Egypt. J. Rad. Sci. Applic., Vol. **26**, No. 1-2, pp. 85-97 (2013)

Disturbances in Pituitary-Thyroid Axis Hormones in Rats Exposed to CCL_4 and/ or Gamma-Irradiation

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THIS WORK aims to detect the disturbances in hormones of pituitary-thyroid axis in male rats exposed to liver injury by carbon tetrachloride (CCl_4) and/ or γ-irradiation, as well as modulating these disturbances by supplementation of hepato-protective agent, silymarin-plus (S+). Subcutaneous injection of CCl_4, as a hepatotoxic agent, 1 ml/ Kg body wt two times/ week for 3 weeks alone or combined with 6Gy fractionated doses of whole body γ-irradiation (1Gy two times/ week for 3 weeks) induced hepato-toxicity as manifested biochemically by an elevation of liver marker enzymes; transaminases (ALT & AST) and alkaline phosphatase (ALP).

Oxidative stress in liver was evidenced by a significant increase of malondialdehyde (MDA) along with reduction of glutathione (GSH) content. Liver damage induced by CCl_4 and/or γ-irradiation was accompanied by a significant decrease in the levels of serum triiodothyronine (T_3) and thyroxin (T_4), while thyroid-stimulating hormone (TSH) showed a significant increase. In addition, significant increases were recorded in total cholesterol and triglycerides levels whereas; significant decrease was recorded in glucose level in group exposed to CCl_4 and γ-irradiation. Oral supplementation of S+ ameliorated the changes induced by exposure to CCl_4 and/ or γ-irradiation.

In conclusion, the present data demonstrated that exposure to chemical as well as physical environmental biohazards induced liver injury concomitant with a hypothyroid state. This disturbance can be modulated by supplementation of hepato-protective agent.

Keywords: CCl_4, γ-rays, rats, liver, thyroid hormones, silymarin.

Exposure to xenobiotic and ionizing radiation induce complex cellular responses in both experimental animals and humans which may lead to adverse outcomes. Several investigations indicated that damaging effects of radiation and xenobiotic as CCl_4 result from production of highly reactive free radicals

and their consequent action on biological molecules which leads to injury of different tissues (Ashry, 2008 and Hanafy *et al* ., 2008).

Liver injury is a prevalent pathology that involves a variety of disorders including oxidative stress, hepatitis, fibrosis, cirrhosis, apoptosis and hepatocellular carcinoma. Numerous reports have shown an indirect effect of liver disorders on serum levels of thyroid hormones (Moustafa *et al*., 2009), where the liver plays an important role in the metabolism of thyroid hormones and regulates their systemic endocrine effects (Malik and Hodgson, 2002). In turn, thyroid hormones regulate the basal metabolic rate of hepatocytes and modulate hepatic function. Hence, liver and thyroid hormones closely connected, and dysfunction of one causes a disturbance in the other (Malik and Hodgson, 2002 and Khan, 2012). Consequently, treatment of liver injury is important in modulation of the disturbance in pituitary-thyroid axis hormones resulting from exposure to chemical and/ or physical environmental biohazards.

Silymarin is a flavonoid derived from milk thistle that has been reported to afford hepato-protection *in vitro* and *in vivo* by inhibiting the production of pro-inflammatory and pro-fibrogenic factors (Grattagliano *et al*., 2013). S+ is a combination of silymarin and other standard antioxidants that include acetyl cysteine, vitamin E, vitamin C, vitamin A, selenium and zinc. It was reported that combination of antioxidants exerts synergistic action in scavenging free radicals (Fang *et al*., 2002) and employs a series of redox reactions (Blokhina *et al*., 2003 and Mandelker, 2004) since deficiency in one component may affect the efficiency of the other (Vertuani *et al*., 2004).

This work aims to underscore the similarity of the toxic effect of CCl_4 metabolites and its highly reactive derivatives to those of gamma irradiation, as well as, their synergistic impact on pituitary-thyroid axis hormones. Investigating the impact of the hepato-protective drug, S+ also is intended.

Material and Methods

Male albino rats weighing 120-150 g (45-60 days) were obtained from the National Research Centre, Giza, Egypt. The animals were maintained under conventional conditions with free access to water and standard pellet concentrated diet.

Radiation exposure

Whole body γ-irradiation was performed at the NCRRT, Cairo, Egypt using a ventilated Canadian ^{137}Cs Gamma Cell-40 at a dose rate of 0.47 Gy/min. Rats were exposed to fractionated doses, 1Gy two times/ week for three weeks.

Chemicals

CCl_4 was purchased from El-Nasr Pharmaceutical Chemical Co., Egypt. Animals were injected subcutaneously 1ml/kg body wt (Ibrahim and Abdel Aziz, 2009) two times/ week for a period of 3 weeks. The S+ produced by SEDICO pharmaceutical Co, Egypt. It was available in the form of sachets containing Silymarin (200 mg), acetylcysteine (200 mg), vitamin A (300 IU), ascorbic acid (30 mg), vitamin E (5 IU), selenium (18.3 µg) and zinc (3.6 mg). It was orally administered 150 mg (dissolved in water)/ kg/day (Omar *et al*., 2012).

Experimental design

Animals were divided into 7 groups: Control untreated normal rats, CCl_4: Rats injected with CCl_4 (1ml/ kg body wt) subcutaneously two times/ week for a period of 3 weeks, S+ plus CCl_4: Rats orally supplemented with S+ daily for one week before and then through CCl_4 administration for a period of 3 weeks. IRR: Rats whole body exposed to γ-irradiation (1Gy) two times/ week for 3 weeks, S+ plus IRR: Rats supplemented with S+ daily for one week before and then through exposure to γ-irradiation for a period of 3 weeks. CCl_4 plus IRR: Rats injected with CCl_4 (1ml/ kg body wt) two times/ week for 3 weeks and exposed to γ-irradiation (1Gy) two times/ week for 3 weeks. S+ plus CCl_4 pus IRR: Rats treated with S+ and CCl_4 and exposed to irradiation as described above. The animals were sacrificed one day after the last dose of irradiation and / or treatment.

Biochemical analysis

Animals were lightly anesthetized with ether and blood was collected by heart puncture. Serum was separated by blood centrifugation at 3000 rpm. Liver was quickly removed and homogenized in ice-cold saline. Both serum and homogenate were stored at –20°C till biochemical analysis. Serum transaminases (ALT & AST) and ALP were determined according to Reitman and Frankel (1957) and Belfield and Goldberg (1971), respectively. Total T_3 and T_4 in serum were measured using radioimmunoassay kits, TSH was

measured using immunoradiometric assay kit produced by Diagnostic Products Corporation, USA. Liver GSH and MDA contents were determined according to Beutler *et al*. (1963) and Yoshioka *et al*. (1979), respectively. Serum cholesterol, triglycerides and glucose levels were determined according to Richmond (1973), Fossati and Principe (1982) and Trinder (1969), respectively.

Statistical analysis

The SPSS computer program was used for statistical analysis of the results. Values were expressed as mean± S.E.. Statistical comparison between groups was done by using one way ANOVA. Differences were considered significant at $P< 0.05$.

Results

The results of the present study revealed that exposure of rats to CCl_4 and/ or γ-radiation induced a significant increase ($P< 0.05$) in hepatic MDA associated with a significant decrease ($P< 0.05$) in GSH content as compared to control values. Oral supplementation with S+ induced significant amelioration of the changes induced by CCl_4 or irradiation as well as their combination (Table 1).

TABLE 1. Changes in liver MDA and GSH levels of adult male albino rats in different groups.

Groups	**MDA** (µmol/g tissue)	**GSH (** mg/ g tissue)
Control	125.40± 6.06	2.64± 0.08
CCl_4	170.80± 5.67^{ac}	1.95± 0.07^{ad}
S+ plus CCl_4	138.00± 5.91^{bd}	2.48± 0.05^{bcd}
IRR	146.80± 4.91^{abd}	1.93± 0.08^{ad}
S+ plus IRR	132.80± 4.07^{bd}	2.45± 0.07^{bcd}
CCl_4 plus IRR	175.80± 4.37^{ac}	1.16± 0.04^{abc}
S+ plus CCl_4 plus IRR	144.00± 5.45^{abd}	2.13± 0.07^{acd}

Data are represented as means± S.E. (n=5). [a:]Significantly different from control. [b:]Significantly different from CCl_4. [c:]Significantly different from irradiated. [d:]Significantly different from CCl_4 plus irradiation.

As shown in Table 2., the administration of CCl_4 and/ or irradiation resulted in a significant increase ($P< 0.05$) of serum ALT, AST and ALP activities as compared to control values, indicating liver injury. Oral supplementation of S+ induced significant decrease in the activity of these enzymes in CCl_4, irradiated, or dual treated group.

TABLE 2. Changes in serum ALT, AST and ALP enzyme activities of adult male albino rats in different groups.

Groups	**ALT** (U/ L)	**AST** (U/ L)	**ALP** (U/ L)
Control	16.78± 0.45	55.86± 1.24	23.40± 0.81
CCL_4	29.٣2± 1.٣0^{ad}	72.60± 1.43^{ad}	34.90± 0.87^{acd}
S+ plus CCl_4	17.64± 0.50^{bcd}	55.96± 0.85^{bcd}	22.56± 1.09^{bcd}
IRR	28.12± 0.78^{ad}	71.22± 0.98^{ad}	31.08± 0.68^{abd}
S+ plus IRR	19.08± 1.15^{bcd}	58.80± 1.77^{bcd}	25.36± 1.15^{bcd}
CCl4 plus IRR	34.58± 1.44^{abc}	78.70±.66^{abc}	40.4± 1.16^{abc}
S+ plus CCl4 plus IRR	21.76± 0.90^{abcd}	60.10± 1.14^{abcd}	25.38± 1.42^{bcd}

Legends as Table 1.

The results in Table 3 showed that exposure of rats to CCl_4 and/ or γ-radiation induced a significant decrease *(P*< 0.05) in both total T_3 and T_4 and a significant increase (*P*< 0.05) in TSH level compared to control values. Administration of S+ significantly elevated the levels of T_3 and T_4 and normalized TSH level in the treated groups.

TABLE 3. Changes in serum levels of T3, T4 and TSH of adult male albino rats in different groups.

Groups	**T_3** (ng/ dl)	**T_4** (µg/ dl)	**TSH** (µIU/ ml)
Control	91.80± 1.91	5.21± 0.09	0.203± 0.012
CCL_4	77.74± 1.63^{acd}	4.63± 0.11^{ad}	0.288± 0.029^{a}
S+ plus CCl_4	89.02± 1.17^{bcd}	4.96± 0.18^{d}	0.216± 0.011^{bcd}
IRR	63.84± 1.21^{ab}	4.58± 0.12^{ad}	0.310± 0.015^{a}
S+ plus IRR	88.42± 1.29^{bcd}	5.03± 0.08^{cd}	0.232± 0.009^{bcd}
CCl4 plus IRR	63.44± 1.76^{ab}	3.10± 0.08^{abc}	0.328± 0.024^{a}
S+ plus CCl4 plus IRR	79.16± 2.37^{acd}	4.17± 0.25^{abcd}	0.236± 0.019^{cd}

Legends as Table 1.

Table 4. showed a significant decrease (*P*< 0.05) in glucose level after exposure to both CCl_4 and γ-rays as compared to control value. Oral supplementation of S+ significantly increased (*P*< 0.05) the glucose level in this group. Whereas, non-significant changes were observed in glucose level in the other groups. A significant elevation (*P*< 0.05) in triglycerides level was recorded in all groups exposed to CCl_4 and/ or γ-rays, compared to control value. Exposure to CCl_4 alone or combined with irradiation induced a significant increase (*P*< 0.05) in cholesterol level. Oral supplementation of S+ significantly decreased (*P*< 0.05) cholesterol and triglycerides levels in these groups to near normal values.

TABLE 4. Changes in serum cholesterol, triglycerides and glucose levels of adult male rats in different groups.

Groups	**Cholesterol** (mg/ dl)	**Triglycerides** (mg/ dl)	**Glucose** (mg/ dl)
Control	69.40± 2.50	83.80± 3.06	124.60± 3.54
CCL_4	79.00± 2.85[a]	95.80± 4.13[a]	117.00± 4.05[cd]
S+ plus CCl_4	70.80± 3.02[d]	85.00± 3.02[bcd]	121.20± 4.86[cd]
IRR	78.00± 2.٩8	99.80± 3.26[a]	135.80± 5.28[bd]
S+ plus IRR	76.80± 4.35[d]	85.64± 2.78[bcd]	130.00± 4.65[bd]
CCl4 plus IRR	86.40± 2.29[a]	101.80± 1.85[a]	93.80± 1.66[abc]
S+ plus CCl4 plus IRR	77.80± 2.56	90.64± 2.65[cd]	115.80± 5.85[cd]

Legends as Table 1.

Discussion

In this study subcutaneous administration of CCl_4 two times a week for three weeks induced significant elevation in the activity of liver marker enzymes; ALT, AST and ALP. Elevated activities of these enzymes are indicative of cellular leakage and loss of functional integrity of liver cell membrane (Rajesh and Latha, 2004) and damage of hepatocyte cells (Shah and Shah, 2012). The additional findings of the elevated levels of hepatic MDA and decreased GSH content in liver corroborated the hepatic toxicity of CCl_4.

The change in the pituitary-thyroid axis hormones, a decrease in total T_3 and T_4 levels and an increase in TSH may be an outcome of CCl_4-induced hepatotoxicity (Itoh *et al*., 1989, Jatwa and Kar, 2008 and Khan *et al.*, 2011). Significant decrease in total T_3 level was also reported in patients with various hepatic disorders (Moustafa *et al.*, 2009). According to Costa *et al*. (2001), Torlak *et al*. (2007) and Khan *et al*. (2011) serum total T_4 entirely originate from thyroid gland, while more than 80% of total T_3 is produced by deiodination of T_4 in other tissues, especially the liver and kidney through iodothyronine 5'-monodeiodinase enzyme. In particular, the hepatic enzyme is thought to be responsible for the major part of peripheral total T_3 production. It was established that CCl_4-induces liver injuries in rat (Ashry, 2008 and Sreelatha *et al*., 2009), reduction in serum T_3 level could partly be due to the decreased conversion of T_4 to T_3 on account of low activity of iodothyronine 5'-monodeiodinase enzyme (Jatwa and Kar, 2008). Furthermore, T_3 concentration appears to parallel the severity of liver dysfunction (Moustafa *et al.*, 2009). However, injuries of CCl_4 metabolites leading to dysfunction of thyroid cannot be excluded (Khan *et al.*, 2011). It could be suggested that the disturbances in thyroid function or thyroid hormone levels in blood after CCl_4 administration may be secondary to hepatotoxicity of CCl_4.

CCl_4 hepatotoxicity derives from its metabolic activation in the liver. Adewole *et al*. (2007) explained that CCl_4 is metabolized by cytochrome P450 2E1 to trichloromethyl radical (CCl_3^-). The CCl_3^- and its highly reactive derivative, the trichloromethyl peroxyl radical ($Cl3COO^-$), are assumed to initiate free radical-mediated lipid peroxidation leading to accumulation of lipid peroxidation products that causes hepatic and renal injuries. These radicals are capable of initiating a chain of lipid peroxidation reactions by abstracting hydrogen from polyunsaturated fatty acids (PUFA). Peroxidation of lipids, particularly those containing PUFA, can dramatically change the properties of biological membranes at cellular and subcellular levels. These changes lead to hepatocyte destruction and release of intracellular enzymes; ALT, AST and ALP as observed in this study. This phenomenon results in the generation of reactive oxygen species (ROS), (like superoxide anion O_2-, H_2O_2 and hydroxyl radical OH^-). Therefore, the elevation of hepatic lipid peroxidation observed in this study could be an outcome of CCl_4-induced cellular damage. It could also be due to the decreased GSH level as observed in this study as well as endogenous antioxidant enzymes, SOD, CAT and GPX (Ashry, 2008 and Chiu *et al*., 2012). The decreased GSH level after CCl_4 administration might be due to its increased utilization by the hepatocytes in scavenging toxic radicals of CCl_4 (Bhadauria *et al*., 2008). On the other hand, ionizing radiation induced lipid peroxidation through the generation of ROS which attack the PUFA constituent of the cell membrane and other cell components (Zahran *et al*., 2006). The increase in ALT, AST and ALP activities in serum-observed in this study reflects an increase of plasma membrane permeability, which may be associated with cell death (Gharib, 2007). In this study, γ-irradiation induced non-significant increase in total cholesterol level and significant increase in triglycerides levels, which runs in agreement with the results of Ashry *et al*. (2009) and Ashry *et al.* (2010). They attributed this increase to the suppression of lipoprotein lipase activity that reduces the uptake of lipids by adipose cells in addition to decreased fatty acid oxidation and increased rate of cholesterol biosynthesis in the liver and other tissues.

The thyroid status disturbance-observed after irradiation-seemed to be due to both inhibited T_4 and T_3 biosynthesis in thyroid and disturbed hormone peripheral metabolism under radiation exposure (Nadol'nik *et al.*, 2004).

Consequently, TSH level in serum increased - as observed in this result-in order to activate the thyroid gland to increase its production of T_3 and T_4 (Abdel Fattah *et al.*, 2003). From the above results, the extent of liver damage and thyroid hormone disturbances upon simultaneous CCl_4 and radiation exposure is greater than that caused by each of them alone.

The significant decrease in glucose level observed in this work can be discussed on the bases that, thyroid hormones stimulate almost all aspects of carbohydrate metabolism, decreasing of these hormones under the effect of free radicals generated from xenobiotics reduced hepatic glucose uptake (Arai *et al*., 2010). Moreover, studies have demonstrated decreased hepatic glycogen content after treatment with CCl_4 (Morsy *et al*., 2002 and Muriel *et al*., 2001), reflecting decreased gluconeogenesis by the liver (Althnaian *et al*., 2013). Furthermore, hypoglycaemia was observed previously in liver cirrhotic rats (Mion *et al*., 1996). As well as, all aspect of fat metabolism are also enhanced under the influence of thyroid hormones. Decreases of thyroid hormones secretion increase the plasma concentration of cholesterol and triglycerides and almost always cause excessive deposition of fat in the liver as well. In addition intracellular T_3 acts as an antioxidant by reducing ROS accumulation through producing the NADPH required for regeneration of reduced GSH, a potent endogenous antioxidant (Moustafa *et al*., 2009).

Oral supplementation of S+ during exposure to CCl_4 and/ or γ-rays ameliorated the disturbances in oxidative stress in liver tissue and decreased the activity of liver enzymes and consequently modulated the disturbances in pituitary-thyroid axis hormones, decreased cholesterol and triglycerides and increased glucose levels in serum. This ameliorating effect of S+ observed in this study is attributed to its components; mainly silymarin which have the ability to reduce membrane permeability and restore impaired liver function (Ozturk *et al*., 2012), acetyl cysteine which exerts its hebato-protective effect by counteracting accumulated ROS in the liver through its antioxidant properties and a GSH precursor (Liu *et al*., 2007), zinc which plays an important role in treatment of liver injury due to its catalytic, structural and regulatory role in a large number of enzymes (Fatimah and Mahboob, 2012), vitamin C which is a major water-soluble antioxidant is believed to decrease lipid peroxidation either directly or indirectly by regenerating vitamin E (Adikwu and Deo, 2013), vitamin E which prevents ROS damage in PUFA as a liposoluble antioxidant acting against damage caused to phospholipids as a membrane-stabilizing agent (UBOH *et al*.,

2012). The ameliorating effect of S+ on thyroid hormones may be due to the activation of 5'-deiodinase enzyme in the liver which stimulates conversion of T_4 to T_3. It is well known that deiodinases contain Se in the form of the amino acid selenocystein located at their active sites, so injection of an antioxidant drug including Se may cause changes in deiodinases activities (Abdel-Fattah *et al*., 2003). Also vitamin E, a lipid soluble antioxidant in the cell membrane, could increase the release of stored T_4 through the membrane of thyroid cells into the blood (Abdel-Fattah *et al*., 2003). The benefit of S+ might be attributed to the synergistic effect of the antioxidants content therein which act as free radical scavengers and lipid peroxidation inhibitor, acting thus to prevent the membrane permeability changes especially those of the hepatocyte membrane transport, thereby improving the xenobiotics induced changes in liver function.

According to the results obtained in the current study, oxidative damage resulting from the metabolism of CCl_4 in the liver as well as exposure to γ-ray exhibit the same effect on liver and pituitary-thyroid axis hormones. As well as, exposure to CCl_4 and ionizing radiation exert a synergistic effect on liver injury associated to a hypothyroid state. Treatment of liver injury by hepato-protective drug S+ modulated liver function and consequently modulated the disturbances in pituitary-thyroid axis hormones.

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(Received: 27/10/2013;

accepted: 08/12/2013)

اضـطرابات هرمونـات محـور النخاميـة-الدرقيـة فـي الجـرذان المعرضة لرابع كلوريد الكربون أو اشعة جاما

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قسم بحوث البيولوجيا الاشعاعية ، المركز القومي لبحوث و تكنولوجيا الإشعاع ، ص. ب. ٢٩ مدينة نصر ، مصر.

يهدف هذا البحث الى دراسه الاضطرابات التى تحدث في هرمون الغدة النخامية المحفز لافراز الغدة الدرقية و كذلك هرمونات الغدة الدرقية- الترای أيودوثيرونين و الثيروكسين- في ذكور الجرذان المعرضة لاصابة الكبد بمادة رابع كلوريد الكربون مع/ أو التعرض لاشعة جاما ومعالجة هذه الاضطرابات بتجريع الجرذان علاج واقى للكبد. وقد تم حقن الجرذان برابع كلوريد الكربون ١مجم/كم من وزن الجسم مرتين اسبوعيا و لمدة ثلاثة اسابيع مع/ أو التعرض لأشعة جاما المجزأة بجرعه قدرها ١ جراى مرتين اسبوعيا و لمدة ثلاثة اسابيع. وقد أدى ذلك الى زيادة مستوى المالوندای الدهايد مصحوبا بنقص فى مستوى الجلوتاثيون فى الكبد. و قد ارتبط بالاجهاد التأكسدى الناتج عن الاشعاع زيادة فى الانزيمات داله على تلف وظيفة الكبد (االاسبارتيت ترانس امينيز والانين امينوترانسفيراز وانزيم الفوسفاتيز القاعدى) وكذلك أدى الي نقص فى هرموني التراى أيودوثيرونين و الثيروكسين في الدم بينما أدى الى زيادة فى هرمون الغدة النخامية. كما لوحظ زيادة فى مستويات كل من الكوليسترول الكلى والدهون الثلاثيه ونقص فى مستوى الجلوكوز. وقد أدى تجريع الجرذان عقار السيليمارين الزائد الى تحسن هذه الاضطرابات. نستخلص من هذه النتائج أن التعرض للملوثات البيئية الكيميائية أو الاشعاعية يؤدى الى تلف الكبد مع اضطرابات فى هرمونات الغدة الدرقية فى الدم و أن تجريع الجرذان عقار السيليمارين الزائد يؤدى الى تحسن هذه الاضطرابات.