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Age-related changes in microsome-dependent conversion of T_4-T_3, thyroid function and cadmium toxicity in albino rat.

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Abstract

The impact of age on microsomal function, manifested by its ability to convert thyroid hormone thyroxine (T_4) to triiodothyronine (T_3), was investigated using four age groups of rats (3, 9, 15 and 24-months). The data show impaired microsomal function with advancing age represented by a significant decrease in serum levels of T_3 and T_3/T_4 ratio. There was a decline in the liver glutathione (GSH), total proteins and serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyl transpeptidase (γGT). There was an-age associated increase in liver content of the lipid peroxidation products, thiobarituric acid (TBA)-reactants and the serum total protein.

Tolerance to cadmium toxicity at old age was investigated using adult (9 months-old) and senile (24 month-old) rats. Each animal of both groups was injected with 5 mg/kg $CdCl_2$, their controls were injected with distilled water. A higher susceptibility of senile rats to cadmium toxicity was manifested as a significantly higher decrease in their serum T_3 level and T_3/T_4 ratio than adult compared to control. A reduction in the adaptive response of senile animals was manifested by a less increase in hepatic GSH in senile than adult as compared to control. The level of hepatic TBA-reactants was significantly higher in treated than in control group. The increase was more pronounced in the senile group. A marked hepatic cellular damage indicated by an increase in the serum levels of the AST and ALT was more pronounced in senile compared with adult rats. Treatment resulted in a decrease in the serum γGT and liver triglycerides (TG). The decrease in both parameters was more evident in senile as compared to adult group.

Key words:

Introduction

As nations become progressively more industrialized, the incidence of overweight, non-insulin dependent diabetes mellitus (NIDDM), and related metabolic disorders has been shown to increase especially at old age. Along with those changes, the metabolic and pathophysiologic sequelae related to those disorders become more common (Tulp and DeBolt, 1999). Aging is associated with progressive decline in the normal dietary and metabolic responses to diet and environment (Tulp and DeBolt, 1999). The aging-associated decline in the above variables may be further complicated by disturbance in the normal metabolism and action of thyroid hormones, particularly T_3 (Wallace & Hofmann, 1998; Tulp & DeBolt, 1999 and Shinohara *et al.,* 2000). However, the basis of these changes is unclear. The importance of studying the age–associated abnormalities of thyroid hormones stems from the fact that age-associated deterioration in thyroid function is directly linked to the decline in the ability of old organism to adapt to

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environmental circumstances. Moreo - ver, thyroid dysfunction in aging has serious consequences: e.g. hypercho - lestrolemia (kanaya *et al*., 2002), Chronic renal failure (Valdes *et al*., 2002) and cardiovascular symptoms (Cheviot *et al*., 1997). Thus the impact of these physiologic changes of aging may impart significant alterations on the efficiency of energy metabolism, which in turn may contribute to some of the pathophysiologic changes associated with longevity, and could influence nutritional indices in affected individuals. What biochemical events are responsible for the physiological deterioration, which accompanies old age? Resolution of this fundamental issue of gerontology may provide a unique opportunity to determine the sequence of events that are responsible for a broad spectrum of senescent changes. This may provide a unique opportunity to deduce a sequence of cellular events, which are responsible for a particular age-dependent change, and to determine its relevance to aging per se. It is within this framework that the current study was undertaken to elucidate the mechanism through which aging may ultimately affect thyroid function.

Additionally, environmental pollutants have a strong impact on the adaptability of old organisms to environmental circumstances (Fujita, 1992). Cadmium is one of the most potent environmental pollutants. It is linked to a number of health problems (Fujita, 1992; Stressing *et al*., 1999 and Moustafa *et al*., 2000, 2001a, b). Cadmium toxicity has been reported to be both age and gender-dependent (Martin *et al*., 1999). In a population of women, both cadmium concentration, and cadmium/zinc ratio increase with age. This indicates that zinc does not increase in proportion to cadmium. The declining zinc/cadmium ratio was suggested to give an explanation for the increased incidence of hypothyroidism with age (Fiala *et al*., 1998). It has also been reported that cadmium is associated with, and probably causes bone demineralization, decreased bone density in women, and decreased height in men (Stressing, 1999). In postmen - opausal women, a twofold increase in urinary cadmium was correlated with a marked decrease in bone density. Even at a low degree of environmental exposure, cadmium may promote skeletal demineralization, which may lead to increased bone fragility and raised risk of fractures (Stressing, 1999). Fujita (1992) explained that osteoporosis, a phenomenon demonst - rated in older smokers, especially women, may be due to the interference of cadmium with the action of the thiol group, therefore, it may interfere with the metabolism of vitamin D, and possibly the conversion of cholesterol into the steroid (sex) hormones. These findings clearly indicate the importance of determining the mechanism(s) of cadmium toxicity in aged thyroid which could open the way to new interventions aimed at halting the progression of age associated thyroid dysfunction and reducing the hazards of Cadmium exposure, especially at old age.

Thus the aim of the present study was two fold: first to through more light on the mechanisms underlying the aging associated thyroid dysfunction. Second to determine the mechanism mediating the poor resistan ce of old individuals to cadmium, which is one of the most potent environmental pollutants?

Material And Methods

Animals

Male Sprague-Dawley rats obtained from the National Research Center, Cairo, Egypt were used for all

experiments. Animals were raised on a standard chow mix with free access to both food and water. For age studies, four age groups of rats (3, 9, 15 and 24-month age groups), with five rats in each, were established.

For $CdCl_2$ & age studies, rats were assigned into two groups: a. adult (9 months age), b. Senile (24-month old). Each group was then divided into two sub groups: control and $CdCl_2$-treated groups each including five animals. $CdCl_2$-treated rats were treated i.p with 5 mg/kg b.wt $CdCl_2$. Rats served as control groups received only the liquid vehicle. The experiments were terminated 24 hours after $CdCl_2$ administration. In this part of the study comparisons were made between adult and senile rats, since earlier studies (Fink *et al.,* 1968; Moustafa *et al.,* 1995 and Moustafa, 1997b) emphasized the importance of avoiding comparisons between young and senile animals in order to discriminate between aging and maturational changes.

Methods

At the specified time prior to sample collection, rats were lightly anesthetized with ether and blood samples were then collected from the orbital sinus and serum was prepared and frozen at -20º C until used for analysis. The rats were sacrificed by decapitation and livers were rapidly excised, rinsed in saline and quickly weighed.

The tissue homogenate (100 mg tissue/ml) was used for the determination of the liver content of total proteins and triglycerides. Serum and liver homogenate samples were analyzed in the Clinical Pathology Laboratory of the Faculty of Medicine, Suez Canal University, using a Hitachi 704 auto-analyzer for the determination of total proteins and triglycerides, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyl transpeptidase (γGT) . T_3 and T_4 serum concentrations were measured by radioimmunoassay using Dslabs kits (catalog Nos: DSL-41100 & DSL-40100 for T_3 & T_4 respectively).

Four parts of 0.15 M KCl_2 were added to liver specimens for the determination of GSH as described by Tieze (1969).

For the estimation of the liver content of thiobarbituric acid (TBA)-reactants, liver homogenates, 10 % w/v in cold water, were used. The level of liver TBA-reactants was determined according to the method of Uchiyama and Mihara (1978).

Data analysis

Data was statistically analyzed by using Student's T-test and regression analysis. Accepted level of significance was at $P \leq 0.05$.

Results

Values of serum thyroid hormones (T_3 & T_4) and T_3/T_4 ratio in different age groups are shown in fig. 1. Serum T_3 and T_3/T_4 ratio were significantly reduced with age ($P = 0.004$ and 0.0315 for T_3 and T_3/T_4 respectively). A high correlation coefficient ($r = -0.949$ and -0.919 for T_3 and T_3/T_4 respectively) was seen between these parameters and rat's age.

The GSH content of the liver declined significantly with advancing rat's age ($P = 0.03$). The decline in GSH content of the liver significantly correlated with age ($r = -0.94$). (fig. 2)

In the present study, the lipid peroxidation products (TBA-reactants)-content of the liver markedly increased as a function of increasing rat's age ($P = 0.0003$) and significantly correlated with this age ($r = 0.857$). (fig.2)

The liver total protein concentration was significantly affected by age (P = 0.001). There was an initial and a highly significant decrease in liver total proteins of 9month-old compared to 3-month-old rats (P = 0.001). After that the total proteins gradually and slightly increased in the livers of 15 and 24months-old rats. The age-associated decrease in the liver total proteins was accompanied with a gradual increase in the serum total proteins that was significantly affected by age (P = 0.00029), and highly correlated with it (r = 0.9780) (fig. 3).

The level of serum enzymes AST, ALT and γGT were significantly affected by age (P= 0.008, 0.0017 and 0.007 for AST, ALT and γGT respectively). The serum level of the three enzymes decreased with age except for ALT that showed a significant increase in the 9month-old rats compared with the 3month-old rats, afterwards, it showed a gradual decrease in the ages 15 and 24 months. A significant correlation coefficient was observed between age and the serum level of γGT enzyme (r = - 0.951) (fig. 4).

Effect of age on $CdCl_2$ Toxicity

Age-related changes in serum thyroid hormones in $CdCl_2$-treated rats are shown in table 1. $CdCl_2$-treatment caused a significant decrease in serum T_3 level in adult as well as in old rats. Non-significant changes were observed in serum T_4 levels due $CdCl_2$ in both groups. The T_3/T_4 ratio was decreased significantly in both groups following $CdCl_2$-treatment. The percent decreases in T_3/T_4 was 20.585 % for adult and 53.106 % for old group.

The current data (table 2) show that hepatic GSH content increased in response to $CdCl_2$ treatment in both adult and old groups. While this increase was 73 % (P = 0.0103 control Vs treated) in the adult group, it was only 12.927 % (P = 0.47 control Vs treated) in the old group.

$CdCl_2$-treatment resulted in a significant increase in hepatic TBA-reactants in both adult and old groups (P = 0.043, 0.038 control Vs treated for adult and old groups respectively). This increase was more pronounced in the senile group, as the percent change relative to the control level was 16.531% in the adult group while it was 70.678 % in the senile group. (table2).

Severe hepatic cellular damage was seen in old $CdCl_2$-treated rats compared with that in the adult group. This was manifested as an increase in the serum levels of the AST and ALT enzymes in adult and senile groups following $CdCl_2$ treatment. The increase in serum AST level over control level was 7.86 % in the adult–treated group (P= 0.337) while it was 73.566 % (P = 0.00057) in the senile group. Moreover, the increase in serum ALT level was 19.048% (P = 0.1) over control level in the adult-treated group, while it was 261.628 % (P = 0.009) in the senile group. The increase in serum AST and ALT enzymes after $CdCl_2$ was accompanied with a decrease in the serum level of γGT enzyme in the adult and senile groups. This decrease was more evident in the senile group. The percent decrease of serum γGT level was 2.913 % in the adult-treated group (P = 0.651 control Vs treated) while it was 50.037 % (P = 0.004) in old rats (table 2).

The liver content of triglycerides (TG) was reduced due to CdCl2-treatment in both adult and old rats. The decline in liver TG was 34.579 % of the control level in the adult rats. This decline was 73.6211% (P = 0.0006) in the senile rats (table 2).

Table 1. Serum levels of triiodothyronine (T_3), thyroxine (T_4) and T_3/T_4 ratio in control and $CdCl_2$-treated groups of adult (9 months-old) and senile (24-month-old) rats.

Parameter	Adult			Senile		
	Control	$CdCl_2$	% change	Control	$CdCl_2$	% change
T_3 (ng/dl)	94.75 ± 10.45	50.667 ± 7.88*	- 46.53	67.167 ± 5.68	26.333 ± 0.333*	- 60.795
T_4 (µg/dl)	4.7± 0.404	3.667±0.384	- 21.978	4.103±0.233	3.646±0.652	- 11.114
T_3 / T_4	19.393±3.78	15.401±1.25	- 20.585	16.563±2.141	7.767±1.547*	- 53.106

Treated rats were injected with $CdCl_2$ (5 mg/kg) (i.p). Rats were sacrificed 24 hours post treatment. Results are given as mean ± SE of five rats in each group. * $P \leq 0.05$ control versus treated.

Table 2. Changes in liver and serum parameters in control and $CdCl_2$-treated groups of adult (9 months-old) and senile (24-month-old) rats.

Parameter	Adult			Senile		
	Control	$CdCl_2$	% change	Control	$CdCl_2$	% change
GSH (µg/g)	10389.19 ± 1854..981	18046.84 ± 1414.155*	73.708	13938.74 ± 1261	15740.54 ± 1872.486	12.927
TBA	0.0369 ± 0.0018	0.043 ± 0.002*	16.531	0.0457 ± 0.0067	0.078 ± 0.008*	70.678
Triglycerides(µg/g)	42.8 ± 2.177	28 ± 1.759*	- 34.579	417 ± 23.671	110.333 ± 5.897*	- 73.6211
γ-GT (U/L)	3.433 ± 0.145	3.533 ± 0.150	2.913	1.333 ± 0.333	2 ± 0.577	50.037
AST (U/L)	152.667 ± 9.023	140.67 ± 6.333	-7.860	104.7 ± 2.848	181. 66 ± 7.219*	73.566
ALT (U/L)	35 ± 2.828	41.66 ± 0.333	19.048	28.67 ± 1.453	103.666 ± 16.169*	261.628

Treated rats were injected with $CdCl_2$ (5 mg/kg) (i.p). Rats were sacrificed 24 hours post treatment. Results are given as mean ± SE of five rats in each group. * $P \leq 0.05$ control versus treated.

Figure (1)

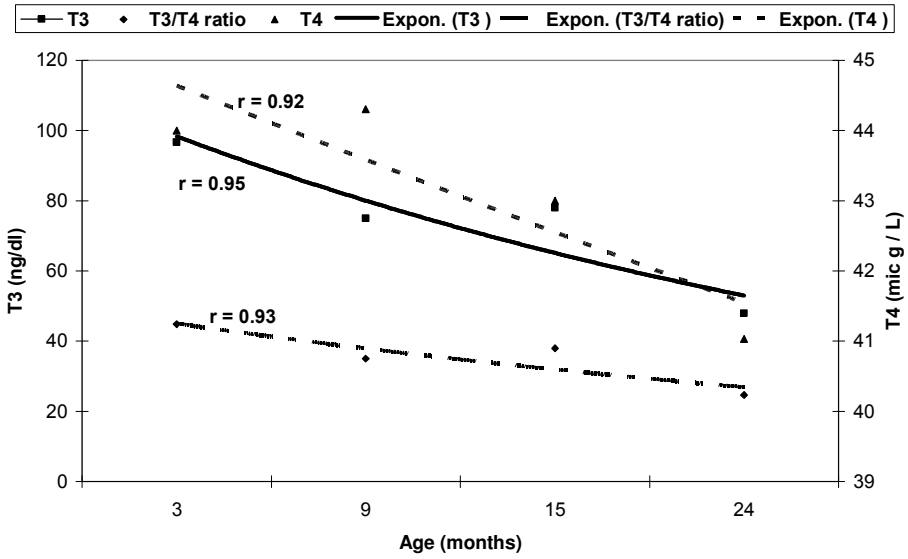

Fig. 1. Changes in the serum levels of T_3 & T_4 and the T_3/T_4 ratio in rats of different ages. Each point represents the mean ± SE of 5 rats. * Significantly affected by age.

Figure (2)

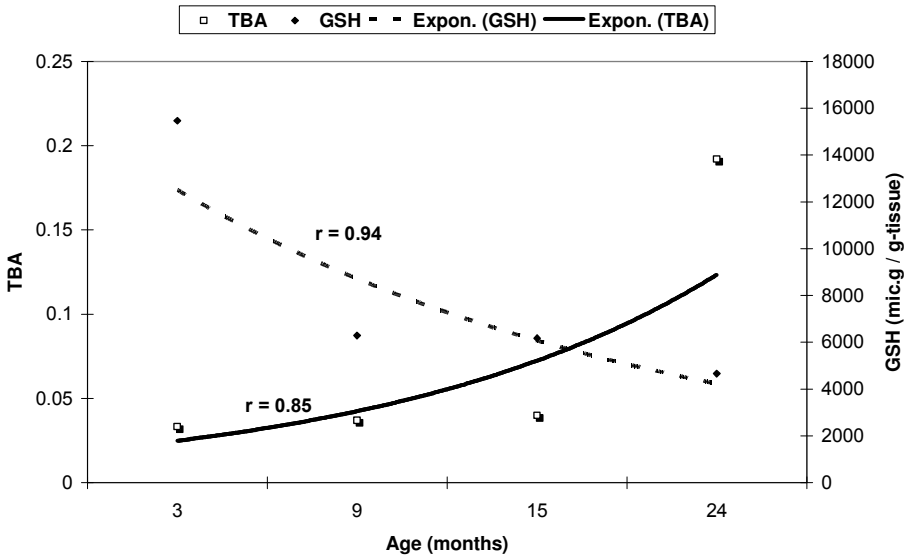

Fig. 2. Changes in liver GSH and TBA contents in rats of different ages. Each point represents the mean ± SE of 5 rats. * Significantly affected by age.

Figure (3)

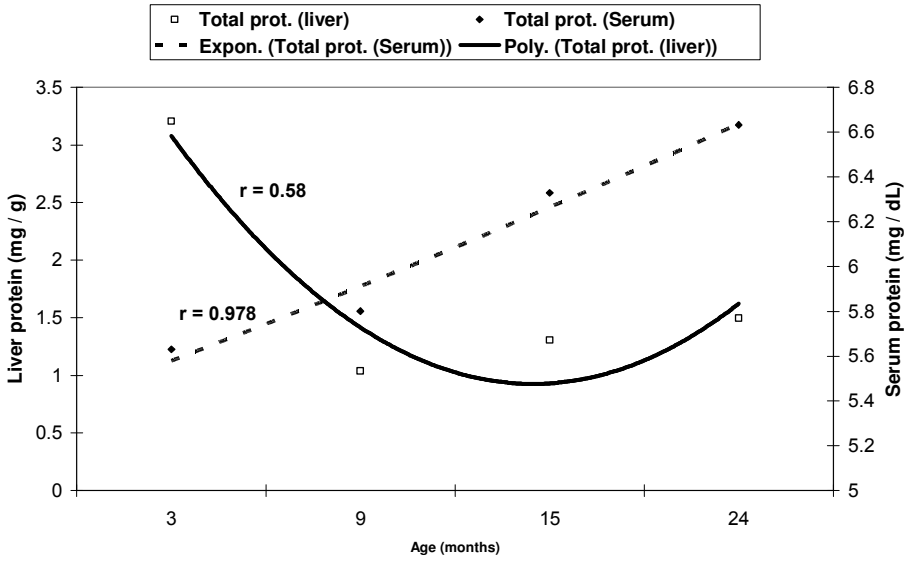

Fig. 3. Changes in the liver and serum concentrations of total proteins in rats of different ages. Each point represents the mean ± SE of 5 rats. * Significantly affected by age.

Figure (4)

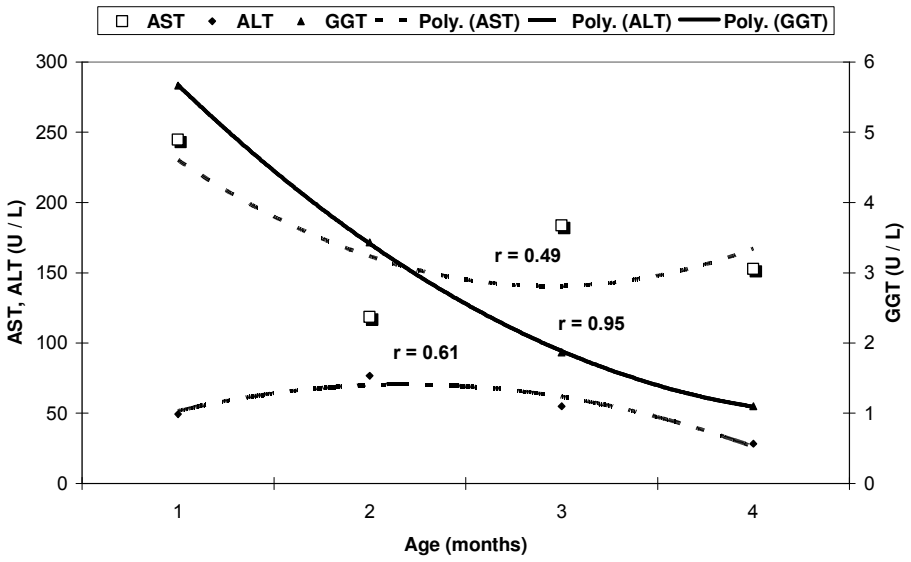

Fig. 4. Changes in the serum levels of AST, ALT and γ GGT enzymes in rats of different ages. Each point represents the mean ± SE of 5 rats. * Significantly affected by age.

Discussion

It has become increasingly evident that biological aging is expressed at the molecular level by an age-dependent modification in the susceptibility of certain hormones to nutritional and environmental changes (Tulp and DeBolt, 1999). Among these hormones are thyroid hormones (Stressing, 1999). The aging thyroid is associated with a number of morphological and functional changes, such as decreased serum T_3 and mean thyroid-stimulating hormone concentrations that are to some extent independent of intercurrent non-thyroidal illnesses (Cheviot *et al*., 1997; Mikkelsen *et al*., 2001 and Kanaya *et al*., 2002). The results of the current study extend and confirm these findings, since they indicate that aging is associated with progressive decline in the normal serum T_3 levels and T_3/T_4 ratio. Earlier studies pointed out that patients with a wide range of liver diseases as well as intoxication with CCl_4 and $CdCl_2$ show subnormal levels of serum T_3, reflecting the impaired microsomal conversion of T_4 to T_3 (Itoh *et al*., 1986,1988 &1989 and Moustafa, 1997a, 2001a, b). Oxidative stress appears to be a common mechanism initiating this defect. It seems that oxidative stress is also the mechanism accounting for the aging associated decrease in both, serum T_3 and the T_3/T_4 ratio. The free radical theory of aging postulates that free radicals are the underlying cause of aging (Harman, 1981 and Kowald, & kirkwood, 1994). GSH is one of the most important endogenous antioxidants that neutralize free radicals (Wilson, 1997). The present study indicates the existence of an age-associated decrease in hepatic GSH that highly correlates with age (R= -0.94). These findings support previous reports indicating an aging-associated decline in the GSH content of the tissues in different species (Hazelon & Lang, 1980). The broad significance of this aging decrease in GSH is exemplified by the central role GSH plays in a variety of metabolic processes. Thus decreased GSH concentrations could alter many important functions: maintenance of SH groups of proteins and small molecules, biosynthetic reaction, membrane and cellular integrity, and detoxification of peroxides and xenobiotics (Hazelton and Lang, 1983). Among the protein molecules that GSH is necessary for the maintenance of their SH groups, are endoplasmic reticulum (ER)-linked group of enzymes that catalyze the conversion of T_4 into T_3 which are deiodenase and cytochrome P450 (Viarengo, 1989; Itoh *et al.* 1988a, and Yamagishi *et al.,* 1994). Therefore, the aging-associated decrease in hepatic GSH may contribute to the age-related decline in the capacity of aged tissues to convert T_4 to T_3. This effect could be mediated via the inactivation of the enzyme system concerned with this process, which depends on GSH for keeping their structural and functional integrity. Moreover, the depletion in GSH in aged tissues may render them more susceptible to free radical attacks that could be manifested in the increased rates of their lipid peroxidation levels. Free radicals-induced lipid peroxidation on microsomal membranes was suggested to be the mechanism underlying the impaired microsomal conversion of T_4 to T_3 under different pathological states (Itoh *et al.,* 1988a, 1989 and Moustafa, 1997a, 2001a,b). It is plausible to suggest that lipid peroxidation on microsomal membranes could be a major mechanism underlying the

impaired T_4 conversion to T_3 in aged rats. Since the current results reveal that aging correlates with a progressive increase in hepatic lipid peroxidation products content (TBA- reactant) (R = 0.859). In addition to the reduced levels of GSH in aged tissues, a reduction in the concentrations of alpha-tocopherol in the old rats was reported in the hypothyroid state (Shinohara *et al*., 2000). Indeed, the study of Shinohara *et al*., (2000) indicates that as rats age, the reduction of the free radical scavenger system and the increase in lipid peroxidation accompanies thyroid dysfunction which might induce myocardial dysfunction. In the current study, microsomal dysfunction in aged rats appears to be marked by two observations: first the decrease in the plasma level of the microsomal enzyme γGT that highly correlates to aging (r = -0.95148). Zilva *et al.,* (1987) reported that the plasma levels of γGT is related to the synthetic capacity of the microsomes and that the increase in the plasma level of γGT may reflect an enhanced capacity of the microsomes to synthesize this enzyme even without disease or cell damage. Second impaired cellular synthetic capacity, that accompanies aging, is revealed by the reduced hepatic levels of total proteins that was accompanied by the increase in their serum levels. The increase in serum total proteins that accompany aging may be due to an increase in the γ-globulin fraction since aging was reported to be accompanied with the decreased albumin production by the liver resulting in relative hyperglobulinaemia to maintain plasma osmotic pressure (Lowseth *et al.,* 1990 and Moustafa, 1997b). Additionally, A decrease in serum AST & ALT was seen with advancing age, which correlates with previous findings of Moustafa (1997b). This decrease was interpreted by the possible decrease in the synthetic capacity of the two enzymes by aged tissues.

Recent studies have lent further support to the impact of cadmium as a potent environmental pollutant affecting the biological activity of almost all organ and body systems (Fujita, 1992; Stressing *et al*., 1999 and Moustafa *et al*., 2000). Cadmium has been found to accumulate in the thyroid tissue with relatively high concentration (Falnoga, 2000). The study of Yoshizuka *et al.* (1991) showed that cadmium damages the cells of the thyroid, reduces thyroglobulin-producing cells, and decreases both serum T_4 and T_3. The current study reveals that old rats responded differently to Cd^{++} intoxication, as compared to adult rats, concerning thyroid function. The T_3 as well as T_3/T_4 ratio were significantly less in both age groups following $CdCl_2$ treatment relative to their controls. However, the percent decrease in both T_3 and T_3/T_4 ratio after $CdCl_2$ treatment was more evident in the senile rats when compared with adult rats. This indicates the severity of the impaired capacity of the old animal microsomes to convert T_4 to T_3 as compared to adults under Cd^{++} intoxication. It has been reported that the low serum T_3 or the T_3/T_4 ratio in patients with acute liver disease are explained by a decreased function of the microsomal enzyme T_4-5'-deiodenase (Itoh *et al*., 1988). T_3 or T_3/T_4 ratio has been found to correlate significantly with this and other liver microsomal enzymes such as carboxylestrase in CCl_4-treated rats (Itoh *et al*., 1989).

The data presented show an increase in liver GSH content in $CdCl_2$-treated rats, however this increase was less pronounced in old rats. The increase in GSH in cadmium-intoxicated rats has previously been

reported (Moustafa, 2002). This increase has been interpreted to be an adaptive response for $CdCl_2$-induced cytotoxic damage (Moustafa, 2002). It is conceivable that during senescence, there is an inability to resynthesize GSH rapidly after depletion via xenobiotics (Hazelton and Lang, 1983) and this could lead to tissue damage. Moreover, it has been shown that cadmium toxicity effects are mediated by decreases in selenium and glutathione peroxidase *(*Long *et al*., 1998). Indeed, the study of Hazelton and Lang (1985) reported an aging-associated decrease in the activities of GSH peroxidase and GSH reductase which would eventually lead to the impaired detoxification capacity via GSH peroxidase and GSH reductase in senescence. The diminished efficiency of GSH synthesis and GSH peroxidase activity of aged tissues in response to $CdCl_2$ intoxication may explain the enhanced lipid peroxidation increase in the livers of aged $CdCl_2$ intoxicated rats as compared to the livers of their adult counterparts. This enhanced lipid peroxidation may account for the marked reduction in the microsomal conversion of T_4 into T_3 in aged intoxicated rats compared with adults. Another mechanism mediating the severity of thyroid dysfunction in aged rats poisoned with Cd^{++} is the disturbance in the Cd^{++} / Zn^{++} balance in these rats. The T_3 receptor is thought to require zinc to adopt its biologically active conformation (Freake *et al*., 2001). Some of the effects of zinc deficiency, therefore, may be due to loss of zinc from the T_3 receptor and impairment of T_3 action.. Cd^{++} has been reported to antagonize Zn^{++} action (Predki and Sarkar, 1992). It has been suggested that the mechanism by which cadmium antag - onizes zinc may be from its ability to substitute for zinc in the zinc finger DNA binding domain and this may be the way cadmium causes toxicity and cancer (Predki and Sarkar, 1992). It has been reported that cadmium concentr - ations increase with age and the cadmium/zinc ratio increases with age indicating that zinc does not increase in proportion to cadmium. This declining zinc/cadmium ratio could be an expla - nation for increased incidence of hypothyroidism with age (Fiala, 1998). The enhanced toxicity of Cd^{++} in old rats which led to the marked decline in the ability of their tissues to convert T_4 to T_3 may also be explained in the light of the findings of Luce *et al*, (1993) who pointed out that in human diploid fibroblasts old cells were more sensitive to the toxic effects of $CdCl_2$ than young cells and that the rate and extent of induction of metallothinein (MT) by $CdCl_2$ was reduced in old cells. This study showed that the changes in MT protein levels occurred in parallel with changes in mRNA levels, which implicates transcriptional control as the origin of these aging changes. However, the study of Shimizu and Morita, (1990) suggests that hepatic GSH plays an important role in protection against Cd^{++} toxicity before the onset of MT synthesis and that animals in bad condition, such as that resulting from interruption of nutrient supply, cannot be protected against Cd^{++} toxicity even if the hepatic MT level is high. Based on the findings of this study the current results show the deterioration of GSH increase in response to Cd^{++} intoxic - ation in aged rats, clearly indicate the impact of GSH deficiency on the impairment T_4 conversion into T_3 in aged tissues and on the poor resistance of these tissues against damage caused by oxidative stress-induced by $CdCl_2$. One of the manifest -ations identifying the importance of GSH in the protection against Cd^{++} -induced tissue damage are

the current data which show that Cd^{++} induces a decrease in liver triglycerides in both adult and old groups. However, this decrease was more evident in the old group. This could be interpreted based on the study of Fujita, (1992) which indicates that Cd^{++} may inhibit lipogenesis by binding with SH of coenzyme A, thereby, reducing the serum levels of free fatty group. The aging- associated decline in GSH tissue content may contribute to the diminished ability of aged tissues to replenish the consumed SH of coenzyme A under Cd^{++} toxicity.

The study of Cizza *et al*. (1995) documented an age-dependent decline in the adaptive response of the hypothalamus to stress in Fischer rats and that this phenomenon is behind the stress-induced decrease in plasma thyroid-stimulating hormone which is in part mediated at the level of the hypothalamic thyrotrophin-releasing hormone neuron and that this phenomenon is attenuated in the aged rats. In support to these findings, the present results indicate an augmented increase in the serum AST, ALT and γGT in old rats following $CdCl_2$ intoxication compared with adults. This reflects the increased sensitivity of these rats to the oxidative stress-induced tissue damage caused by cadmium intoxication.

A greater understanding of mechanisms of impaired energy metabolism and energy balance in aging may provide new insight into the nutritional factors that may contribute to obesity in aging, their modulation, and the emergence of a longer, healthier lifestyle. Moreover, the current study suggests that supplementation with antioxidants especially zinc can offer an achievable and inexpensive adjunct therapy to help inhibit and halt the progression of aging associated deteriorations both in thyroid function and in the resistance against environmental pollution.

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التغيرات المرتبطة بالتقدم في العمر في مقدرة الميكروزومات علي تحويل T_4 إلي T_3، وظائف الغدة الدرقية وسمية الكادميوم في الجرذان البيضاء.

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في هذه الدراسة تم استخدام أربعة مجا ميع عمريه من الفئران (3، 9,15، 24 شهر) وذلك لإيضاح مدى تأثير التقدم في العمر علي وظائف الميكروسومات (microsoms) وخاصة وظيفتها في تحويل هرمون الغدة الدرقية المعروف بالثيروكسين [thyroxine (T_4)] إلي هرمون ثلاثي يود يد الثيرونين [(T_3) triiodothyronine] وتشير نتائج الدراسة إلي أن نقصا مصاحبا للتقدم في العمر قد حدث في كل من مستوى هرمون T_3 في المصل ونسبة T_3 إلى T_4 (T_3/T_4) و أن ارتباطا معنويا قد لوحظ بين كل من مستوي المصل من هرمون T_3 ونسبة T_3/T_4 و عمر الفئران وهو ما يعكس اختلال وظائف الميكروسومات في العمر المتقدم. وقد لوحظ أيضا أن التقدم في عمر الفئران يكون مصحوبا بالانخفاض في محتوي الكبد من كل من مضاد التأكسد الجلوتاثيون (GSH) والبروتينيات وفي مستوى المصل من إنزيمات أسبرتات أمينوترانسفيراس (AST) و ألانين أمينوترانسفيراس (ALT) وجاماجلوتاميل ترانسبيبتيداس (γGGT) . وقد كان التقدم في العمر مصحوبا بالازدياد في محتوي الكبد من نواتج أكسدة الدهون (TBA-reactants) وفي محتوى المصل من البر وتينات. ولدراسة آلية سمية الكادميوم في الشيخوخة فقد تم حقن مجموعتين عمريتين من الفئران: مجموعة ناضجة (9 أشهر) و مجموعة في مرحلة الشيخوخة (24 شهرا) بكلوريد الكادميوم ($CdCl_2$) بجرعة قدرها (5 مج/ كجم) وقد تسبب الحقن بهذه المادة في النقص المعنوي في محتوي المصل من هرمون T_3 و نسبة T_3/T_4 في كلا المجموعتين العمريتين علي أن درجة انقص كانت أوضح في الفئران المسنة مقارنة بالفئران الناضجة. وهو ما يشير إلي زيادة قابلية الفئران المسنة إلي التسمم بالكادميوم. بالإضافة إلي ذلك فإن الزيادة في محتوى الكبد من ال GSH عقب الحقن بكلوريد الكادميوم كانت اقل وضوحا في الفئران المتقدمة في العمر مقارنة بالمجموعة الأصغر عمرا. هذا وقد كانت الزيادة في محتوي الكبد من ال (TBA)-reactants أكثر حدة في الفئران المسنة نتيجة للتسمم بكلوريد الكادميوم عنها في المجموعة العمرية الأصغر. كما لوحظ أن الزيادة في نشاط إنزيمي AST و ALT (الدليل علي درجة تلف الخلايا) بعد الحقن بكلوريد الكادميوم كانت أشد في الفئران المسنة. كما شملت الزيادة في درجة النقص في الفئران متقدمة العمر نتيجة الحقن بكلوريد الكادميوم كلا من إنزيم γGGT و محتوي الكبد من ثلاثيات الجليسيريد. ويستخلص من الدراسة الحالية أن التقدم في العمر يكون مصحوبا بالاختلال في مقدرة الميكروسومات علي تحويل T_4 إلي T_3 كما لوحظ أيضا زيادة قابلية الفئران المسنة إلي التسمم بالكادميوم و إلي حدوث تلف مضاعف في خلايا الكبد للفئران المتقدمة في العمر نتيجة للتسمم بالكادميوم مقارنة بالتلف الحادث في الفئران الأصغر عمرا. كما تشير الدراسة أيضا إلي ضعف تكيف هذه الفئران لإجهاد الأكسدة.