

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

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

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FREQUENTLY ASKED QUESTIONS

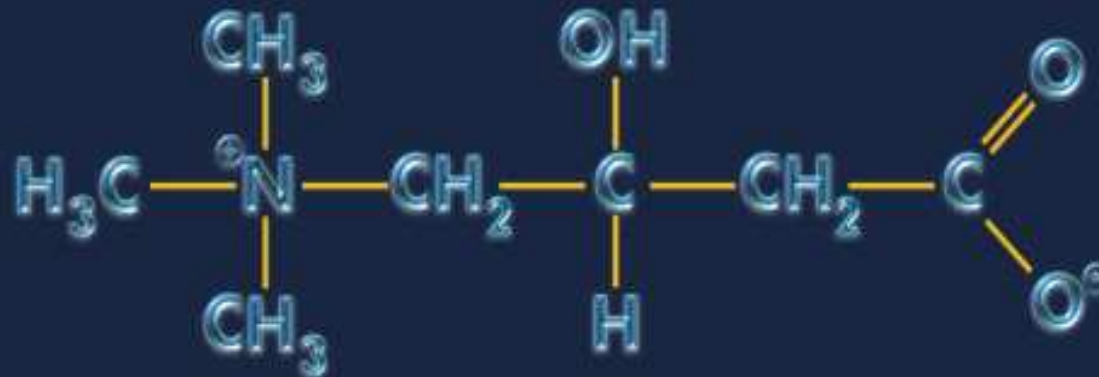
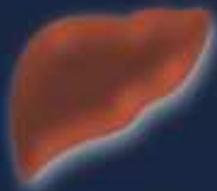
- * What is Carnitine ?**
- * What are the Carnitine sources ?**
- * What are the physiological roles of Carnitine ?**
- * What are the clinical indications of Carnitine ?**
- * Is Carnitine Deficiency a disease ?**
- * What is Carnitine Insufficiency ?**

L-CARNITINE: Historical Background

- | | | | |
|------|--|---|---------------|
| 1905 | Discovery |  | Carnis |
| 1927 | Chemical structure identification | | |
| 1935 | Transmitter | | |
| 1940 | Vitamin B_T | | |
| 1955 | Cofactor in the Oxidation of long chain fatty acids | | |
| 1960 | Biosynthesis from Lysine | | |
| 1973 | Carnitine Deficiency Syndrome | | |

CARNITINE SOURCES

Endogenous



25%



75%



Exogenous



MITOCHONDRIAL CARNITINE PATHWAY

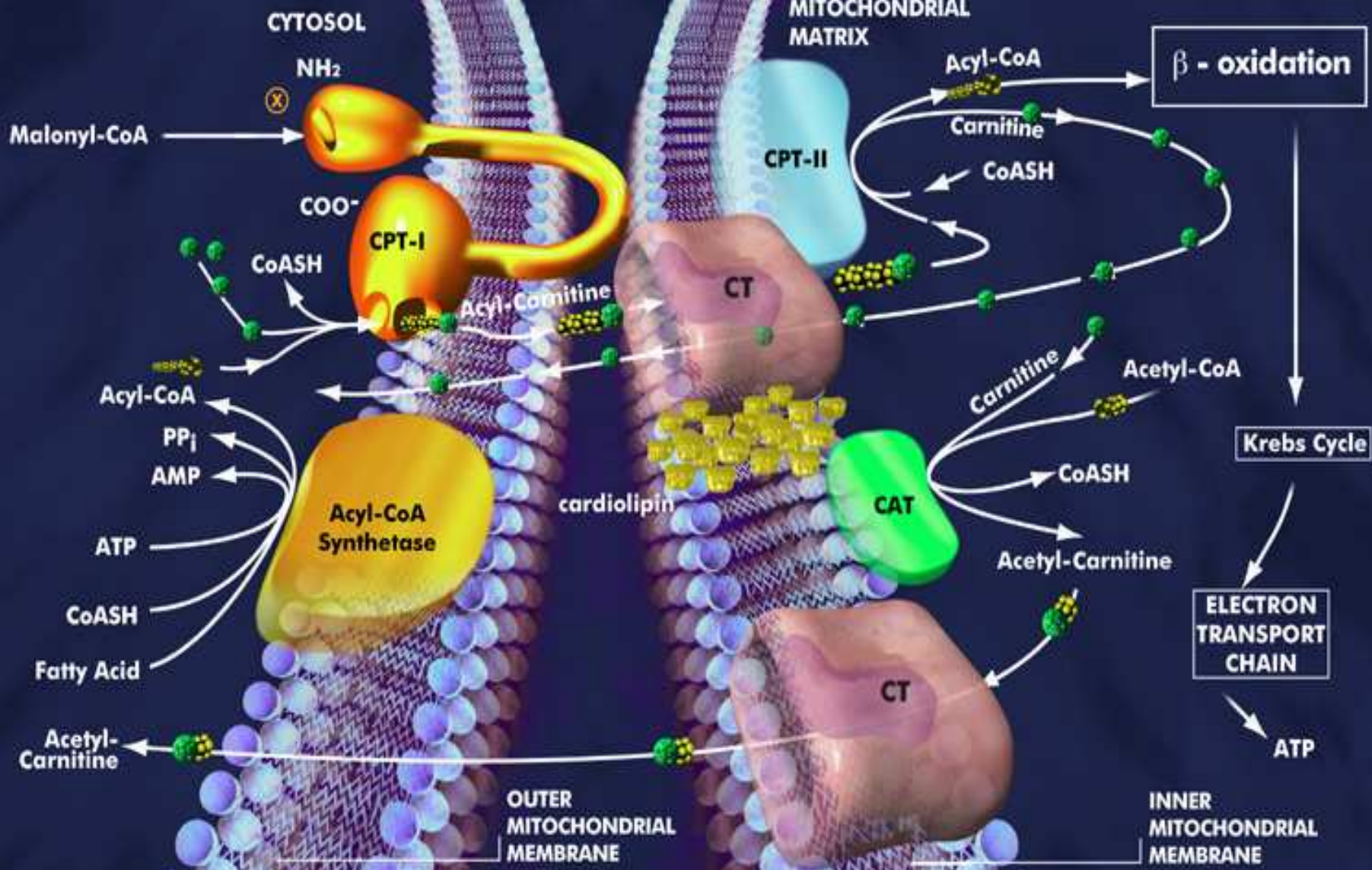
INTERPLAY between LIPID and GLUCOSE METABOLISM

CPT-I= Carnitine Palmitoyl Transferase I

CPT-II= Carnitine Palmitoyl Transferase II

CT= Carnitine Translocase

CAT= Carnitine Acetyl Transferase



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FDA Approved Clinical Indications of L-Carnitine

- * Cardiovascular disorders**
- * Patients undergoing Hemodialysis**
- * Beta Thalassemia Major**
- * Male infertility**
- * Doxorubicin-induced cardiomyopathy**
- * Carnitine Deficiency Syndromes**

CARNITINE DEFICIENCY

Primary Carnitine Deficiency

Systemic

Myopathic

Secondary Carnitine Deficiency

Acquired Medical Conditions

- Chronic Renal and Hepatic Failure
- Extreme Prematurity

Genetic Metabolic Error

- LCAD
- MCAD
- SCAD

Iatrogenic Factors

- Chronic Valproate Therapy
- Chronic Hemodialysis
- Zidovudine Therapy

Plasma Carnitine Level

- * Normal values: (40-50 $\mu\text{mol/L}$)

Free Carnitine (FC)	80 %
Acyl-Carnitine (AC)	20 %
AC/FC	0.25

- * Carnitine Deficiency:

Plasma Carnitine < 20 $\mu\text{mol/L}$

- Carnitine Insufficiency :

Normal plasma Carnitine

AC/FC > 0.4

Propionyl-L-carnitine

CAT

L-carnitine

Propionyl-CoA

↑ Fatty Acid Oxidation

PCC

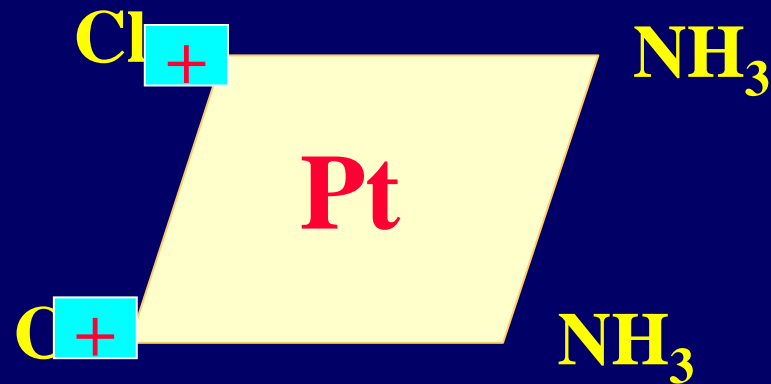
Succinyl-CoA

Acetyl-CoA

Krebs Cycle

ATP

CISPLATIN



Cisdiaminedichloroplatinum II, CDDP

CDDP-INDUCED ORGAN TOXICITY

- * **Nephrotoxicity**

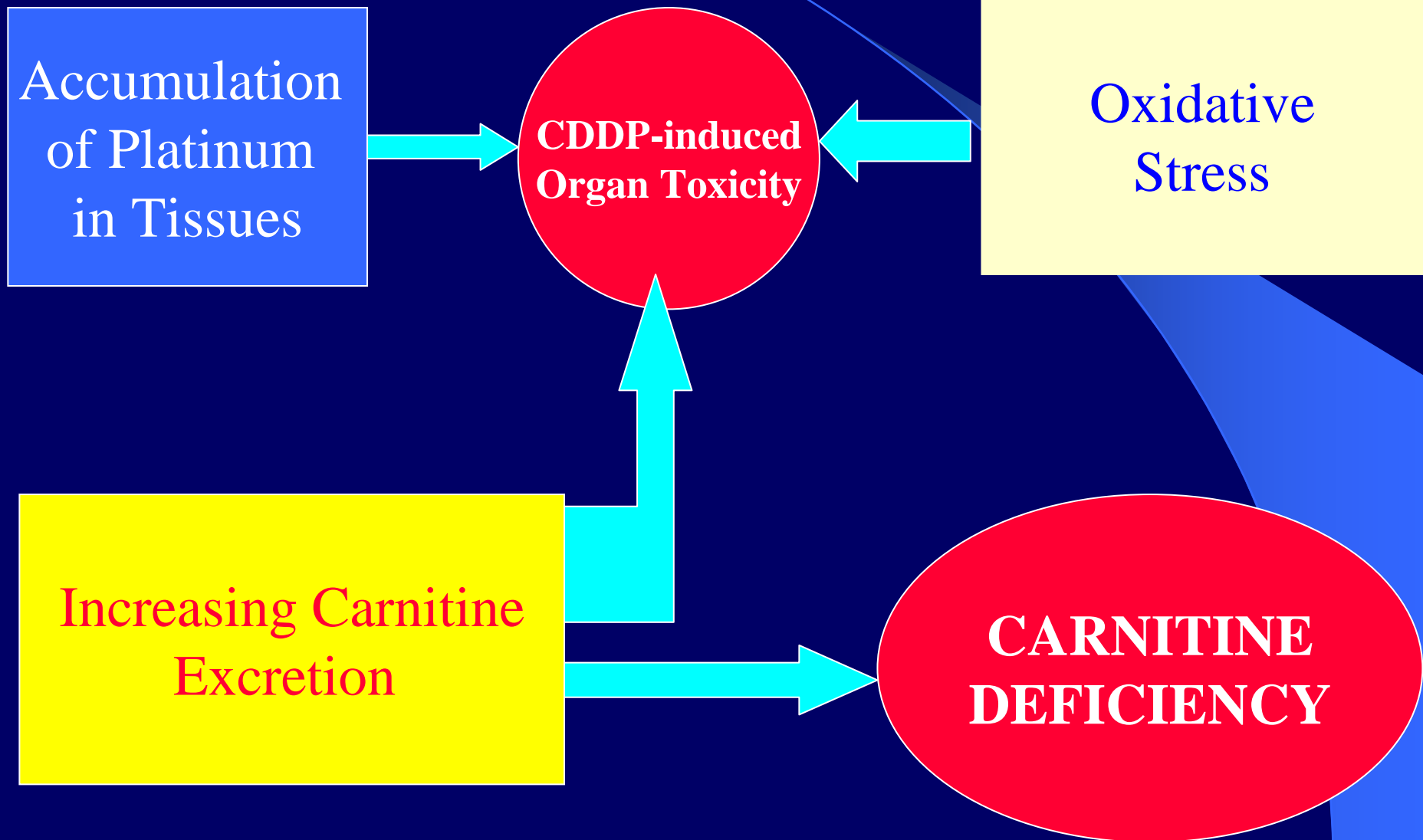
- * **Neurotoxicity**

- * **Cardiomyopathy**

CDDP CARDIOMYOPATHY

- 1- Electrocardiographic changes
- 2- Myocarditis
- 3- Arrhythmia
- 4- Congestive heart failure
- 5- Bradycardia
- 6- **Lethal cardiomyopathy** when **CDDP** is given in combination chemotherapy protocols containing **MTX, 5-FU, BLM, and DOX**

CDDP and L-CARNITINE



CDDP-Induced Secondary Carnitine Deficiency

Heuberger et al. **Eur J Clin Pharmacol, 1998**

CDDP inhibits Carnitine reabsorption at the proximal tubular level

CDDP increases urinary excretion of Carnitine

Sayed-Ahmed et al. **Chemotherapy, 2004**

Progression of CDDP-induced nephrotoxicity in carnitine depleted rats.

CDDP inhibits endogenous synthesis of L-carnitine

AIM OF WORK

- * To determine whether **Carnitine Deficiency** is risk factor and should be viewed as a mechanism in CDDP-induced **cardiomyopathy**
- * To study whether **Carnitine supplementation**, using **PLC**, could offer protection against this toxicity, and if so, what are the **possible protective mechanisms**

EXPERIMENTAL DESIGN

Control

Normal saline, I.P., 10 days

PLC

500 mg/kg, I.P., 10 days

D-carnitine

500 mg/kg, I.P., 10 days

Saline-CDDP-saline

7 mg/kg, I.P.

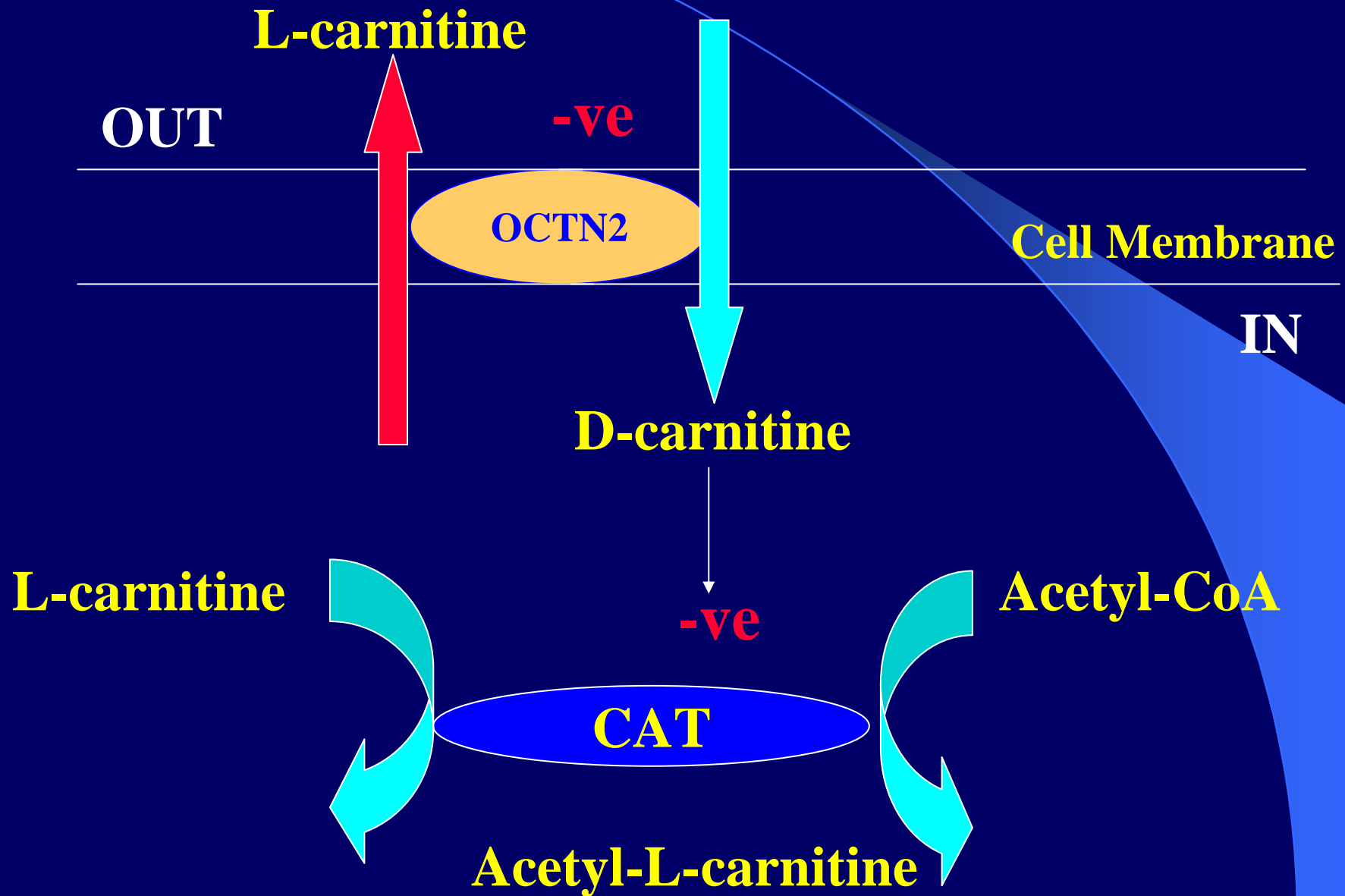
PLC-CDDP-PLC

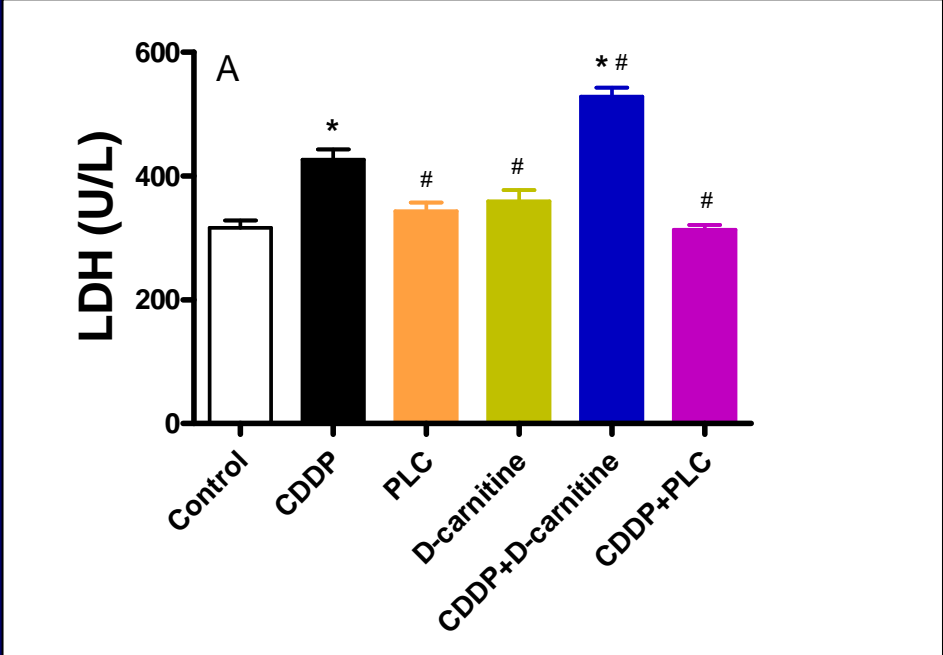
7 mg/kg, I.P.

D-carnitine-CDDP-D-carnitine

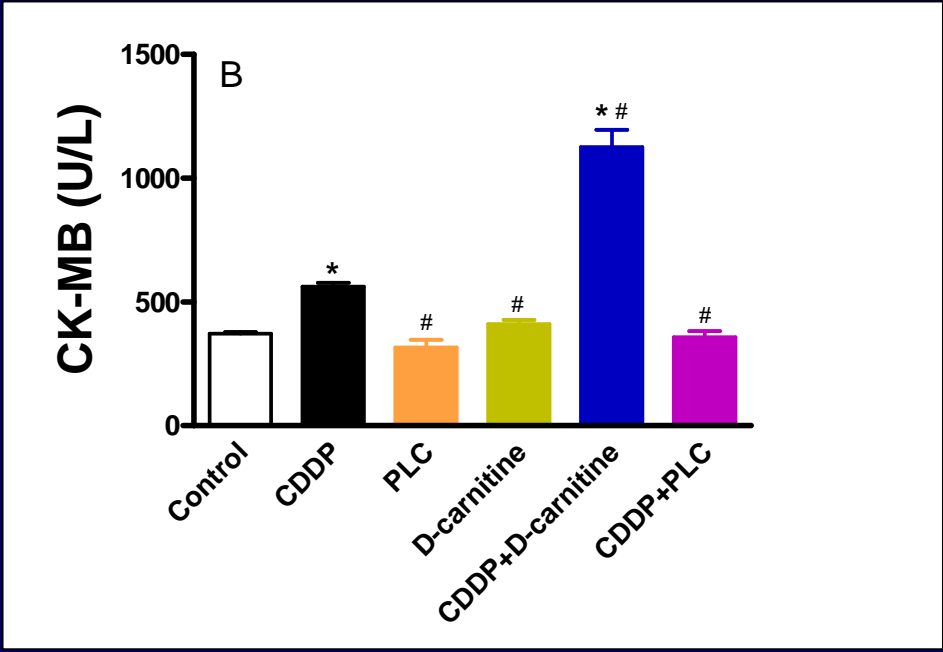
7 mg/kg, I.P.

Carnitine-Depleted Rat Model





LDH



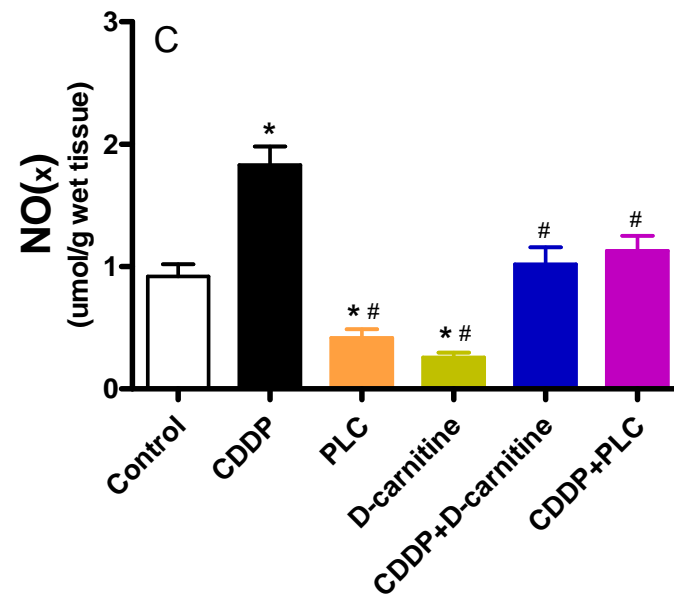
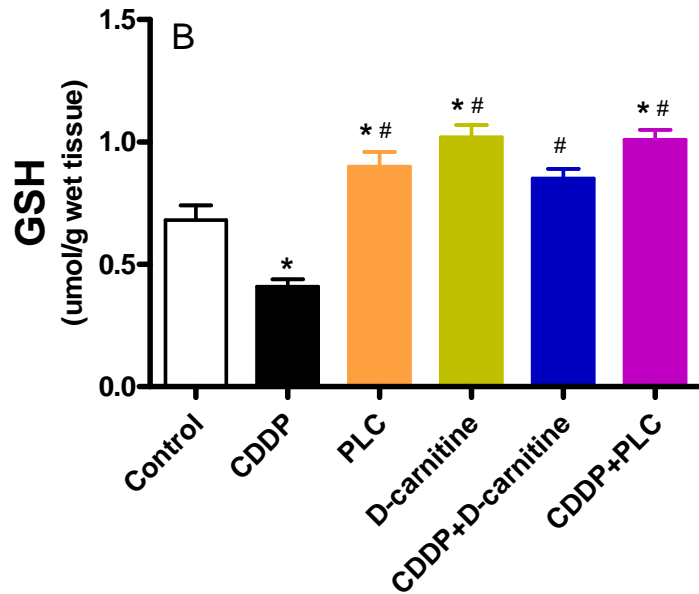
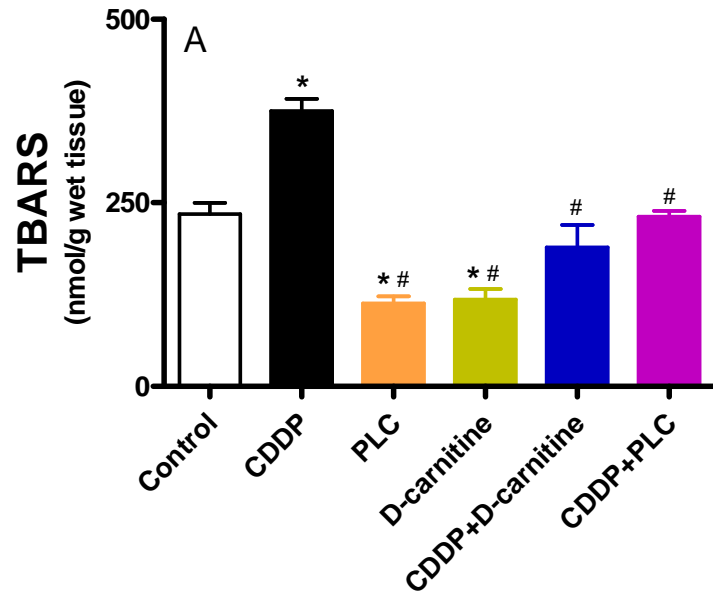
CK-MB

Oxidative Stress Biomarkers

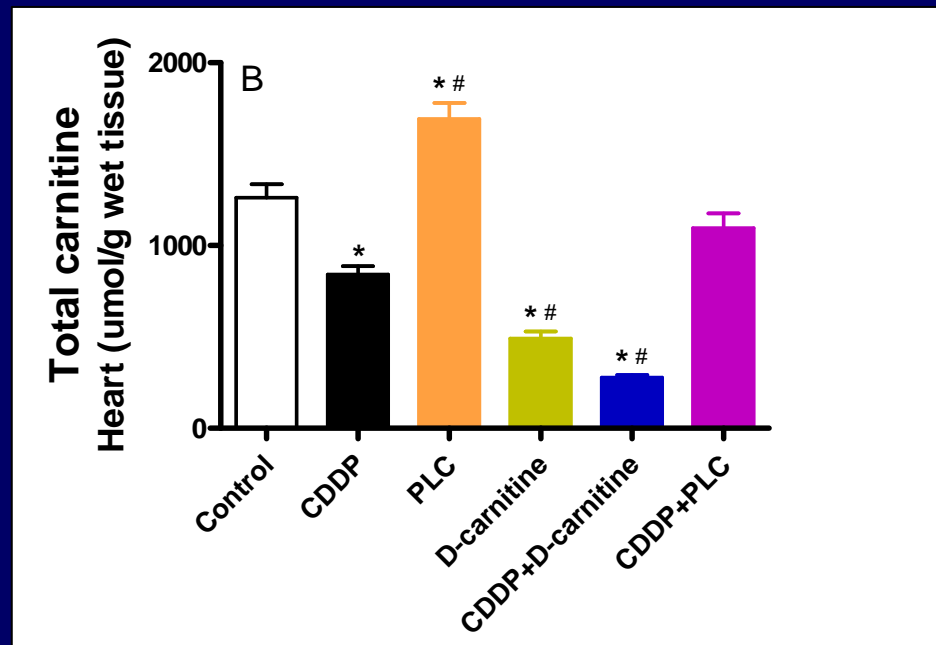
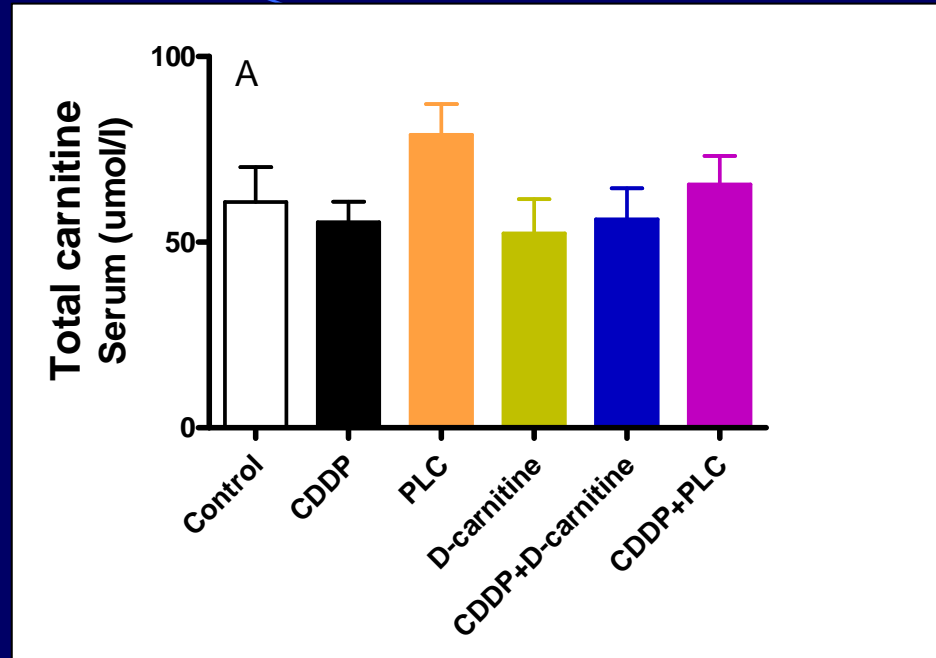
TBARS,

GSH,

NO(x)



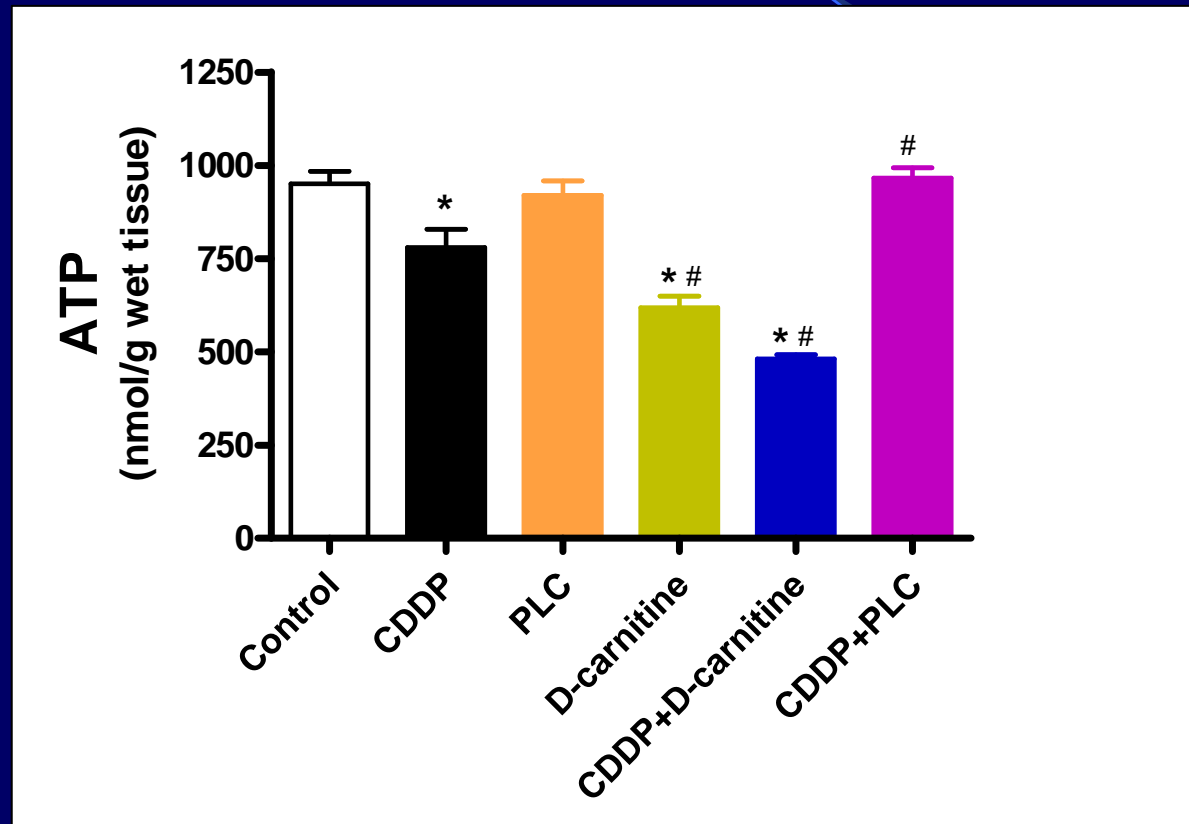
Total Carnitine



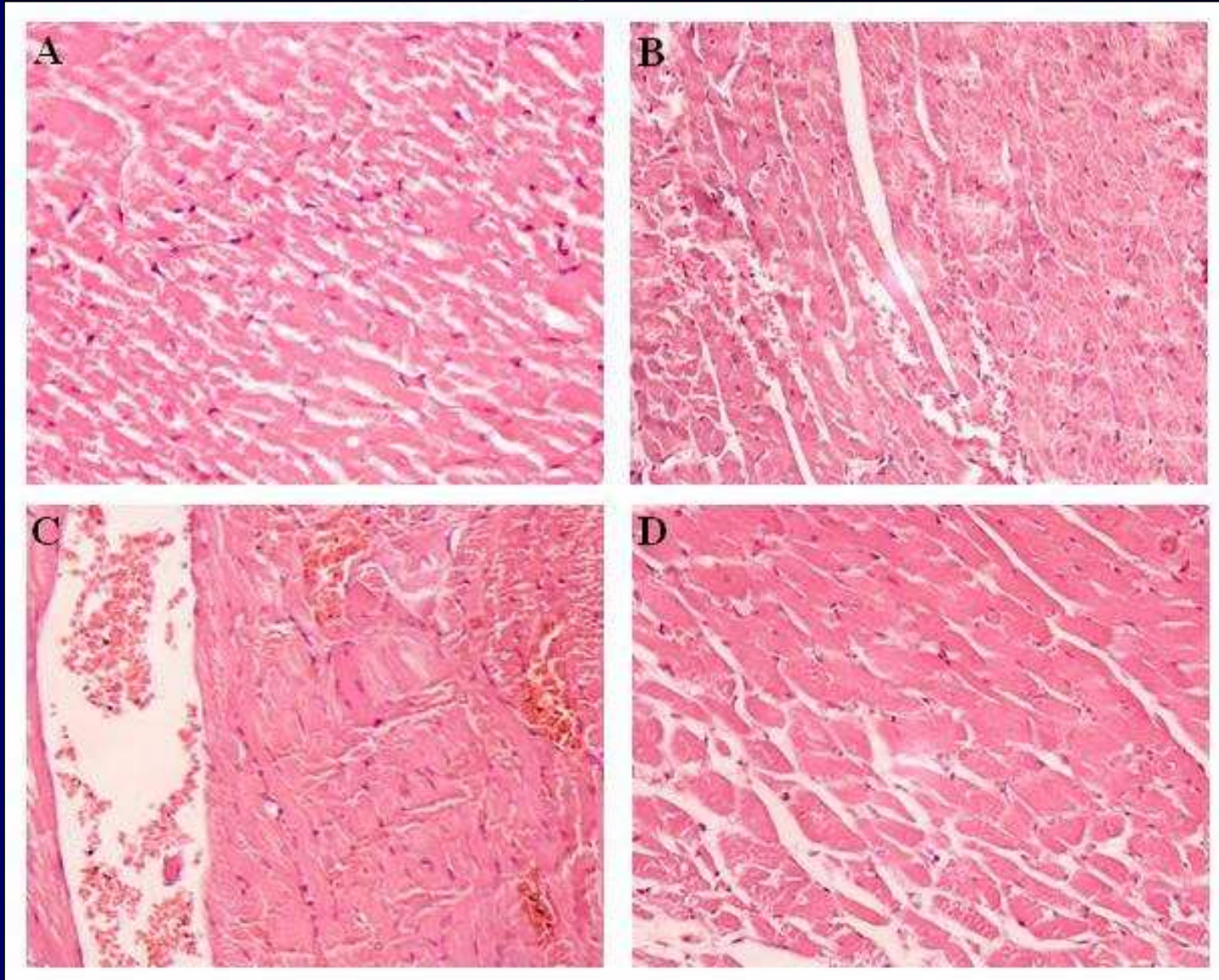
Serum

Heart

ADENOSINE TRIPHOSPHATE



HISTOPATHOLOGY



CONCLUSION

- * **Carnitine Deficiency** is a risk factor and should be viewed as a mechanism during development of CDDP-induced cardiomyopathy
- * **Oxidative stress** plays an important role in CDDP-induced cardiomyopathy

CONCLUSION

- * **Carnitine supplementation**, using PLC, prevents the progression of CDDP-induced cardiomyopathy
- * It would be worthwhile studying the effects of **carnitine supplementation in CDDP-treated cancer patients**, in the hope of reducing CDDP-induced nephrotoxicity, ototoxicity, and cardiomyopathy

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THANK YOU