بسم الله الرحـــــمن الرحيم

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

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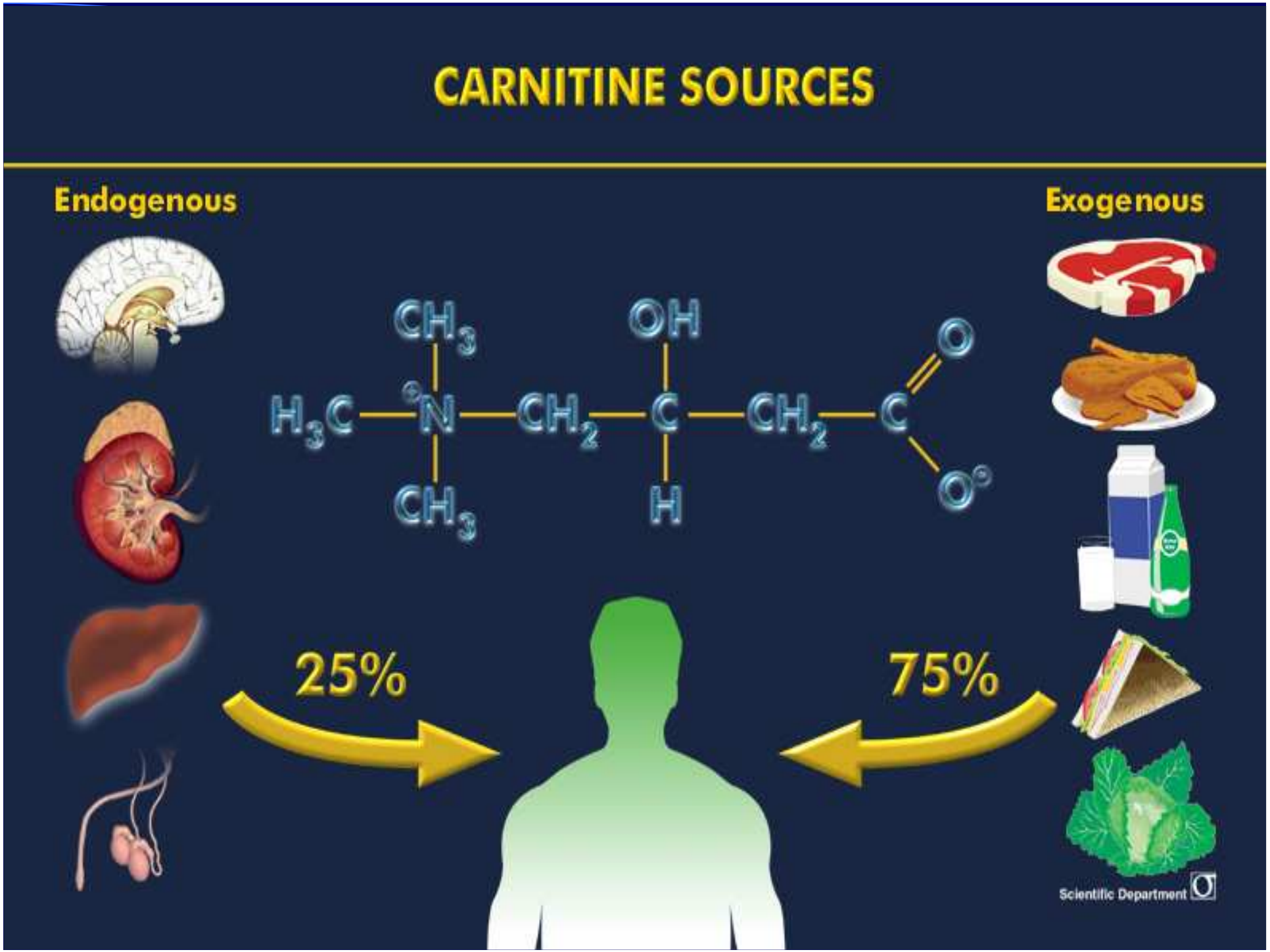
FREQUENTLY ASKED QUESTIONS

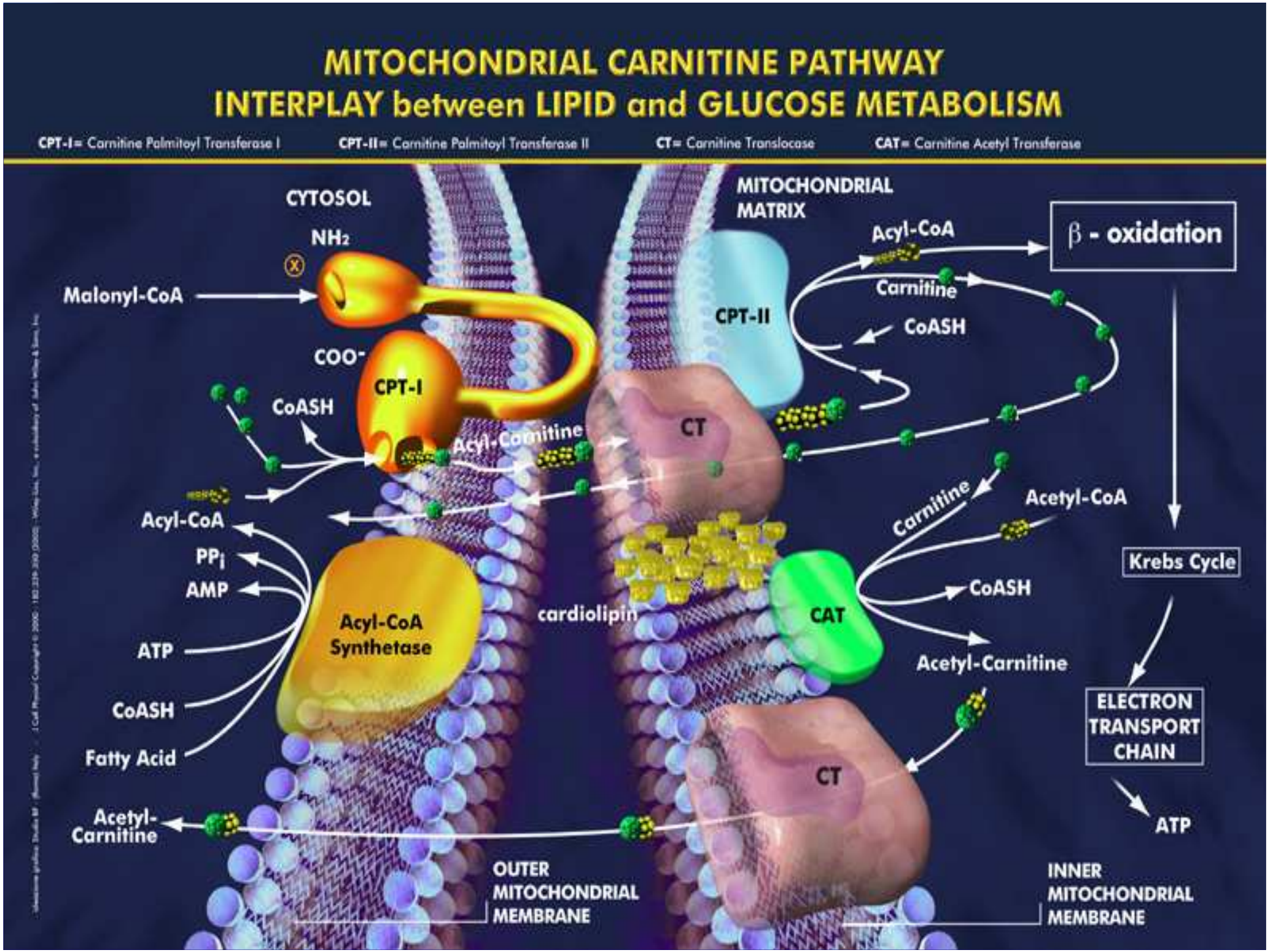
* What is Carnitine ?
* What are the Carnitine sources ?
* What are the physiological roles of Carnitine ?
* What are the clinical indications of Carnitine ?
* Is Carnitine Deficiency a disease ?
* What is Carnitine Insufficiency ?

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

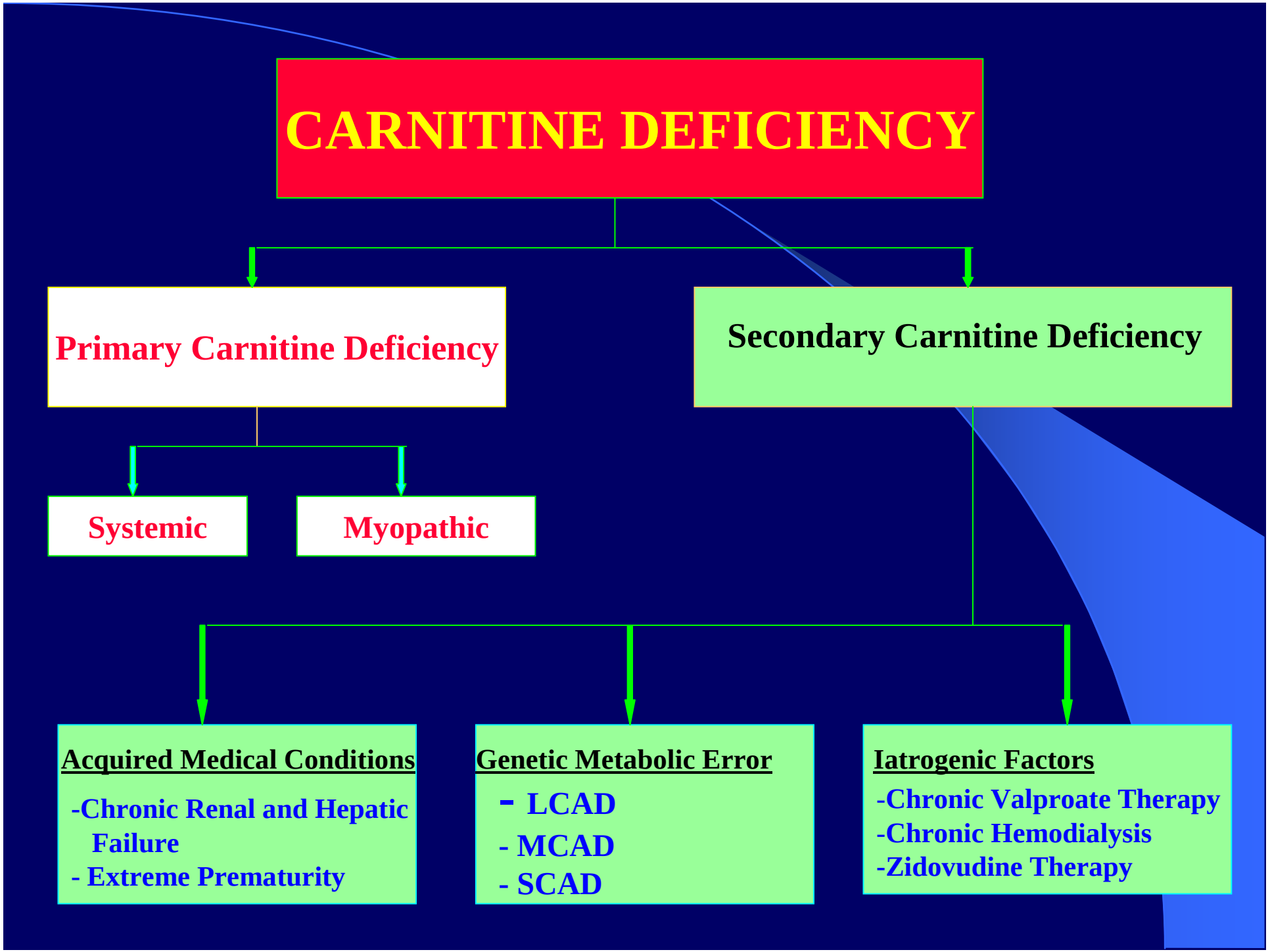
CARNITINE SOURCES




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
CYTOSOL
MITOCHONDRIAL MATRIX
NH2
Malonyl-CoA
COO-
CPT-I
CPT-II
CoASH
Acyl-Carnitine
CT
Acyl-CoA
β - oxidation
Carnitine
Acetyl-CoA
PPi
AMP
ATP
CoASH
Fatty Acid
Acyl-CoA Synthetase
cardiolipin
CAT
Acetyl-Carnitine
Krebs Cycle
ELECTRON TRANSPORT CHAIN
ATP
Acetyl-Carnitine
OUTER MITOCHONDRIAL MEMBRANE
INNER MITOCHONDRIAL MEMBRANE

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
Secondary Carnitine Deficiency
Systemic
Myopathic
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 umol/L)**

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

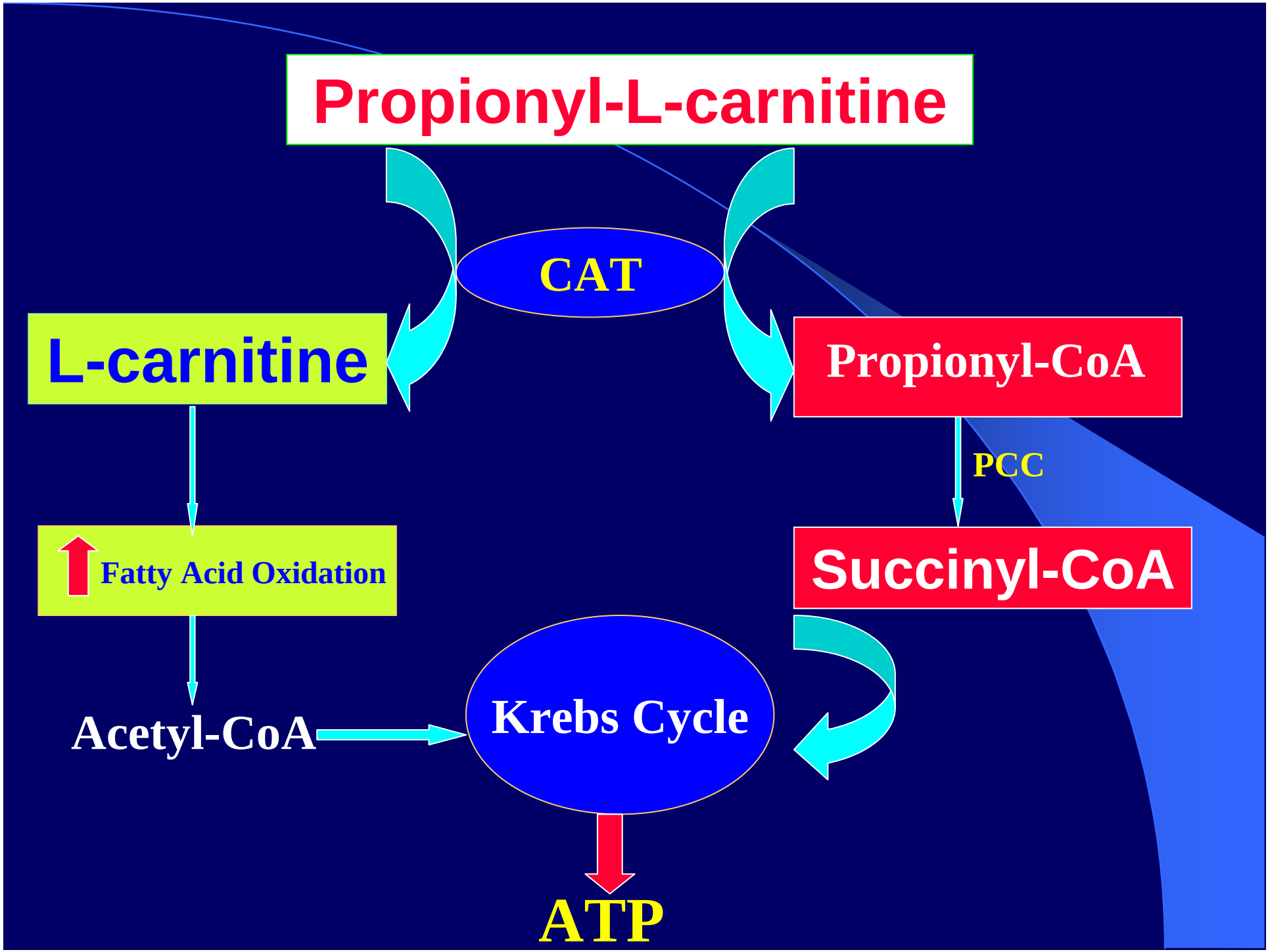
* **Carnitine Deficiency:**

Plasma Carnitine < 20 umol/L

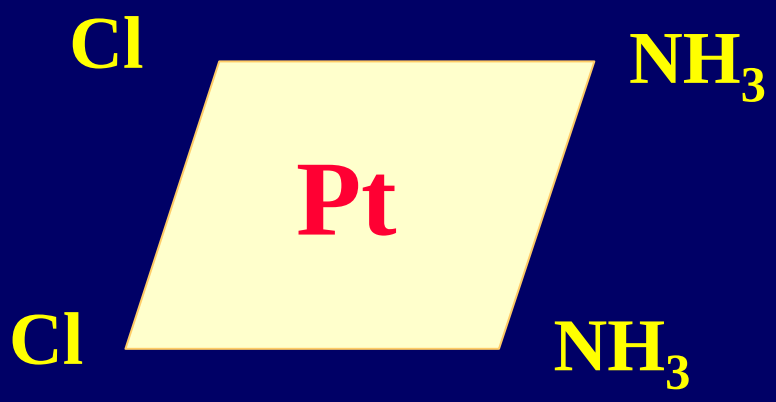
- **Carnitine Insufficiency :**

Normal plasma Carnitine

AC/FC > 0.4


Propionyl-L-carnitine
CAT
L-carnitine
Propionyl-CoA
PCC
Fatty Acid Oxidation
Succinyl-CoA
Acetyl-CoA
Krebs Cycle
ATP

CISPLATIN



Cisdiaminedichloroplatinum II, CDDP

CDDP-INDUCED ORGAN TOXICITY

* **Nephrotoxicity**

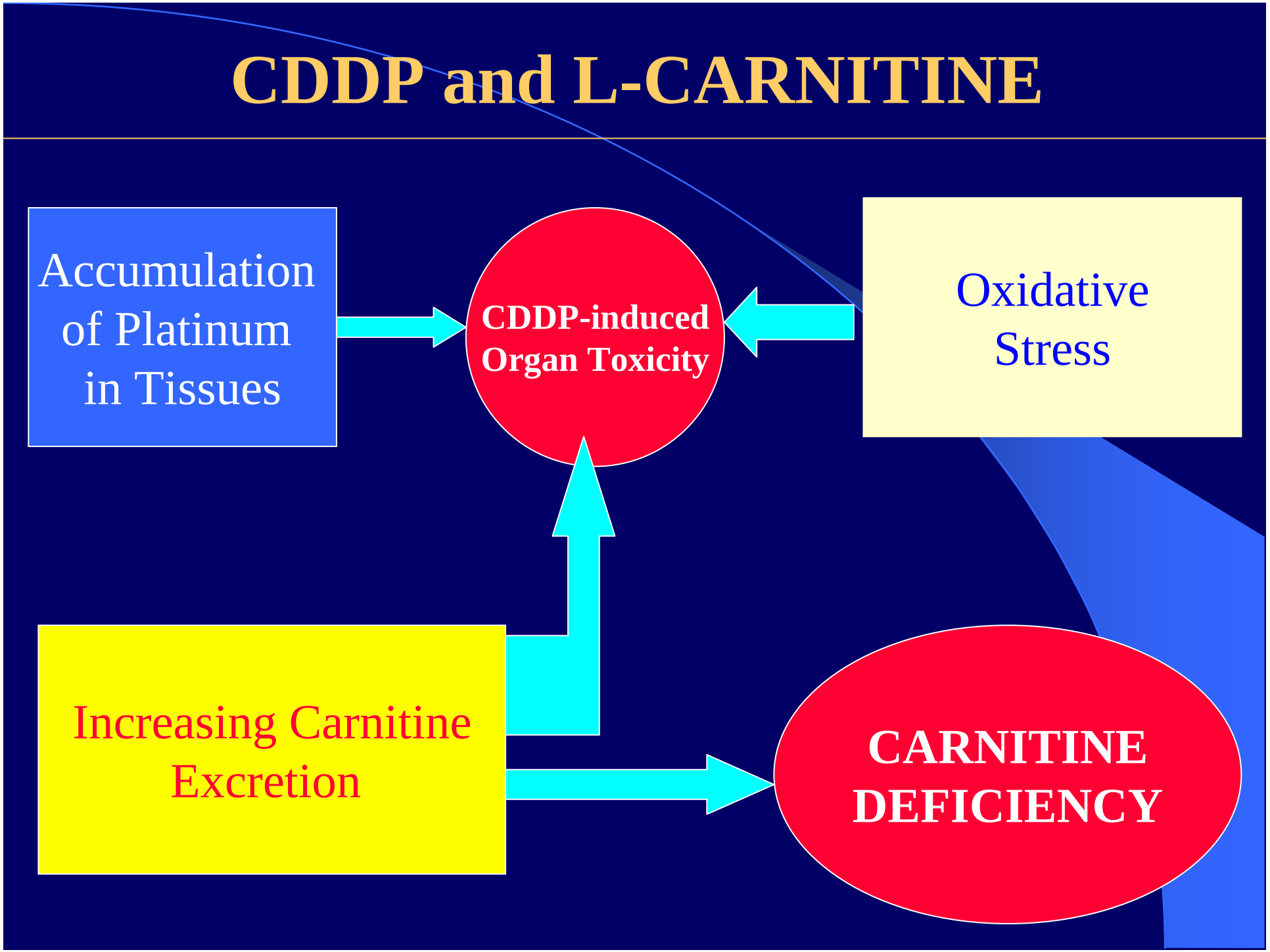
* Neurotoxicity

* Cardiomyopathy

CDDP CARDIOMYOPATHY

1- Electrocardiographic changes
2- Myocarditis
3- Arrythmia
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

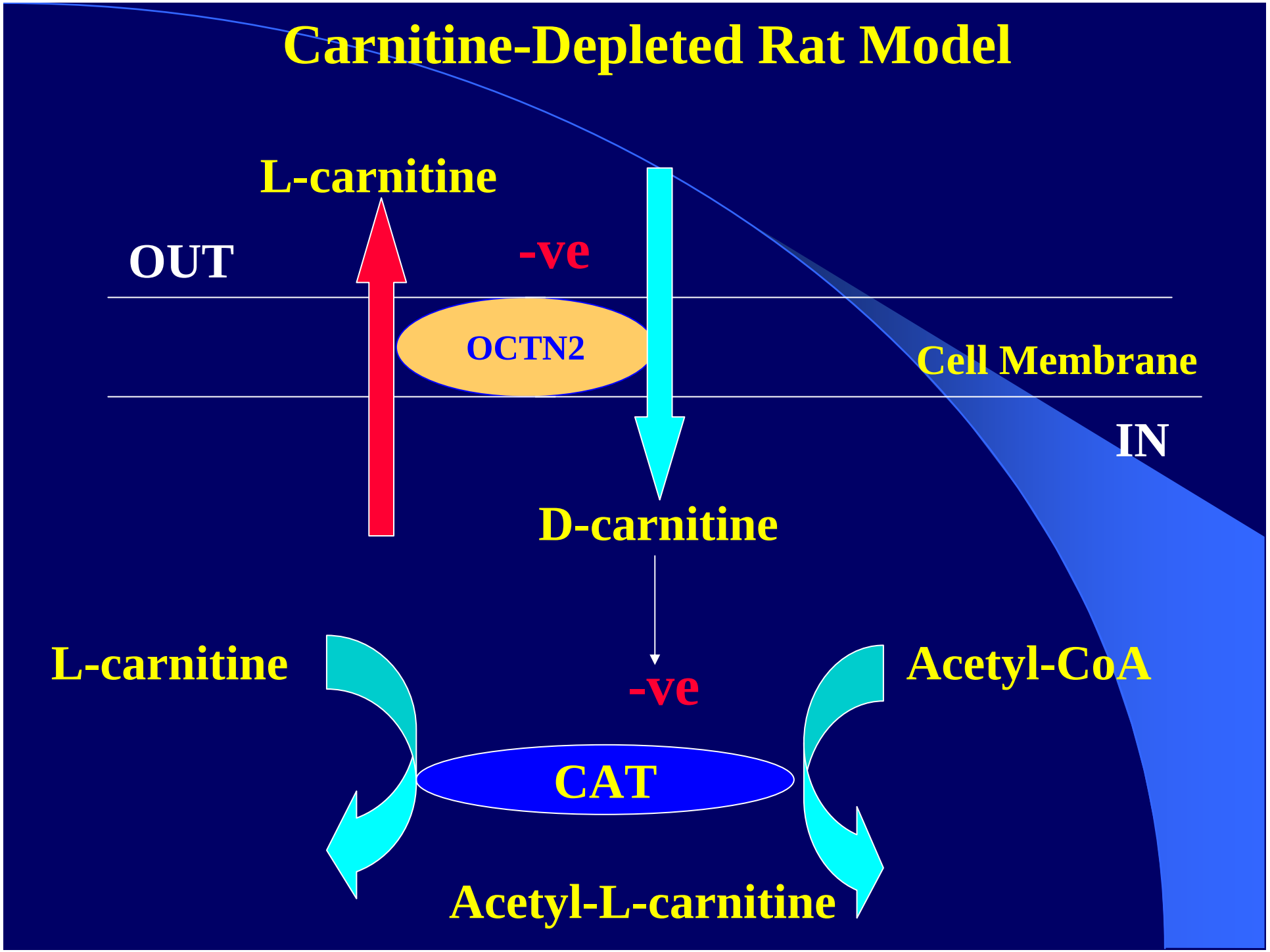
PLC
500 mg/kg, I.P., 10 days

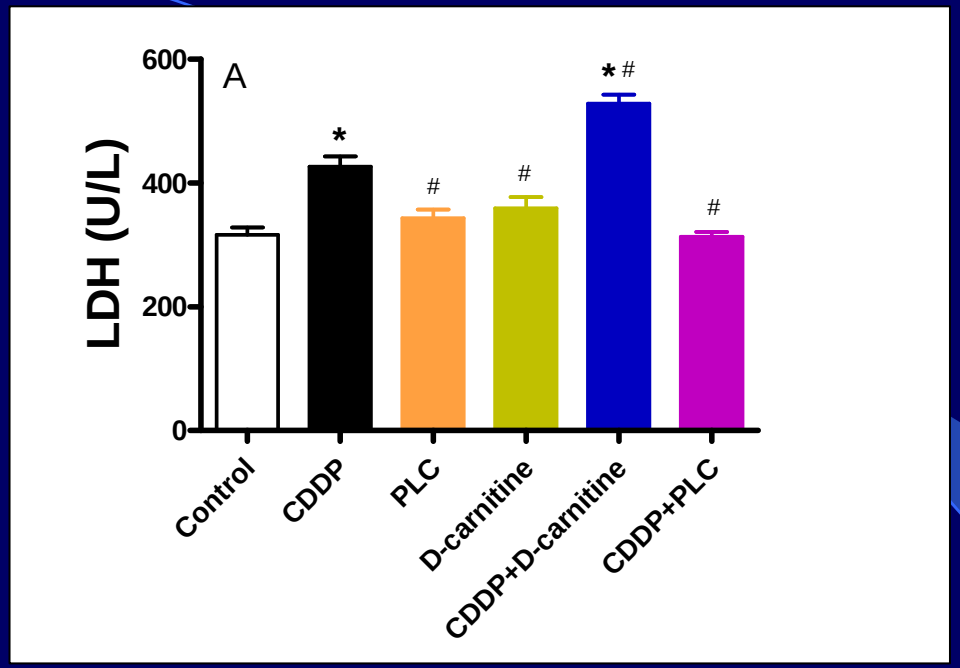
D-carnitine
500 mg/kg, I.P., 10 days

Saline-CDDP-saline
7 mg/kg, I.P.

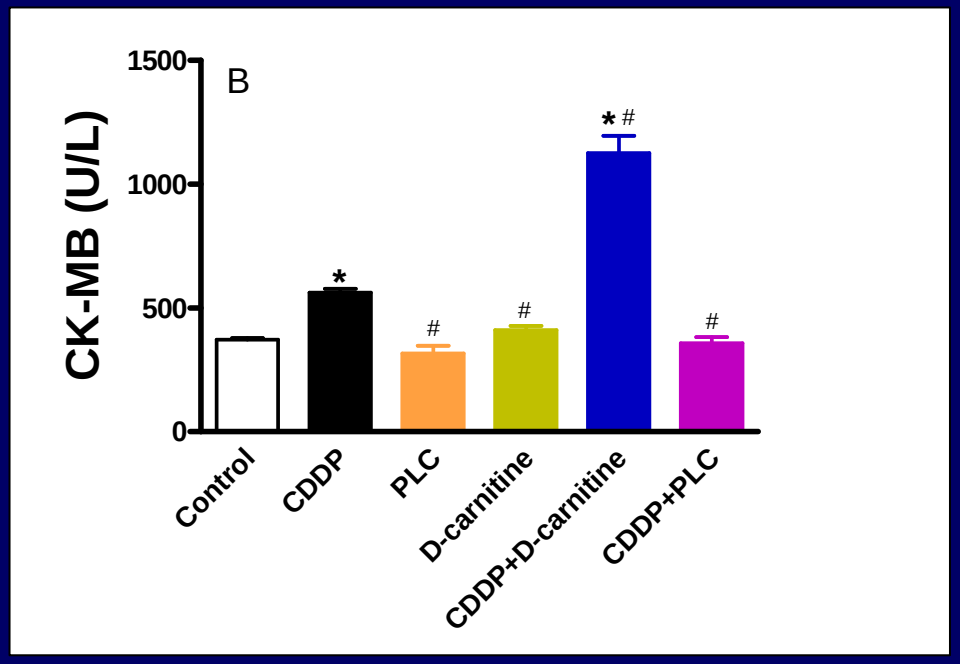
PLC-CDDP-PLC
7 mg/kg, I.P.

D-carnitine-CDDP-D-carnitine
7 mg/kg, I.P.


Carnitine-Depleted Rat Model
L-carnitine
OUT
-ve
OCTN2
Cell Membrane
IN
D-carnitine
L-carnitine
-ve
Acetyl-CoA
CAT
Acetyl-L-carnitine


A
LDH (U/L)
600
400
200
0
*
*#
#
#
#
Control
CDDP
PLC
D-carnitine
CDDP+D-carnitine
CDDP+PLC

LDH


B
CK-MB (U/L)
1500
1000
500
0
*
*#
#
#
#
Control
CDDP
PLC
D-carnitine
CDDP+D-carnitine
CDDP+PLC

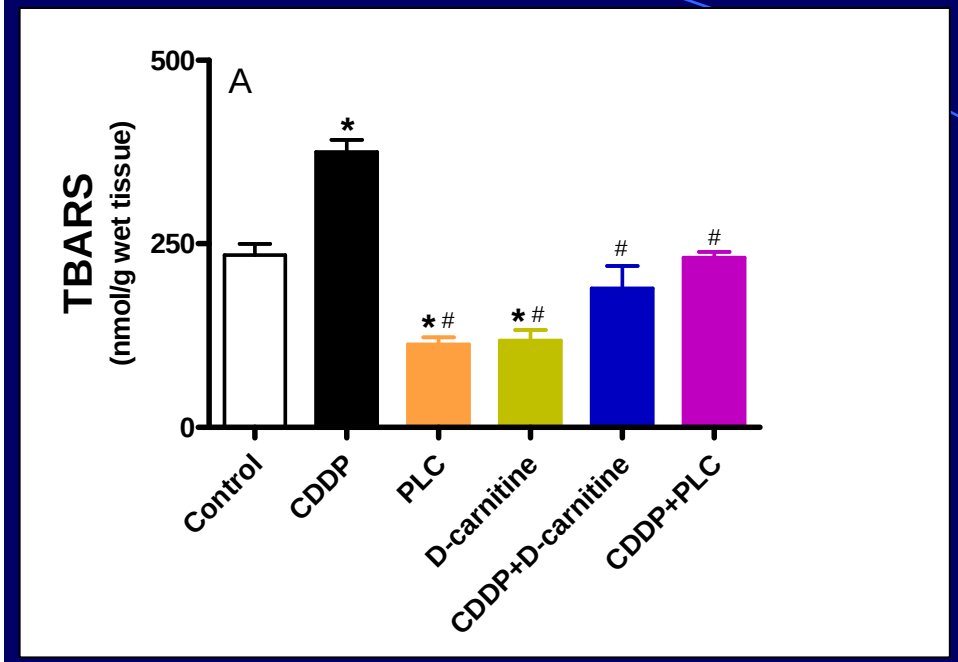
CK-MB

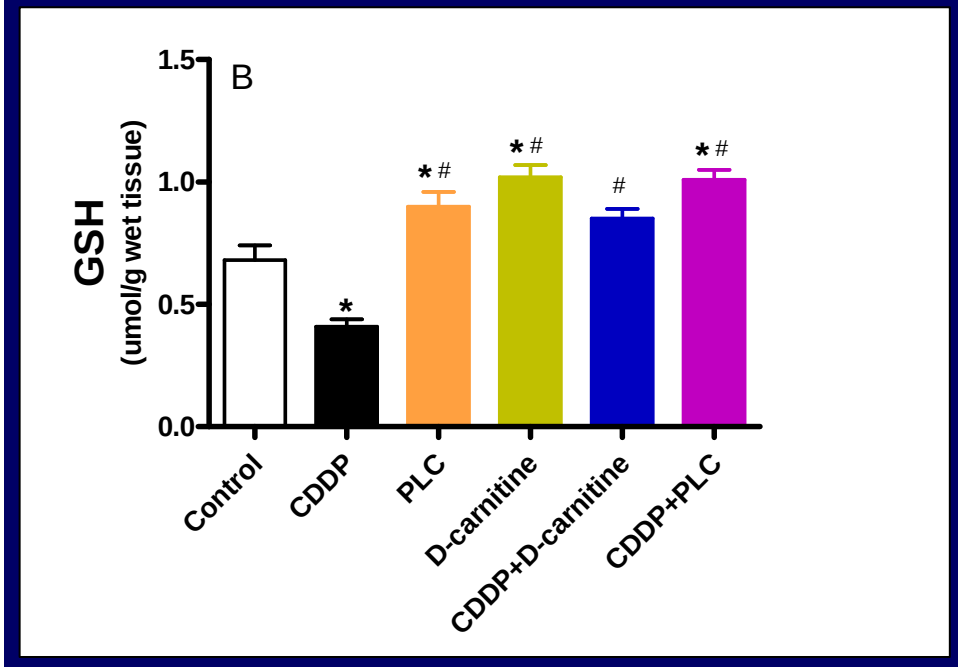
Oxidative Stress Biomarkers

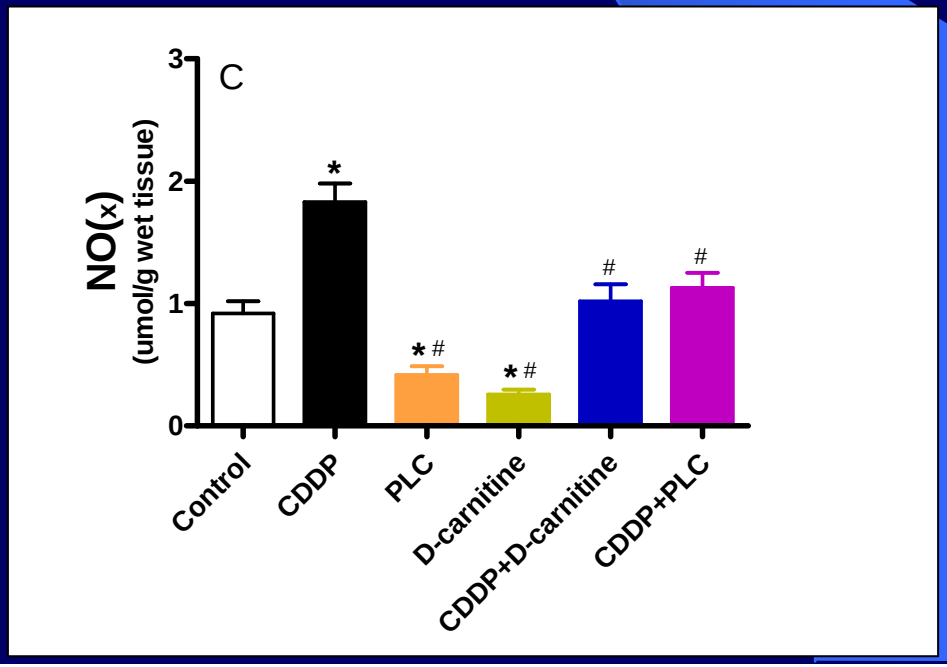
TBARS,

GSH,

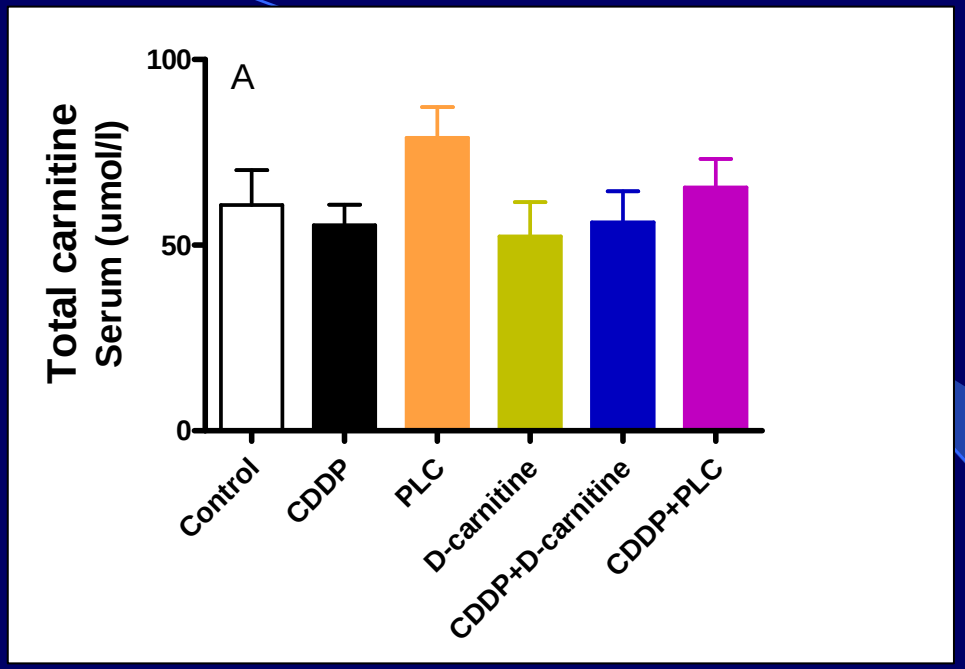
NO(x)



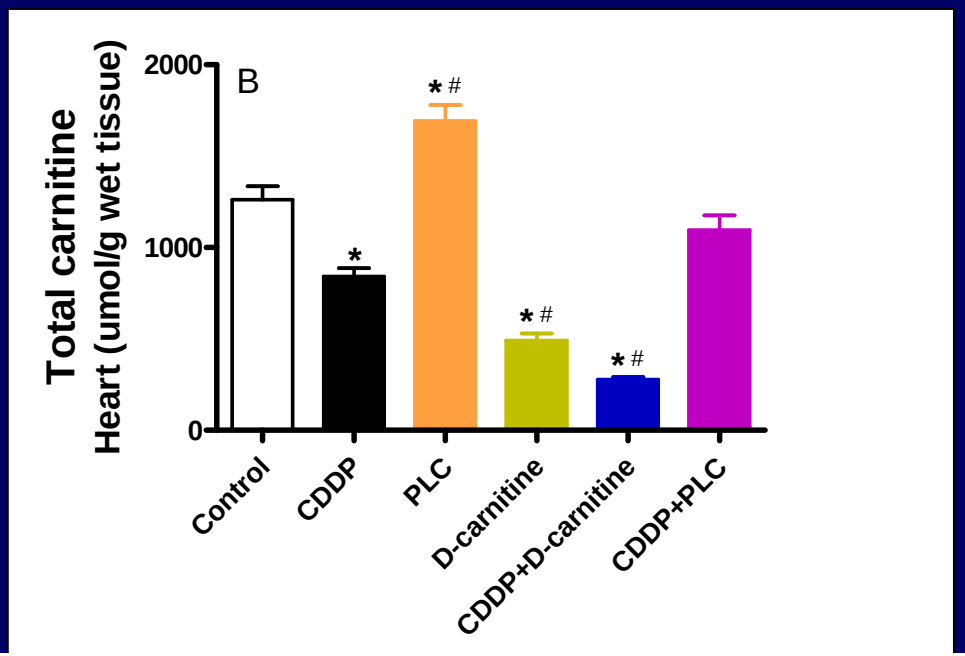




Total Carnitine

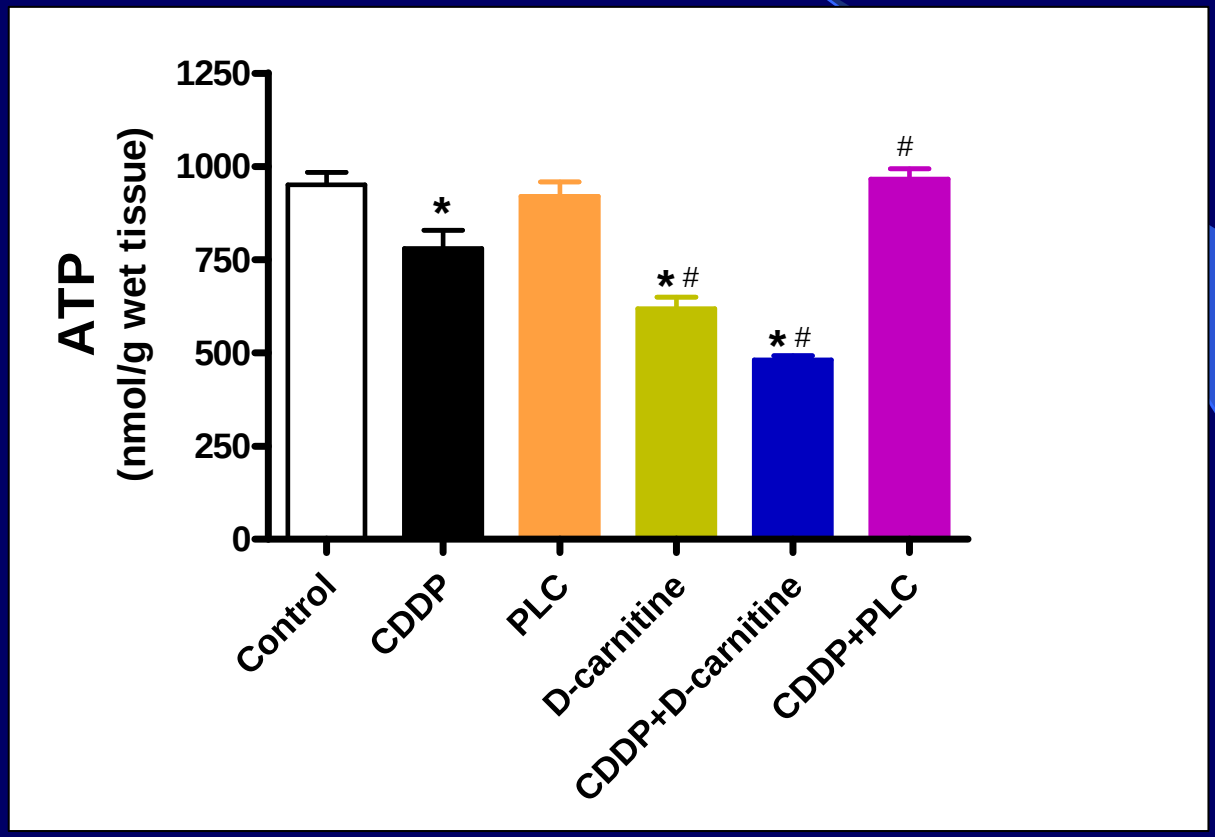


Serum

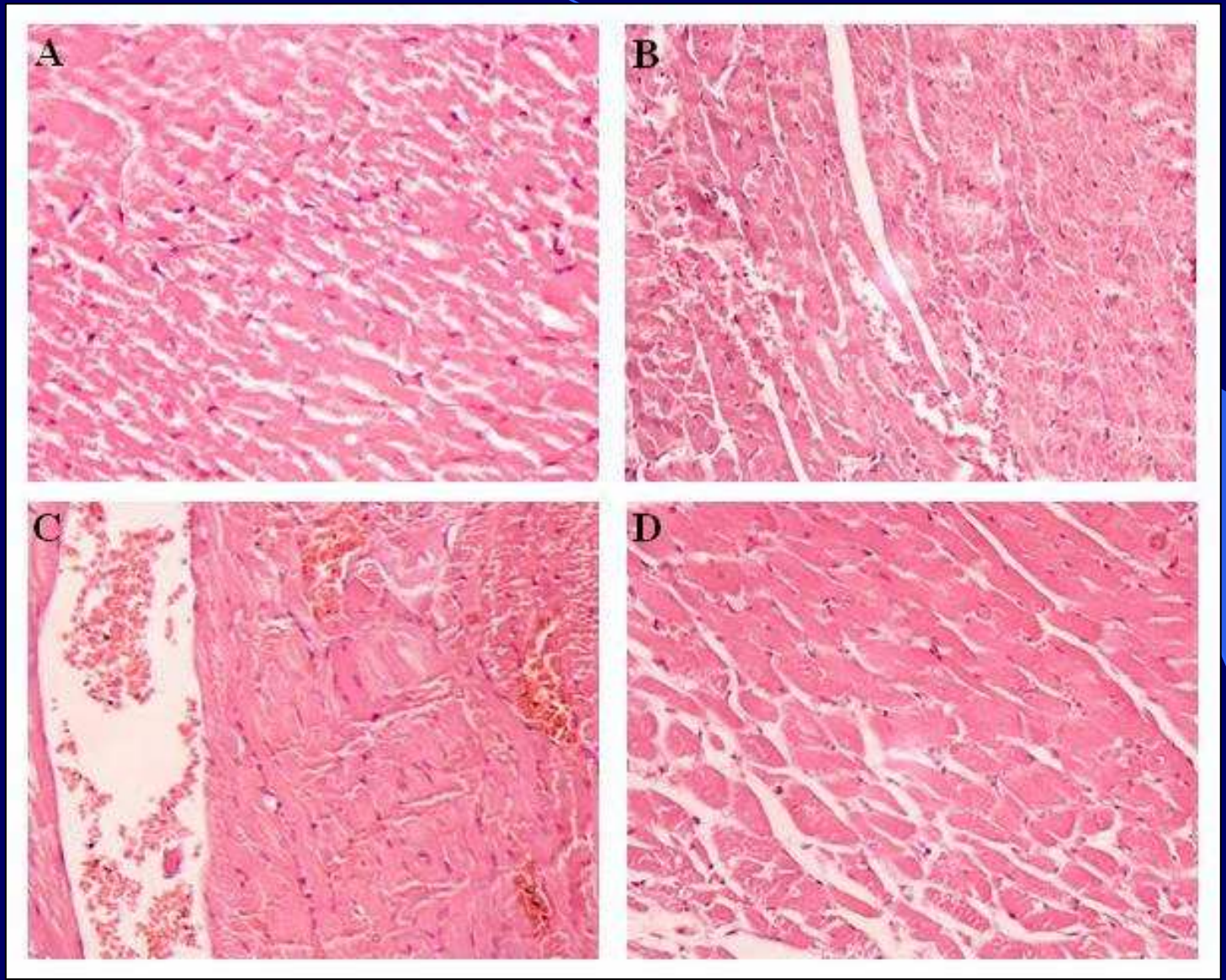


Heart

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**

Acknowledgements

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