-fold increase in both substrates. Preincubation of mitochondria with 5 mM PLC caused complete reversal of ADR-induced inhibition in the oxidation of both substrates. Also ADR induced concentration-dependent inhibition of CPT I which is parallel to the inhibition of its substrate palmitoyl-CoA. In rat heart slices, ADR induced a significant (65%) decrease in adenosine triphosphate (ATP) and this effect is reduced to 17% only by PLC. Results of this study revealed that ADR induced its cardiotoxicity by inhibition of CPT I and beta-oxidation of long-chain fatty acids with the consequent depletion of ATP in cardiac tissues, and that PLC can be used as a protective agent against ADR-induced cardiotoxicity. Copyright 2000 Academic Press.

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- 15: [Pharmacol Res.](#) 1999 Apr;39(4):289-95.

**Reversal of doxorubicin-induced cardiac metabolic damage by L-carnitine.**

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Biopharmacological evaluations of the protective effects of L-carnitine (a naturally occurring quaternary ammonium compound) against doxorubicin-induced metabolic damage were carried out in isolated cardiac myocytes and in isolated rat heart mitochondria. Perfusion of the heart with DOX (0.5 mM) caused a significant 70% inhibition of palmitate oxidation in cardiac myocytes, while L-carnitine (5 mM) perfusion caused stimulation which accounted for 37%. Perfusion of the heart with L-carnitine after 10-min perfusion with DOX (0.5 mM) caused 88% reversal of DOX-induced inhibition of palmitate oxidation in cardiac cells. In rat heart mitochondria, DOX has no effect on either palmitate oxidation or acyl-CoA synthetase activity, whereas Enoximone (c-AMP-dependent phosphodiesterase inhibitor), caused a significant inhibition of palmitate oxidation and acyl-CoA activity (40 and 27%, respectively). The oxidation of palmitoyl-CoA, an index of carnitine palmitoyltransferase reaction was significantly inhibited by DOX as a function of DOX concentration. Preincubation of mitochondria with L-carnitine caused reversal of DOX-induced inhibition of palmitoyl-CoA oxidation depending on the concentration of L-carnitine. Moreover, L-carnitine treatment did not interfere with the cytotoxic effect of doxorubicin against the growth of solid Ehrlich carcinoma. The findings of this study may suggest that inhibition of fatty acid oxidation in the heart is at least a part of doxorubicin cardiotoxicity and that L-carnitine can be used to prevent the doxorubicin-induced cardiac metabolic damage without interfering with its antitumour activities. Copyright 1999 The Italian Pharmacological Society.

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- 16: [J Mol Cell Cardiol.](#) 1997 Feb;29(2):789-97.

**Acute and chronic effects of adriamycin on fatty acid oxidation in isolated cardiac myocytes.**

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This study was designed to determine if acute (in vitro) or chronic (in vivo) adriamycin inhibits cardiac fatty acid oxidation and if so at what sites in the fatty acid oxidation pathway. In addition, the role of L-carnitine in reversing or preventing this effect was examined. We determined the effects of adriamycin in the presence or absence of L-carnitine on the oxidation of the metabolic substrates [1-<sup>14</sup>C]palmitate, [1-(<sup>14</sup>C)] octanoate, [1-(<sup>14</sup>C)]butyrate, [U-<sup>14</sup>C]glucose, and [2-(<sup>14</sup>C)]pyruvate in isolated cardiac myocytes. Acute exposure to adriamycin caused a concentration- and time-dependent inhibition of carnitine palmitoyl transferase 1 (CPT 1) dependent long-chain fatty acid, palmitate, oxidation. Chronic exposure to (18 mg/kg) adriamycin inhibited palmitate oxidation 40% to a similar extent seen in vitro with 0.5 mM adriamycin. Acute or chronic administration of L-carnitine completely abolished the adriamycin-induced inhibition of palmitate oxidation. Interestingly, medium- and short-chain fatty acid oxidation, which are independent of CPT 1, were also inhibited acutely by adriamycin and could be reversed by L-carnitine. In isolated rat heart mitochondria, adriamycin significantly decreased oxidation of the CPT 1 dependent substrate palmitoyl-CoA by 50%. However, the oxidation of a non-CPT 1 dependent substrate palmitoylcarnitine was unaffected by adriamycin except at concentrations greater than 1 mM. These data suggest that after in vitro or in vivo administration, adriamycin, inhibits fatty acid oxidation in part secondary to inhibition of CPT 1 and/or depletion of its substrate, L-carnitine, in cardiac tissue. However, these findings also suggest that L-carnitine plays an additional role in fatty acid oxidation independent of CPT 1 or fatty acid chain length.

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- ✓ 17: [J Mol Cell Cardiol.](#) 1996 May;28(5):825-33.

**Regulation of fatty acid oxidation by acetyl-CoA generated from glucose utilization in isolated myocytes.**

[Abdel-aleem S](#), [Nada MA](#), [Sayed-Ahmed M](#), [Hendrickson SC](#), [St Louis J](#), [Walthall HP](#), [Lowe JE](#).

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The regulation of fatty acid oxidation in isolated myocytes was examined by manipulating mitochondrial acetyl-CoA levels produced by carbohydrate and fatty acid oxidation. L-carnitine had no effect on the oxidation of [U-14C]glucose, but stimulated oxidation of [1-14C]palmitate in a concentration-dependent manner. L-carnitine (5 mM) increased palmitate oxidation by 37%. The phosphodiesterase inhibitor, enoximone (250 microM), also increased palmitate oxidation by 51%. Addition of L-carnitine to enoximone resulted in a two-fold increase of palmitate oxidation. Whereas, dichloroacetate (DCA, 1 mM), which stimulates PDH activity, decreased palmitate oxidation by 25%. Furthermore, the addition of DCA to myocytes preincubated with either L-carnitine or enoximone, had no effect on the carnitine-induced stimulation of palmitate, and reduced that of enoximone by 50%. Varied concentrations of DCA decreased the oxidation of palmitate and octanoate; but increased glucose oxidation in myocytes. The rate of efflux of acetylcarnitine was highest when pyruvate was present in the medium compared to efflux rates in presence of palmitate or palmitate plus glucose. Although the addition of L-carnitine plus enoximone resulted in a two-fold increase in palmitate oxidation, acetylcarnitine efflux was minimal under these conditions. Acetylcarnitine efflux was highest when pyruvate was present in the medium. These rates were dramatically decreased when myocytes were preincubated with enoximone, despite the stimulation of palmitate oxidation by this compound. These data suggest that: (1) fatty acid oxidation is influenced by acetyl-CoA produced from pyruvate metabolism; (2) L-carnitine may be specific for mitochondrial acetyl-CoA derived from pyruvate oxidation; and (3) it is probable that acetyl-CoA from beta-oxidation of fatty acids is directly channeled into the citric acid cycle.

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- 18: [J Mol Cell Cardiol.](#) 1995 Nov;27(11):2465-72.

**Stimulation of non-oxidative glucose utilization by L-carnitine in isolated myocytes.**

[Abdel-aleem S](#), [Sayed-Ahmed M](#), [Nada MA](#), [Hendrickson SC](#), [St Louis J](#), [Lowe JE](#).

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The effects of L-carnitine on  $^{14}\text{CO}_2$  release from [1- $^{14}\text{C}$ ]pyruvate oxidation (an index of pyruvate dehydrogenase activity, PDH), [2- $^{14}\text{C}$ ]pyruvate, and [6- $^{14}\text{C}$ ]glucose oxidation (indices of the acetyl-CoA flux through citric acid cycle), and [U- $^{14}\text{C}$ ]glucose (an index of both PDH activity and the flux of acetyl-CoA through the citric acid cycle), were studied using isolated rat cardiac myocytes. L-carnitine increased the release of  $^{14}\text{CO}_2$  from [1- $^{14}\text{C}$ ]pyruvate, and decreased that of [2- $^{14}\text{C}$ ]pyruvate in a time and concentration-dependent manner. At a concentration of 2.5 mM, L-carnitine produced a 50% increase of  $\text{CO}_2$  release from [1- $^{14}\text{C}$ ]pyruvate and a 50% decrease from [2- $^{14}\text{C}$ ]pyruvate oxidation. L-carnitine also increased  $\text{CO}_2$  release from [1- $^{14}\text{C}$ ]pyruvate oxidation by 35%, and decreased that of [2- $^{14}\text{C}$ ]pyruvate oxidation 30%, in isolated rat heart mitochondria. The fatty acid oxidation inhibitor, etomoxir, stimulated the release of  $\text{CO}_2$  from both [1- $^{14}\text{C}$ ]pyruvate and [2- $^{14}\text{C}$ ]pyruvate. These results were supported by the effects of L-carnitine on the  $\text{CO}_2$  release from [6- $^{14}\text{C}$ ]- and [U- $^{14}\text{C}$ ]glucose oxidation. L-carnitine (5 mM) decreased the  $\text{CO}_2$  release from [6- $^{14}\text{C}$ ]glucose by 37%, while etomoxir (50  $\mu\text{M}$ ) increased its release by 24%. L-carnitine had no effect on the oxidation of [U- $^{14}\text{C}$ ]glucose. L-carnitine increased palmitate oxidation in a time- and concentration-dependent manner in myocytes. Also, it increased the rate of efflux of acetylcarnitine generated from pyruvate in myocytes. These results suggest that L-carnitine stimulates pyruvate dehydrogenase complex activity and enhances non-oxidative glucose metabolism by increasing the mitochondrial acetylcarnitine efflux in the absence of exogenous fatty acids.

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- 19: [Horm Metab Res.](#) 1995 Feb;27(2):104-6.

**Reduced induction of carbohydrate utilization by inhibition of fatty acid oxidation in myocytes from diabetic animals.**

**[Abdel-aleem S](#), [Sharwi S](#), [Badr M](#), [Sayed-Ahmed M](#), [Anstadt MP](#), [Lowe JE](#).**

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## **New Aspects in Probucol Cardioprotection Against Doxorubicin-Induced Cardiotoxicity**

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**Cancer Chemotherapy and Pharmacology 2003; 52(5): 411-416.**

Doxorubicin (DOX) is a broad-spectrum anticancer drug with dose-dependent cardiotoxicity. Probucol has been reported to completely prevent DOX-induced cardiomyopathy. The aim of the present study was to determine the possible effect of probucol pretreatment on the pharmacokinetics of DOX and its role in cardioprotection as well as the possible contribution of the lipid-lowering effect of probucol on the disposition of DOX in cardiac tissue. Two groups of male albino rats were given either probucol (10 mg/kg, i.p.) or corn oil daily for 12 days followed by a single dose of DOX (15 mg/kg, i.p.). The concentration-time profile of DOX in plasma and its concentration in different tissues, and plasma and myocardial lipids were determined. A rapid and significant increase in plasma DOX clearance was observed in rats pretreated with probucol. Probucol induced a significant increase in DOX concentration in both liver and kidney tissues and a significant decrease in DOX concentration in the spleen. However, heart and lung DOX concentrations were not affected. Also, probucol pretreatment resulted in a significant reduction in cardiotoxicity indices including peak serum creatine kinase (CK) concentration and the area under the CK concentration-time curve. Moreover, probucol pretreatment not only counteracted significantly the decrease in the ATP/ADP ratio induced by DOX, but also induced a significant increase as compared with the control group. In addition, probucol significantly reduced plasma total cholesterol and low-density lipoprotein, but it did not induce any significant changes in myocardial lipids. The present study demonstrated, for the first time, that probucol pretreatment alters the pharmacokinetics of DOX. Besides its antioxidant properties, the cardioprotective effect of probucol may be related to its enhancing action on the ATP/ADP ratio.

# **Progression of Cisplatin-Induced Nephrotoxicity in a Carnitine-Depleted Rat Model**

**Mohamed M. Sayed-Ahmed<sup>1</sup>, Maha A. Eissa<sup>1</sup>, Sanaa A. Kenawy<sup>2</sup>, Nadia Mostafa<sup>3</sup>, Menotti Calvani<sup>4</sup> and Abdel-Moneim M. Osman<sup>1</sup>.**

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## **Chemotherapy 2004; 50: 162-170**

This study has been initiated to investigate whether endogenous carnitine depletion and/or carnitine deficiency is an additional risk factor and/or a mechanism in cisplatin-induced nephrotoxicity and to gain insights into the possibility of a mechanism-based protection by L-carnitine against this toxicity. A total of 60 male Sprague-Dawley rats were divided into six groups of 10 animals each and received one of the following treatments: The first three groups were injected intraperitoneally with normal saline, L-carnitine (500 mg/kg), and D-carnitine (750 mg/kg), respectively, for 10 successive days. The 4th, 5th, and 6th groups were injected intraperitoneally with the same doses of normal saline, L-carnitine and D-carnitine, respectively, for 5 successive days before and after a single dose of cisplatin (7 mg/kg). Six days after cisplatin treatment, the animals were sacrificed, and serum as well as kidneys were isolated and analyzed. A single dose of cisplatin resulted in a significant increase in blood urea nitrogen (BUN), serum creatinine, malondialdehyde (MDA) and nitric oxide (NO) and a significant decrease in total carnitine, reduced glutathione (GSH) and adenosine triphosphate (ATP) content in kidney tissues. Interestingly, L-carnitine supplementation attenuated cisplatin-induced nephrotoxicity manifested by normalizing the increase of serum creatinine, BUN, MDA and NO and the decrease in total carnitine, GSH and ATP content in kidney tissues. In the carnitine-depleted rat model, cisplatin induced a progressive increase in serum creatinine and BUN as well as a progressive reduction in total carnitine and ATP content in kidney tissue. Histopathological examination of kidney tissues confirmed the biochemical data, i.e. L-carnitine supplementation protected against cisplatin-induced kidney damage, whereas D-carnitine aggravated cisplatin-induced renal injury. Data from this study suggest that: (1) oxidative stress plays an important role in cisplatin-induced kidney damage; (2) carnitine deficiency should be viewed as an additional risk factor and/or a mechanism in cisplatin-induced renal dysfunction, and (3) L-carnitine supplementation attenuates cisplatin-induced renal dysfunction.

## **Probucol Attenuates Oxidative Stress and Energy Decline in Isoproterenol-Induced Heart Failure in Rat**

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### **Pharmacological Research 2005; 51: 311–318.**

In the present study, we examined whether the powerful antioxidant probucol (a clinically used lipid-lowering drug) would attenuate the oxidative stress and energy starvation in experimental model of heart failure (HF) using isoproterenol. Rats were injected subcutaneously with isoproterenol (2.4 mg/kg) daily for 1 week, and then treated with probucol (61 mg/kg) daily for 2 weeks. Oxidative stress was assessed by measuring myocardial lipid peroxides level and antioxidant enzymes activities, glutathione peroxidase (GPx) and superoxide dismutase. In addition, cardiac metabolic damage was estimated by measuring myocardial ATP, ADP and AMP levels as well as ATP/ADP ratio. It was found that isoproterenol induced a significant increase in heart rate by approximately 30% as compared with the pre-value. These changes were significantly attenuated by post-treatment of rats with probucol. Also, isoproterenol induced several pathological changes including lymphocyte infiltration, myofibrillar hemorrhage and degeneration, and these changes were attenuated by probucol. In addition, animals treated with isoproterenol showed a significant increase in myocardial lipid peroxides level up to 163% and a significant decrease in myocardial GPx activity by 35% as compared with the control group. Probucol not only counteracted significantly the pronounced oxidative stress effect of isoproterenol but also it induced a significant increase in myocardial GPx as compared with the control group. The major new finding of the present study is that treatment with probucol induced a significant increase in myocardial ATP level (the source of energy) and ATP/ADP ratio. Moreover, there is a significant correlation between ATP/ADP ratio and myocardial probucol level. In conclusion, the cardioprotective effect of probucol in treatment of HF is a result of not only its antioxidant properties and an enhancement of endogenous antioxidant reserve (mainly GPx) but also an enhancement of myocardial energy state.

## **Contribution of Nitric Oxide and Epidermal Growth Factor Receptor in Anti-Metastatic Potential of Paclitaxel in Human Liver Cancer Cell (HebG2)**

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**Journal of the Egyptian National Cancer Institute 2005; 17: 35-41.**

Paclitaxel is a general antineoplastic drug used against different types of experimental and human tumors. Several anti-cancer drugs have been shown to stimulate nitric oxide (NO) production, which has been shown to affect many aspects of tumor biology. This study was initiated to determine if paclitaxel stimulates NO production in HebG2 cells, and if so, whether NO interferes with the metastatic potential of HebG2 cells and contributes to paclitaxel cytotoxicity. In addition, we sought to determine the relationship between NO production and the expression of epidermal growth factor receptor (EGFR) and matrix metalloproteinases (MMPs) in HebG2 cells. The effects of paclitaxel (0.1-1000nM) on surviving fraction, NO production and the expression of EGFR, MMP-2 and MMP-9 were studied in human liver cancer cells (HebG2). Paclitaxel resulted in a significant dosedependent decrease in the surviving fraction of HebG2 cells. A 62% and 86% decrease in the surviving fraction was attained at 10nM and 100nM paclitaxel, respectively. Paclitaxel produced a significant increase in NO production, starting from 1nM. A 64% and 111% increase in NO production was attained after exposure to 10nM and 100nM of paclitaxel, respectively. In all of the HebG2 cells treated with paclitaxel (1.0-1000nM) mRNA specific for EGFR, MMP-2 and MMP-9 were undetectable. However, untreated HebG2 cells and those treated with paclitaxel (0.1nM) expressed mRNA specific for these markers. This study suggests that: (1) increased production of NO may contribute to paclitaxel's cytotoxicity against HebG2 cells, (2) paclitaxel may inhibit tumor metastasis via inhibition of the expression of EGFR and MMPs and (3) an inverse correlation exists between NO production and expression of EGFR and MMPs.

# **Carnitine Esters Prevent Oxidative Stress Damage and Energy Depletion Following Transient Forebrain Ischaemia in the Rat Hippocampus**

**Abdulhakeem A. Al-Majed, Mohamed M. Sayed-Ahmed, Fadhal A. Al-Omar, Abdulaziz A. Al-Yahya, Abdulaziz M. Aleisa and Othman A. Al-Shabanah**  
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**Clinical and Experimental Pharmacology and Physiology 2006; 33: 725–733.**

The present study investigated whether propionyl-L-carnitine (PLC) has neuroprotective effects, similar to those reported for acetyl-L-carnitine (AC), against transient forebrain ischaemia-induced neuronal damage and biochemical derangement in the rat hippocampal CA1 region. In total, 105 adult male Wistar albino rats were divided into seven groups of 15 animals each. The first three groups were injected i.p. with normal saline, AC (300 mg/kg) or PLC (300 mg/kg) for 7 successive days. The next three groups were injected i.p. with the same doses of normal saline, AC or PLC immediately after the induction of 10 min forebrain ischaemia and i.p. injections were continued for 7 successive days. Rats in the seventh group were subjected to sham-operated ischaemia and injected with normal saline for 7 successive days. Seven days after treatment, animals were killed and their brains isolated for histopathological examination and biochemical studies. Forebrain ischaemia resulted in a significant decrease in the number of intact neurons (77%), ATP concentration (51%) and glutathione content (32%), whereas there was a significant increase in the production of thiobarbituric acid-reactive substances (TBARS; 71%) and total nitrate/nitrite (NO<sub>x</sub>; 260%) in hippocampal tissues. Administration of either AC or PLC attenuated forebrain ischaemia-induced neuronal damage, manifested by a greater number of intact neurons, ATP and glutathione, as well as a decrease in TBARS and NO<sub>x</sub> in hippocampal tissues. Results from the present study suggest, for the first time, that PLC attenuates forebrain ischaemia-induced neuronal injury, oxidative stress and energy depletion in the hippocampal CA1 region. Propionyl-L-carnitine has neuroprotective effects similar to AC and could have a potential use in the treatment of neurodegenerative diseases. The results of the present study will open up new perspectives for the use of PLC in the treatment of neurodegenerative diseases associated with, or secondary to, myocardial ischaemia–reperfusion injury and chronic circulatory failure.

# **Propionyl-L-carnitine Prevents the Progression of Cisplatin-Induced Cardiomyopathy in a Carnitine-Depleted Rat Model**

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**Pharmacological Research 2006; 53: 278–286.**

This study has been initiated to investigate whether endogenous carnitine depletion and/or carnitine deficiency is a risk factor during development of cisplatin (CDDP)-induced cardiomyopathy and if so, whether carnitine supplementation by propionyl-L-carnitine (PLC) could offer protection against this toxicity. To achieve the ultimate goal of this study, a total of 60 adult male Wistar albino rats were divided into six groups. The first three groups were injected intraperitoneally with normal saline, PLC (500 mg kg<sup>-1</sup>), and d-carnitine (500 mg kg<sup>-1</sup>) respectively, for 10 successive days. The 4th, 5th, and 6th groups were injected intraperitoneally with the same doses of normal saline, PLC and d-carnitine, respectively, for 5 successive days before and after a single dose of CDDP (7 mg kg<sup>-1</sup>). On day 6 after CDDP treatment, animals were sacrificed, serum as well as hearts were isolated and analyzed. CDDP resulted in a significant increase in serum creatine phosphokinase isoenzyme (CK-MB) and lactate dehydrogenase (LDH), thiobarbituric acid reactive substances (TBARS) and total nitrate/nitrite (NO(x)) and a significant decrease in reduced glutathione (GSH), total carnitine, and adenosine triphosphate (ATP) content in cardiac tissues. In the carnitine-depleted rat model, CDDP induced dramatic increase in serum cardiomyopathy enzymatic indices, CK-MB and LDH, as well as progressive reduction in total carnitine and ATP content in cardiac tissue. Interestingly, PLC supplementation resulted in a complete reversal of the increase in cardiac enzymes, TBARS and NO<sub>x</sub>, and the decrease in total carnitine, GSH and ATP, induced by CDDP, to the control values. Moreover, histopathological examination of cardiac tissues confirmed the biochemical data, where PLC prevents CDDP-induced cardiac degenerative changes while d-carnitine aggravated CDDP-induced cardiac tissue damage. In conclusion, data from this study suggest for the first time that carnitine deficiency and oxidative stress are risk factors and should be viewed as mechanisms during development of CDDP-related cardiomyopathy and that carnitine supplementation, using PLC, prevents the progression of CDDP-induced cardiotoxicity.

# **Thymoquinone Supplementation Prevents the Development of Gentamicin-Induced Acute Renal Toxicity in Rats**

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**Clinical and Experimental Pharmacology and Physiology 2007; 34: 399-405**

The present study investigated the possible protective effects of thymoquinone (TQ), a compound derived from *Nigella sativa* with strong anti-oxidant properties, against gentamicin (GM)-induced nephrotoxicity. A total of 40 adult male Wistar albino rats was divided into four groups. Rats in the first group were injected daily with normal saline (2.5 mL/kg, i.p.) for 8 consecutive days, whereas rats in the second group received TQ (50 mg/L in drinking water) for 8 consecutive days. Animals in the third group were injected daily with GM (80 mg/kg, i.p.) for 8 consecutive days, whereas animals in the fourth group received a combination of GM (80 mg/kg, i.p.) and TQ (50 mg/L in drinking water) for 8 consecutive days. Gentamicin resulted in a significant increase in serum creatinine, blood urea nitrogen (BUN), thiobarbituric acid-reactive substances (TBARS) and total nitrate/nitrite (NO<sub>x</sub>) and a significant decrease in reduced glutathione (GSH), glutathione peroxidase (GPx), catalase (CAT) and ATP levels in kidney tissues. Interestingly, TQ supplementation resulted in a complete reversal of the GM-induced increase in BUN, creatinine, TBARS and NO<sub>x</sub> and decrease in GSH, GPx, CAT and ATP to control values. Moreover, histopathological examination of kidney tissues confirmed the biochemical data, wherein TQ supplementation prevents GM-induced degenerative changes in kidney tissues. Data from the present study suggest that TQ supplementation prevents the development of GM-induced acute renal failure by a mechanism related, at least in part, to its ability to decrease oxidative stress and to preserve the activity of the anti-oxidant enzymes, as well as its ability to prevent the energy decline in kidney tissues.

# **Acetyl-L-Carnitine Modulates Bleomycin-Induced Oxidative Stress and Energy Depletion in Lung Tissues**

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**and Hafez F.Hafez<sup>1</sup>**

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**Journal of the Egyptian National Cancer Institute 2004; 16: 237-243.**

The usefulness of Bleomycin (BLM) as an important antineoplastic drug is usually limited to the development of dose and time-dependent interstitial pneumonitis and pulmonary fibrosis. This study has been initiated to investigate the possible protective effects of acetyl-L-carnitine (AC) against BLM-induced lung toxicity at an early stage of its development. A total of 40 male Sprague-Dawley rats weighing from 200-250g each, were divided into 4 groups of 10 animals each. The first group received a daily i.p. injection of normal saline (0.5ml/200gm body weight) for 5 consecutive days and served as a control. Animals in the second, third and fourth groups were daily injected intraperitoneally (i.p.) with BLM (15mg/kg body weight), AC (250mg/kg body weight) and AC (250mg/kg) 2 hrs before BLM (15mg/kg) each for 5 consecutive days, respectively. Treatment of rats with BLM (15mg/kg) resulted in a significant 3.4 and 2.9 folds increase in malondialdehyde (MDA) and nitric oxide (NO) production in lung tissue, respectively and a significant 39%, 35%, 54% and 44% decrease in reduced glutathione (GSH), superoxide dismutase (SOD), glutathione peroxidase (GSHPx) and adenosine triphosphate (ATP), respectively as compared to the control group. Treatment of rats with AC did not lead to any significant change in the mentioned biochemical parameters in the lung tissue. Administration of AC two hours before BLM attenuated BLM-induced increase in MDA and NO and the decrease in GSH, SOD, GSHPx and ATP in lung tissue. The present data suggests that the protective effect of AC against BLM-induced acute lung injury could be, at least in part, due to its free radical scavenging properties with the consequent improvement in mitochondrial function and ATP production.

## **Reversal of Doxorubicin Resistance by Adenovirus-Mediated Transfer of Cyclooxygenase-2 Antisense in Multidrug-Resistant MCF-7 cells**

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### **Cancer Therapy 2007; 5: 1-10**

Increased expression of cyclooxygenase-2 (COX-2) has been implicated in many human malignancies, and it is associated with tumor progression, angiogenesis, inhibition of apoptosis, and development of multidrug-resistant (MDR) phenotype. Both selective and nonselective COX-2 inhibitors have been used in clinical trials as adjuvant therapy too often at the expense of increased systemic toxicity. In the current study, we evaluated whether adenovirus vector expressing COX-2 antisense (Ad-COX-2 AS) has therapeutic potential to modulate the drug resistance and the expression of MDR gene MDR1, antiapoptotic gene Bcl-2, and cell cycle regulating gene cyclin D1 in doxorubicin-resistant breast cancer cell line (MCF-7/DOX). Our data show that MCF-7/DOX cells are more efficiently transduced by adenovirus compared with the parental MCF-7 cell line. Transduction of MCF-7/DOX cells with Ad-COX-2 AS (multiplicity of infection [MOI] of 10, 20, 50, plaque forming units [PFU]/cell) reduced the IC<sub>50</sub> value of doxorubicin by 13-, 19-, and 20-fold, respectively, compared with Ad-LacZ-transduced cells ( $P < 0.05$ ). Furthermore, Ad-COX-2 AS downregulates the expression of the MDR1, the antiapoptotic protein Bcl-2, and the cell cycle regulating protein cyclin D1 in MCF-7/DOX cells. In conclusion, MCF-7/DOX cells are more efficiently transduced with Ad-COX-2 AS compared with parental MCF-7 cells. Transduction of MCF-7/DOX cells with Ad-COX-2 AS reverses their resistance to doxorubicin. The promising efficacy of Ad-COX-2 AS in reversing drug resistance deserves further investigation.

# **Protective Role of Carnitine Esters Against Alcohol-Induced Gastric Lesions in Rats**

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**Pharmacological Research 2003; 48: 285–290.**

We have investigated in the current study the possible protective effects of two carnitine esters known to have powerful anti-oxidant potential namely, propionyl-L-carnitine (PLC) and acetyl L-carnitine (AC) against alcohol-induced gastric lesions in rats. Both drugs were administered as a single oral dose of 200 mg kg<sup>-1</sup> body weight 1 h before alcohol intake. Both carnitine esters could protect the gastric mucosa against the injurious effect of absolute alcohol and promote ulcer healing as evidenced from the ulcer index (UI) values. Propionyl L-carnitine prevented alcohol-induced increase in thiobarbituric acid-reactive substances (TBARS), an index of lipid peroxidation. The propionyl carnitine ester also increased the gastric content of reduced glutathione (GSH), besides it increased the enzymatic activities of gastric superoxide dismutase (SOD) and glutathione-S-transferase (GST). Likewise, AC did protect against the ulcerating effect of alcohol and mitigate most of the biochemical adverse effects induced by alcohol in gastric mucosa, but to a lesser extent than PLC. Neither PLC nor AC did affect catalase activity in gastric tissue. Based on these observations, one could conclude that carnitine esters, particularly PLC could partly protect gastric mucosa from alcohol-induced acute mucosal injury, and these gastroprotective effects might be probably induced, at least partly, through anti-oxidant mechanisms.

