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Histopathological And Histochemical Studies On The Effect Of Taurine In Preventing Carbon Tetrachloride –Induced Hepatic Injury In The Albino Rat

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Abstract

Taurine is an amino acid– like compound, it is found mostly in meat and fish.This study was designed to evaluate the effects of carbon tetrachloride (CCL4) on liver Histopathological & Histochemical changes and the protective role of taurine (2amino-ethanosulfonic acid) was studied **.** Fourty two albino rats were divided into seven groups : control, taurine alone (200mg/kg), CCL4 alone, CCL4 plus 50mg/kg of taurine, CCL4 plus 100mg/kg of taurine, CCL4 plus 200mg/kg of taurine (taurine was injected twice daily for one week before CCL4 treatment), CCL4 plus 200mg/kg of taurine with and after CCL4 treatment. The sections (six microns) of rat liver were stained with haematoxyline and eosin for histological examination. Total protein content, alkaline phosphatase (Alk.ph), succinic dehydrogenase (SDH) ,and lipids were demonstrated**.**CCL4 treatment showed vacuolar degeneration , necrosis , mononuclear cellular infiltration around the central vein and fatty degeneration .These histological changes which appeared in the animals treated with CCL4 alone were more extensive and severe than those seen in the animals treated with CCL4 plus taurine . The incidences of total protein content, and SDH reaction were markedly reduced in CCL4 treated rats than in those protected with taurine . The Alk.ph. activity and lipid content were markedly higher in the CCL4 treated rats than in those protected with taurine.Taurine in this study ,not only reduced the hepatocellular damage but also improved the hepatocellular functions.

Key words -:Taurine, carbon tetrachloride, liver , histopathology, histochemistry.

Introduction

Many studies have shown that reactive oxygen species including oxygen free radicals are causative factors in the etiology of degenerative diseases, including some hepatopathies (Ames et al.,1993and Hung et al.,2002) .Carbon tetrachloride (CCL4) was most frequently used as a chemical inducer of experimental liver cirrhosis(Waring et al., 2001).It has been suggested that hepatic necrosis caused by carbon tetrachloride involved bioactivation by the microsomal cytochrome P450-dependent monooxygenase system, resulting in the formation of trichloromethyl free radical and reactive oxygen species that initiate lipid peroxidation and protein oxidation (Nobuo,1986 and Lin et al., 1998). Free radicals in both *in vitro* and *in vivo* models have also been shown to modify and damage proteins, carbohydrates, and DNA(Halliwell and Gutteridge, 1984 and Waters et al., 2001) Therefore, under such disseminated oxidative stress,bioactive molecules

were disturbed or inactivated. Furthermore, hepatic microsomes, mitochondria, and nuclei of hepatocytes were also impaired by lipid peroxide, with hepatocytes ultimately being destroyed(Hsiao et al.,2001).

Liver dysfunction can be exhibited as an elevation of serum hepatic enzymes (Castro et al., 1997), AlK.Ph. activity (Yokohama et al.,1999), and lipid (Ohta et al.,2000)

A major defense mechanism is the antioxidant enzymes (especially super - oxide dismutase ,catalase and glutathione peroxidase) which convert active oxygen molecules into non- toxic compounds(Shaw et al., 1993).

According to Waters et al.,(2001) *in vitro* and *in vivo* studies, several classical antioxidants have been shown to protect hepatocytes against lipid peroxidation or inflammation, therefore preventing the occurrence of hepatic necrosis.

Taurine,(2amino-ethanosulfonic acid), is the major free intracellular amino acid present in many tissues and has many important histological and physiological functions such as the development of brain,CNS and regulation of Ca^{+2} transport (Son et al., 1996) .Also, taurine plays an important role in protecting liver from different toxic substances (Heibashy ,2000). Taurine is able to attenuate DNA damage caused by aromatic amine compounds in vitro ,it is usually used for the treatment of various medical conditions .The human body is able to make taurine from cystine, it helps in regulating the heart beats , maintains cell membrane stability, and prevents brain cell over- activity (Franconi etal ., 2002) .

Taurine is ,a conditionally essential amino acid which possesses a number of cytoprotective properties through its actions as an antioxidant osmoregulator, and intracellular calcium flux regulator (Huxtable,1992). Taurine at a pharmacological dose abrogated endothelial cell apoptosis through its antioxidant activity and regulation of intracellular calcium homeostasis (Wang et al.,1996) and attenuated apoptosis and necrosis in hepatocytes through inhibition of reactive oxygen intermediates ,nitric oxide(Waters et al.,2001), and peroxynitrite formed by superoxide anion and nitric oxide reaction (Redmond et al.,1996) .These findings led us to investigate the hypothesis that taurine may exert a beneficial effect in preventing CCL4 – induced hepatotoxicity through its unique cytoprotective properties. Therefore, we decided to investigate the effect of taurine in preventing hepatotoxicity induced by CCL4 and we are interested in evaluating the histological and histochemical changes .

Materials and Methods

Chemicals:-All chemicals which used in this experiment including)-:Taurine ,ccl4 and paraffin oil were purchased from Sigma Chem.Com.,St .Louis, Mo.U.S.A.

Animals -: All animals which used in this Experiment were divided into seven groups as follows:- (1) The control animals were treated with a single dose of paraffin oil (0.5ml/100g body wt)., (2) served as a positive control ,rats were treated i.p.with taurine twice daily at a dose of 200mg/kg for one week,(3) rats were treated by gavage with a single dose of ccl4 paraffin oil (1:1,1.5ml/100g.b.wt.) ,(4), (5) and (6), Rats were treated with taurine twice daily at a dose of 50,100 or 200 mg/kg i.p. for one week , then a single dose of CCL4 was treated,(7)rats were treated by gagave with a single dose of CCL4 followed with i.p taurine at 200 mg/kg. Taurine dose was repeated again 4

hours following CCL4.The treated animals were killed on day three after CCL4 administration.

At the end of the experiment all animals were sacrificed and small pecies of liver were fixed in formol saline,Bouin and carnoy fluid for histopathological and histochemical investigations . The paraffin sections were stained with Hx. and E , for the histopathological examination and mercury-bromophenol blue stain for total protein contents .The Frozen sections were prepared and stained with Gomori's method for demonstrating alkaline phosphatase activity and with nitro blue tetrazolium for demonstrating succinic dehydrogenase and with sudan black (B) for lipids investigations .

Results

The histopathological results-:

The light microscopic examination revealed normal hepatocytes architec - ture of control animals (Fig.1A).

The histopathological examination of CCL4 treated group,showed centril- obular necrosis, ballooning and fatty degeneration of hepatocytes around the central vein. Inflammatory cells infiltr - ation could be detected(Fig.1B).No pathological changes could be noticed in liver treated with taurine alone. Pretreatment of rats with taurine for one week prior to the CCL4 treatment resulted in a dose dependent protective effect.Partial protective effect was seen when low dose (50mg/kg) of taurine was given to rats prior to the CCL4 treatment , the areas of liver damage were reduced .By increasing the dose of taurine (100 or 200 mg/kg),the ballooning damage , necrotic areas ,and the lipid droplets were reduced (Fig.1C) A high dose of taurine (200mg/kg) essentially prevented liver damage manifested by decreased mortality and extent of liver damage.Taurine administration at (200mg/kg) simultane -ously with and after CCL4 treatment resulted in moderate improvement in hepatocytes (Fig.1D).

The histochemical observations

Total protein :-

A positive reaction could be noticed as a bluish colouration .In control and taurine treated animals ,all the hepatocytes were characterized by a high content of total protein (Figs. 2A&B). In the CCL4 treated rats , the hepatocytes showed a marked decrease in the amount of total protein (Fig.2C).Moderate to marked reaction was seen in the hepatocytes of animals treated with CCL4 and taurine in a dose –dependent protective effect (Fig.2D).

Succinic dehydrogenase reaction (SDH):-

A strong SDH reaction could be observed around the central vein of lobules of normal and taurine treated rats liver (Figs.3A&B).In the CCL4 treated rats ,SDH reaction was decreased (Fig.3C). Partial improvem - ent was presented in the liver tissues of animals treated with CCL4 and,different doses of taurine revealed moderate to marked increase in SDH in a dose – dependent protective effect (Fig.3D).

Alkaline Phosphatase activity (AL.Ph):-

The activity of AL.Ph. in the liver cells of control and taurine treated rats were seen in (Figs.4A&B). The hepatocytes of CCL4 treated rats revealed marked increase in AL.Ph. reaction (Fig.4C).In taurine plus CCL4 treated animals ,the intensity of the reaction varied in the different groups in a dose- dependent protective effect (Fig.4D).

Lipids- :

In the control and taurine treated animals, the majority of liver cells showed aggregations of numerous minute lipid granules (Figs.5A&B). In

the CCL4 treated rats ,liver cells showed marked increase in lipid content (Fig.5C),compared to the other groups of rats treated with CCL4 plus taurine which revealed mild ,moderate and marked reduction in lipid content in a dose- dependent protective effect (Fig.5D).

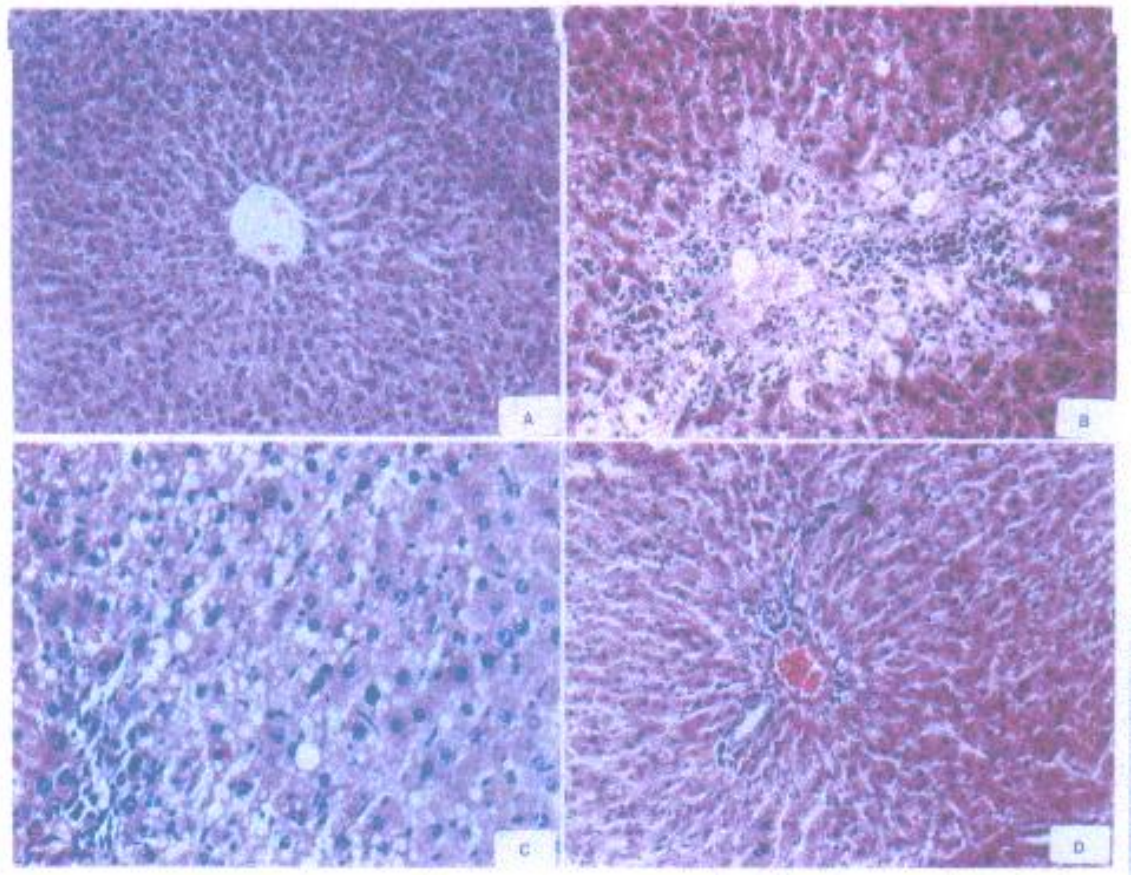

Fig .(1):
A-Normal structure of hepatocytes of control animals.
B- Section from liver of CCL4 treated rats.
C- Section from liver of rats treated with high dose of taurine injected twice daily for one week before CCL4 treatment.
D- Section from liver of rats treated with taurine plus ccl4 simultaneously and after CCL4 treatment .

(HX&E.X300)

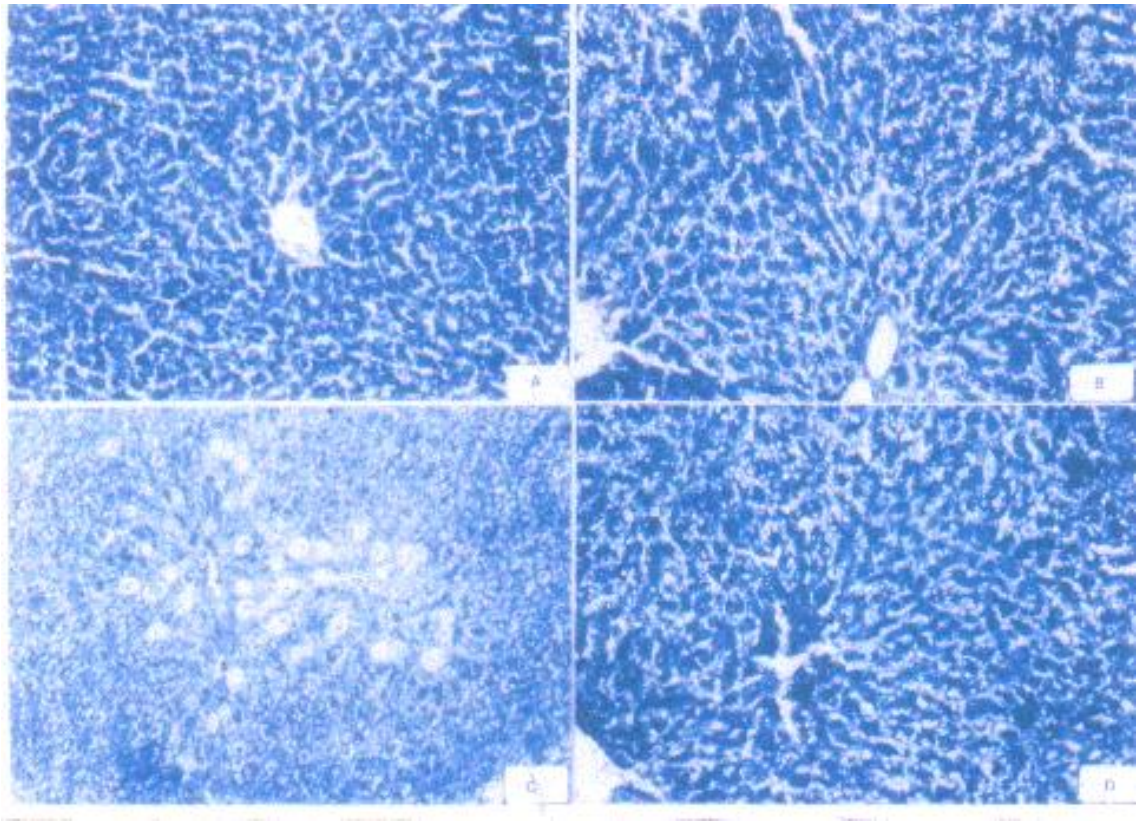

Fig.(2):-
Sections stained with mercury bromophenole blue for demonstrating total protein showing :-
A- Hepatocytes of a rat treated with saline as control showing high content of total proteins.
B-Hepatocytes of a rat treated with taurine showing high content of total protein.
C- Hepatocytes of a rat treated with CCL4 alone showing a decrease in total proteins content around the damaged blood vessels.
D- Hepatocytes of a rat treated with CCL4 plus taurine,notice marked improvement in the total protein content.

(Bromophenol blue stain X150)

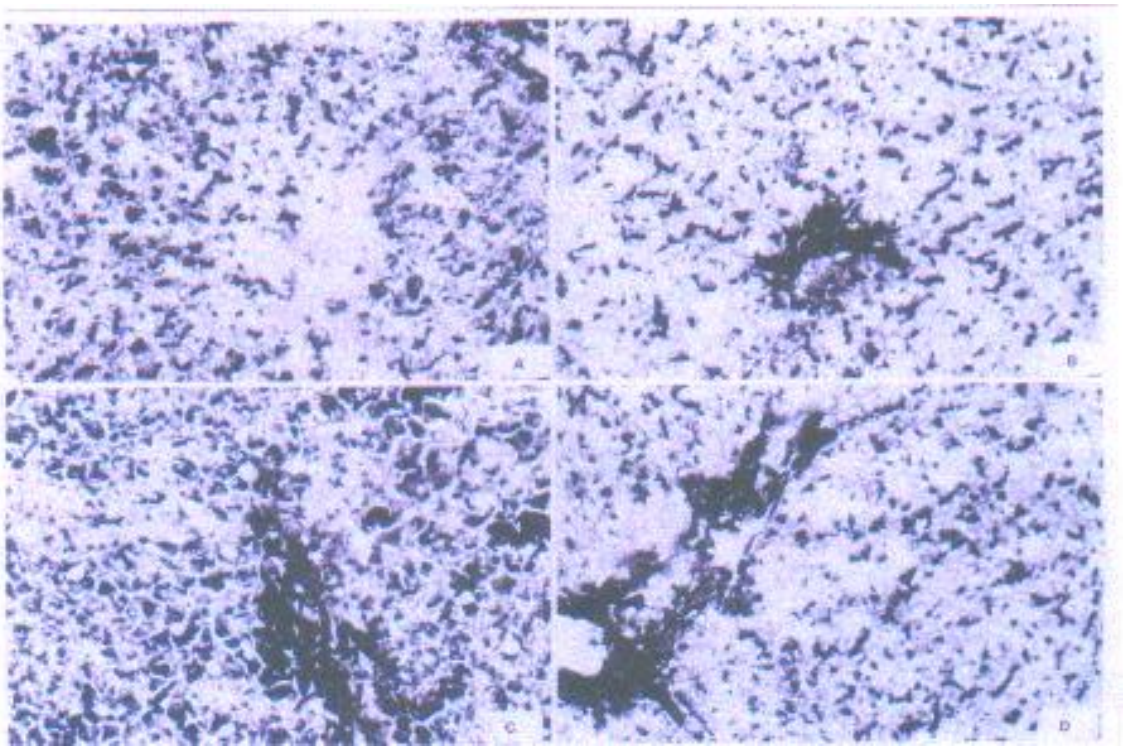

Fig.(3):-

Liver sections stained with Gomori's technique for demonstration of alkaline phosphatase activity showing:-

A&B-Normal distribution of the enzyme in the nuclei and cytoplasm of hepatocytes and blood sinusoids of normal and taurine treated rats.

C-Notice marked increase in alk.Ph. activity in the nuclei and cytoplasm of hepatocytes of CCL4 treated rats .

D-Notice a considerable decrease in alk.ph. activity in liver cells of CCL4 plus taurine treated rats .

(Alkaline Phosphatase reaction X150)

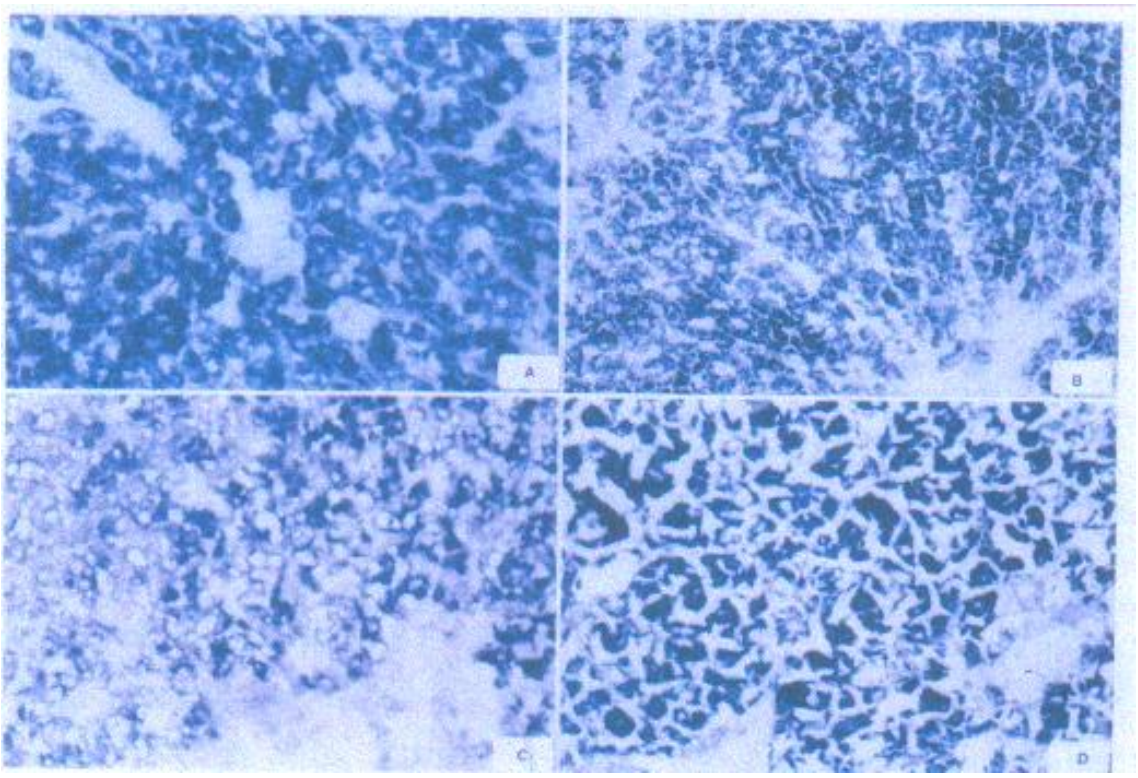

Fig.(4):-

Liver sections stained with Nitroblue-tetrazolium for demonstration of succinic dehydrogenase (SDH) showing :-

A&B-Notice the marked reaction of SDH in hepatocytes of control and taurine treaeted rats.

C- Marked reduction in SDH reaction in ccl4 treated rats.

D-Moderate reaction in CCL4 plus taurine treated rats .

(NitroBlue –tetrazolium X150)

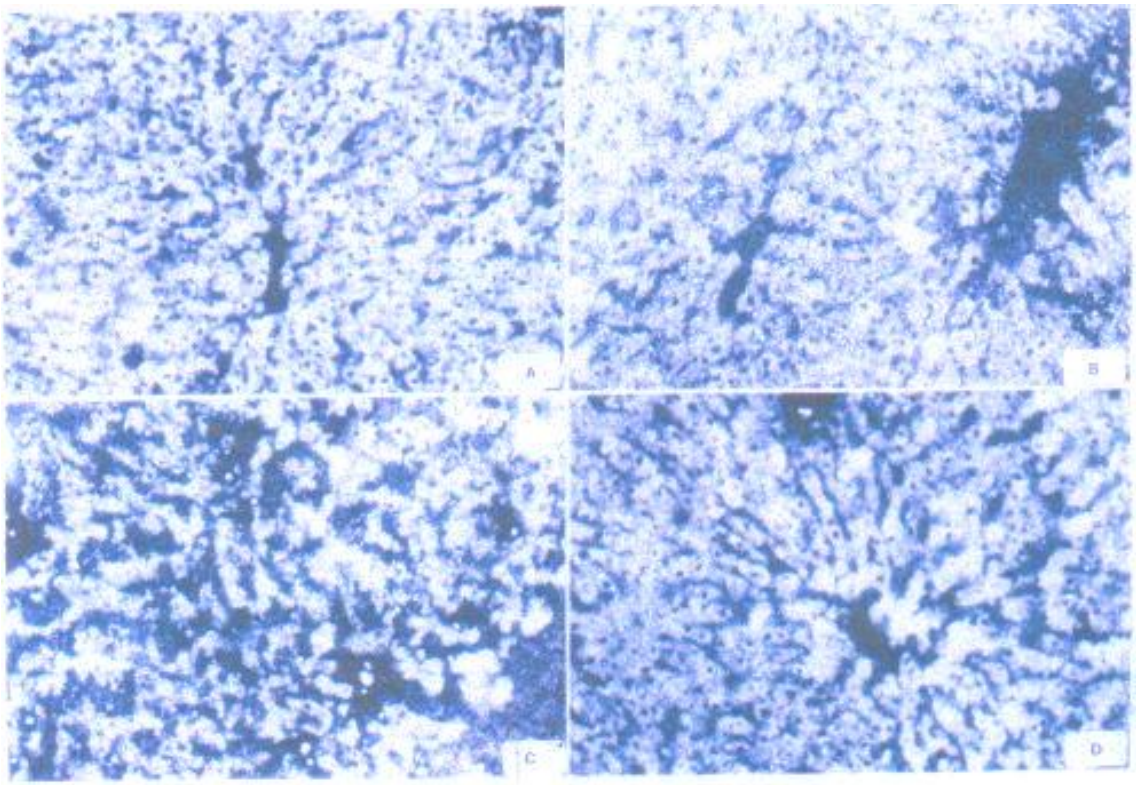

Fig.(5):-
Liver sections stained with Sudan Black B for demonstration of fat bodies showing :-
A&B-Few aggregation of minute lipid granules in the cytoplasm of hepatocytes of control group.
C-Marked increase in Sudan Black reaction in hepatocytes of CCL4 treated rats
D- Moderate reaction in CCL4 plus taurine treated rats .
(Sudan Black –B stain X150

Discussion

Taurine (a sulfur amino acid) is one of the lesser- known amino acids,it plays several important roles in the body and is essential to newborns of many species along with methionine, cystine and cysteine (Laidlaw *et al*., 1990).For a long time, taurine was considered a nonessential nutrient for human. However, in recent years it has become clear that taurine is a very important amino acid involved in a large number of metabolic processes. Basically, its function is to facilitate the passage of sodium, potassium and possibly calcium and magnesium ions into and out of cells and to stabilize electrically the cell membranes. Franconi *et al* ., (2002), suggested that since human never develop a high level of cystein sulfinic acid decarboxylase, an enzyme necessary for formation of taurine from the amino acid cysteine, people are probably all somewhat dependent upon dietary taurine. Under certain conditions of high stress or in disease states the need for taurine probably increases. Another important function of taurine is detoxification. Taurine is required for efficent fat absorption & solubilization. Main functions of taurine in mammals are:bile acidconjugation,detoxification, osmoregulation, membrane stabilization and regulation of intracellular Ca2+ Homeostasis**.** In the body taurine went mostly to the cortex of the kidney, the liver, pituitary, thymus and adrenal glands, the eye, basal mucous membranes, salivary glands, heart and the mucous membranes lining the digestive tract. It is the most abundant amino acid in the retina of all species studied.(Hartley et al.,1999and Franconi *et al* ., 2002)

Studies also showed that dietary taurine supplementation ameliorates experimental renal disease,and protected the body against carbon tetrachloride-induced toxicity (Zhou *et al*., 1996).It was postulated that taurine has a cytoprotective role on hepatocytes against some severe hepatotoxic substances like CCL4 (Son *et al*., 1996);in treatment of liver cirrhosis (Butler,1996);ischemic liver disease (Wettstein and Haussinger, 1997), hepatocarcinogenesis (You and Chang, 1998)and fibrosis (Zhonghua ,1999).

Carbon tetrachloride (CCl4) is a well–known hepatotoxicant, which increases liver weight and causes lipid peroxidation ,fatty infiltration , and liver necrosis (Recknagel and Glende, 1973).Recent studies (Shimizu *et al*.,2001) and (Hsiao,etal., 2001)) ,as well as the present one ,showed that CCL4 causes various pathological changes in the liver of rats . It was presented as ballooning and vacuolar degeneration of hepatocytes around the central vein and lipid vacuolation in the mid zone and some periportal hepatoc - ytes .Necrotic cells and inflammatory cells infiltration around most central veins. The hepatic damage following CCL4 intoxication has been demons - trated may be attributed to the free radical metabolites (CCl3) formed by which interaction with hepatic microsomal drug –metabolizing enzy - mes (Recknagel and Glende, 1973).Further ,(Glend ,1972) have shown that CCL4 itself rapidly induced a loss of liver microsome enzyme activity and cytochrome P-450 content.Early studies by Noguchi *et al*., (1982) and Moody *et al* ., (1982) have shown that the cytochrome P-450 involved in the metabolism of CCL4 to CCl3 is closely associated with that destroyed by CCl4 itself .The interaction of this radical with hepatic lipids (Hartely etal.,1999) and proteins (Ohta *et al*.,,2000) has been confirmed .

Furthermore,in the present study the addition of taurine to CCL4 treated rats substantially reduced the pathol - ogical changes described above .The frequency of ballooning degeneration , hydropic vacuolation was much lower , with the reduction of fatty vacuolation . Taurine has been considered as a direct antioxidant that scavenges or quenches oxygen free radicals and inhibits lipid peroxidation and as an indirect antiox - idant that prevents the increase in membrane permeability resulting from oxidant injury in many tissues including liver (Waters *et al*,2001). Therefore , the possible mechanism by which taurine prevents CCL4 hepatotoxicity may be associated with its antioxidant property as clearly noticed in the present study. Our results are in agreement with those of (Zhou *et al*., 1996).

According to Waterfield et al., (1991), Gardner *et al*.,(1998)and Vohra and Hui(2001) ,CCL4 toxicity of decreasing the taurine content in the liver and increasing the urinary taurine , this was correlated with both the histological and biochemical assesse - ment of liver damage .

In addition (Waters *et al*., 2001) stated that 200mg/kg taurine signific - antly attenuated acetaminophen–induced liver injury and prevented plasma Alk-ph.elevation ,hepatic DNA fragmentation and hepatocyte necrosis. On the other hand , taurine, as an indirect antioxidant ,has been proposed as a membrane stabilizer, which has been shown to maintain membrane organization ,prevents ion leakage and water influx ,and subsequently prevents cell swelling Milei *et al.,* (1992) and Chen,(1993)).The histochemical invest - ingations of the present study revealead that CCl4 induced a decrease in protein content ,this is in agreement with the results of (Timbrell and Waterfield 1996), also a decrease in succinic dehydrogenase reaction and an increase in alkaline phosphatase activity as well as lipid granules and this may be due to the oxidative damage of cellular proteins and alteration in cellular function (Sundari and Ramakrishna 1997) and (Ohta *et al*.,2000).

CCL4 caused a disturbance of Ca 2+ homeostasis in liver cells,the Ca2+ transport system in the liver nuclei was altered and induced elevation of calcium in liver nuclei due to hepatotoxicity(Omura et al.,1999).

Ding *et al*.,(1993) stated that taurine- like immuno positive granules were distributed unevenly in each liver lobules , and were located predomi - nantly in the peripheral region ,in the cisternal lumen of smooth surfaced endoplasmic reticulum in the mouse liver.So that in our study the CCL4 damage was involved in all liver lobules

In the present study the administration of taurine to CCL4 treated rats reavealed marked improv - ement in the activity of Alk.ph. , succinic dehydrogenase reaction ,total protein and lipid droplets. Our results are in agreement with the studies of Nakashima *et al*., (1982)

These results proved that the administration of taurine prior,with or after to CCL4 treatment was able to protect the liver against CCL4 toxicity ,and this may be due to increase in the liver taurine content which increase the ability to remove the toxicity of CCL4 from cells since taurine has an antioxidant properties or by its ability to make the membrane stabilization and regulation of intracellular Ca2+ homeostasis which altered by CCL4 administration.(Omura *et al*.,1999).

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دراسات هستوباثولوجية وهستوكيميائية لتأثير التورين فى منع رابع كلوريد الكربون من اصابة كبد الجرذان البيضاء

نبيلة صلاح حسن ، نجلاء فتحى عباس ، حفيظة عبد السميع شرف
المركز القومى للبحوث- قسم الباثولوجى

تلعب الأحماض الأمينية دورا هاما فى الحفاظ على نشاط وحيوية الجسم ،والتورين أحد الأحماض الأمينية التى تقوم بوظائف عد يدة منها امتصاص الدهون ، تنظيم ضربات القلب ،المحافظة على جدار الخلايا ، ومنع الزيادة فى نشاط خلايا المخ .لذلك ينصح الأطباء بتعاطى التورين فى معظم الحالات المرضية مثل مرض السكر .ويوجد التورين بكثرة فى اللحم والبيض واللبن والأسماك .لذلك

اشتمل البحث على دراسة هستوباثولوجية وهستوكيميائية للتأثير الوقائى للتورين ضد التسمم الكبدى الناجم عن المعاملة بر ابع كلوريد الكربون فى أناث الجرذان البيضاء . أستخدم فى هذا البحث أثنان وأربعون جرذا ، تم تقسيمهم إلى سبع مجموعات على أن يستعمل التورين مع أو قبل أو بعد الحقن برابع كلوريد الكربون

وبالمقارنة مع المجموعة الضابطة أكد البحث أنه توجد تغيرات هستوباثولوجية مابين فجوات مائية ودهنية الى وجود مساحات مختلفة من الخلايا الالتهابية فى أنسجة الجرذان المصابة برابع كلوريد الكربون والتى اظهرت تحسنا خلويا ملحوظا بعد معالجتها بالتورين. كما أظهرت النتائج الهستوكيميائية نقصا ملحوظا فى محتوى كل من البروتين وأنزيم السكسينك ا لد يهيدروجينى ، وزيادة فى أنزيم الفوسفاتيز القاعدى وكمية الدهون فى خلايا الفئران المصابة برابع كلوريد الكربون ، بينما أظهرت الدراسة تحسنا ملحوظا فى تللك المحتويات الكيميائية للخلايا بعد معالجتها بمادة التورين. هذا ويستفاد من القيمة العلمية لنتائج هذا البحث بالنصح لكل المرضى الذين يعانون من أمراض الكبد بأستخدام التورين كمادة محسنة لبعض التغيرات الباثولوجية او الهستوكيميائية الناجمة عن امراض الكبد ، وينصح أيضا بتناول الأسماك ومنتجات الألبان واللحوم والبيض كلما أمكن على أن يراعى المريض ما هو مناسب لحالتة الصحية .