Minufiya J. Agric. Res. Vol.38 No. 1(2): 199 - 202 (2013) "http://www.mujar.net"

HEPATOPROTECTIVE EFFECT OF BIOSYENTHESIZED L-CARNITINE AGAINST PARACETAMOL TOXICITY

Saadiya A. EL-Nahas[(1)], Hoda Mahrous[(1)] and Yousseria M. Hassan[(2)]

[(1)]Department of Industrial Biotechnology, Genetic Engineering and Biotechnology Research Institute, Menuofiya University, Egypt.

[(2)] Faculty of science, Ain Shams University.

(Received: Oct. 17, 2012)

ABSTRACT: *L-carnitine is a cofactor in the transfer of long-chain fatty acid allowing the b-oxidation of fatty acid in the mitochondria. It is also known as antioxidant with protective effects against lipid peroxidation. In this study,the effect of biosynthesized L-carnitine was investigated against paracetamol acetaminophen (ApAp)-induced liver toxicity where mitochondrial dysfunction and oxidative stress are thought to be involved in (ApAp) hepatotoxicity. Thirty male swiss albino mice were divided into three groups. In group 1 mice were dosed with 1ml water for injection as control,group2 mice were injected with a single-(ApAp) injection (500 mg/kg via the intra peritoneal route) ,group 3 was injected with L-carnitine (500 mg/kg for 10 days starting before (ApAp) injection via intra peritoneal route) and sampled 24 h following (ApAp) injection.Biochemical assay indicate increase in serum alanine aminotranseferase(ALT) and aspartate aminotranseferase(AST) level in paracetamol group. Administration of biosyenthesized L-carnitine significantly reduce (ApAp)-induced elevations in AST, ALT and reduce the induced necrosis in the liver tissue.*

Key words: *L-carnitine, paracetamol hepatotoxicity, alanine aminotranseferase(ALT), aspartate aminotranseferase(AST) ,oxidative stress .*

INTRODUCTION

Acetaminophen or paracetamol(APAP) is widely prescribed as an analgesic and antipyretic drug in the clinic and is sold in numerous over-the-counter preparations as (panadol and cetal) as a single compound or in combination with other medications(Kaplowitz , 2004,Whitcomb , 1994) At normal doses, APAP is metabolized by cytochrome P450 (CYP) to form the highly reactive species, N-acetyl-p-benzoquinone imine (NAPQI), which under normal conditions is readily detoxified by conjugation with glutathione (GSH). However, in humans and mice, high doses of APAP saturate detoxification pathways, leading to hepatic glutathione depletion and excessive production of NAPQI, which freely binds to cellular molecules(Hinson et al.,2004) L-Carnitine has a protective effect on lipid peroxidation by reducing the formation of hydrogen peroxide (Brass, 2000; Rani and Panneerselvam, 2002). L-carnitine could also improve antioxidant status in rats and showed free radical scavenging activity as well (Kalaiselvi and Panneerselvam, 1998; Rani and Panneerselvam, 2001).this study was investigate the effect of biosynthesized L-carnitine against paracetamol induced hepatotoxicity.

MATERIALS AND METHODS

Thirty adult swiss albino male mice (14-week old about 20-25 g bw)mice were acclimatized two weeks prior to the experiment .mice housed in cages in a temperature range at 25-30C and 12-h light\dark cycle. The mice were divided into 3 groups each one contain 10 mice,group 1(control)was injected with water for injection via intraperitoneal route (i.p). group2mice injected with 500mg\kg paracetamol one single dose via (i.p) route,group 3 injected with 500mg\kg L-carnitine for 10 days before receiving adose of 500mg\kg paracetamol one single toxic dose , all groups were decapitated at 24 hours following paracetamol injection . Blood sample were collected from the heart via cardiac puncture for AST,ALT.,determination all tubes were centrifuged at (1200 r.p.m at

4 C)for 10 min . to obtain serum then serum kept at -25 C for biochemical analysis of AST,ALT by using AST activity in serum was determined by using Randox diagnostic kit method according to (Reitman and Frankel, 1957). For histopathological examinations, samples of liver tissue were taken and fixed in 10% neutral buffered formalin, stained with haematoxylin–eosin (H&E).

Results

Data of biochemical assay indicate that single administration of APAP induced severe hepatic injury, as shown by marked increases in AST and ALT (Table 1). pretreatment with biosyenthesized l-carnitine reduce plasma levelof AST and ALT.

Histopathological examination showed typical inflammatory hepatic tissues, including centrilobular necrosis, confirming the hepatic damage indicated by biochemical and enzymatic assays as shown in Figure 2 (paracetamol group) which indicate Extensive necrosis with some vacuolations and karyopicnosis (H&E,) compared with figure 1(control group) indicate the normal healhy liver. pretreatment with biosyenthised l- carnitine reduce necrosis and infiltration of inflammatory cell significantly as shown in Figure 3 (paracetamol+L-carnitinegroup).

Discussion

Previous stugies showed that several factors could be involved in the mechanism and pathophysiology of AA hepatotoxicty at the cellular level. Role of oxidative stress was reported to be one of the important factors inthe development of hepatic cell injury ((Mitchell et al., 1985;Knight et al., 2001). Lipid peroxidation was suggested to be closely related to AA-induced tissue damage, biosyenthesized L-carnitine treatment effectively protected the liver tissue against oxidative damage. In addition, it was reported that mitochondrial proteins could be the target for AA toxicity leading to the loss of energy production and cellular ion control (Masubuchi et al., 2005;Al-Majed et al.,2006). The action of L-carnitine in mitochondrial energy production is to facilitate the transfer of long-chain fatty acids from cytosol to mitochondria, thereby playing an important role in the production of ATP (Kelly, 1998). Indeed, L-carnitine was shown to increase ATP production in the myocardium in cisplatin-induced cardiomyopathy (Al-Majed et al., 2006).

In conclusion, findings of the present study showed that (ApAp) administered above the recommended therapeutic dose causes hepatic toxicity in mice, and pretreatment with biosyenthesized L-carnitine also has a prominent protective effect against paracetamol (ApAp) toxicity.

Table 1. Biochemical alterations in Enzyme marker

Groups	AST(U/L)	ALT(U/L)
Control	128.22± 2.40^{c}	44.25± 7.08^{c}
Paracetamol	290.75± 9.97^{a}	103.12± 7.22^{a}
l-car+paracet	194.17± 4.84^{b}	85.33± 2.68^{b}

Different superscripts in the same row indicate significant differences ($p < 0.05$).

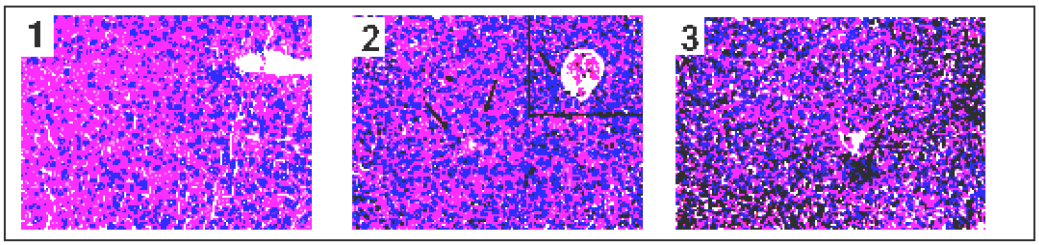

Figure (1):1-Control group **Figure (2):Paracetamol group** **Figure (3):Paracetamol+L-carnitine group**

REFERENCES

Al-Majed, A.A., M.M. Sayed-Ahmed, A.A. Al-Yahya, A.M. Aleisa, S.S. Al-Rejaie, O.A. Al-Shabanah (2006). Propionyl-L-carnitine prevents the progression of cisplatin-induced cardiomyopathy in a carnitine-depleted rat model. Pharmacol. Res. 53:278–86.

Brass, E.M., Supplemental carnitine and exercise (2000). Am. J. Clin. Nutr,72:618–23.

Hinson, J.A., A.B. Reid, S.S. McCullough, L.P. James (2004). Acetaminophen-induced hepatotoxicity: role of metabolic activation, reactive oxygen/nitrogen species, and mitochondrial permeability transition.*Drug Metabolism Reviews.* 36(3-4):805–822

Kalaiselvi, T. and C. Panneerselvam (1998). Effect of L-carnitine on the status of lipid peroxidation and antioxidants in aging rats. J Nutr Biochem; 9:575–81.

Kaplowitz, N. *(*2004). Acetaminophen hepatoxicity: what do we know, what don't we know, and what do we do next? *Hepatology.* 40(1):23–26.

Kelly, G.S.L. (1998). Therapeutic applications of a conditionallyessential amino acid. Altern Med Rev. 3: 345–60.

Knight, T.R., A. Kurtz, M.L. Bajt, J.A. Hinson, Jaeschke H. Vascular and hepatocellular peroxynitrite formation during acetaminophen toxicity: role of mitochondrial oxidantstres. Toxicol Sci 2001;62:212–20.

Masubuchi, Y., C. Suda and T. Horie (2005). Involvement of mitochondrial permeability transition in acetaminophen-induced liver injury in mice. J Hepatol. 42:110–6.

Mitchell, D.B., D. Acosta and JV. Bruckner (1985). Role of glutathione depletion in the cytotoxicity of acetaminophen in a primary culture system of rat hepatocytes. Toxicol. 37:127–46.

Rani, P.J. and C. Panneerselvam 2001). Carnitine as a free radical scavenger in aging. Exp Gerontol. 36:1713–26.

Rani, P.J. and C. Panneerselvam (2002). Effect of L-carnitine on brain lipid peroxidation and antioxidant enzymes in old rats. J Gerontol A Biol Sci Med Sci. 57:134–7

Reitman, S. and S. Frankel (1957). Determination of aspartate aminotransferase. Am. J. Clin. Path. 2: 856. 7

Whitcomb, D.C. (1994). Acetaminophen poisoning and liver function. *The New England Journal of Medicine.*331(19):1310–1312.

تأثير ال ل- كارنتين المنتج حيويا ضد تسمم الكبد بالباراسيتامول

سعدية عبدالرازق النحاس[١] ، هدى محروس[١] ، يسرية محمد حسان[٢]

(١) قسم البيوتكنولوجيا الصناعية . معهد بحوث الهندسة الوراثية . السادات . جامعة المنوفية

(٢) كلية العلوم . جامعة عين شمس

الملخص العربى

من المعروف ان الكارنتين له دور هام وحيوى فى نقل الاحماض الامينية طويلة السلسلة وأكسدة هذه الأحماض داخل الميتوكوندريا بالإضافة الى دوره كمضاد للأكسدة و تهدف هذه الدراسة الى دراسة تأثير الكارنتين المنتج حيويا ضد تسمم الكبد بالباراسيتامول. تم استخدام ٣٠ فار من الذكور السويسرية البيضاء حيث تم تقسيمها الى ٣ مجموعات المجموعة الاولى تم حقنها بماء فقط الثانية حقنت بجرعة سامة من الباراسيتامول والثالثة حقنت بالكارنتين والباراسيتامول معا كل المجموعات تم تشريحها بعد ٢٤ ساعة من الجرعة لإجراء فحص الدم والأنسجة ودراسة النتيجة التى بينت بالفحص الكيميائى للدم ارتفاع شديد فى AST,ALT بعد الحقن جرعة الباراسيتامول السامة وتحسن هذا الارتفاع بعد اعطاء ال ل-كارنيتين المنتج حيويا كما ان نتائج الفحص الهيستولوجى لانسجة الكبد بينت تحسن ملحوظ فى داخل النسيج مما يؤكد دور ال ل-كارنيتين فى حماية الكبد.