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Omega-3 Polyunsaturated Fatty Acids Attenuate Radiation-induced Oxidative Stress and Organ Dysfunctions in Rats

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THE AIM of the present study was to determine the possible protective effect of omega-3 polyunsaturated fatty acids **(**omega-3 PUFA) against radiation-induced oxidative stress associated with organ dysfunctions. Omega-3 PUFA was administered by oral gavages to male albino rats at a dose of 0.4 g/ kg body wt daily for 4 weeks before whole body γ-irradiation with 4Gy. Significant increase of serum lipid peroxidation end product as malondialdehyde (MDA) along with the reduction in blood glutathione (GSH) content, superoxide dismutase (SOD) and glutathione peroxidase (GPX) enzyme activities were recorded on 3rd and 8th days post-irradiation.

Oxidative stress was associated with a significant increase in lactate dehydrogenase (LDH) and creatine phosphokinase (CPK) enzyme activities, markers of heart damage, significant increases in uric acid, urea and creatinine levels, markers of kidney damage, significant increases of alkaline phosphatase (ALP) and transaminases (ALT & AST) activities, markers of liver damage. Moreover significant increases in total cholesterol and triglycerides levels were recorded. Omega-3 PUFA administration pre-irradiation significantly attenuated the radiation-induced oxidative stress and organ dysfunctions tested in this study. It could be concluded that oral supplementation of omega-3 PUFA before irradiation may afford protection against radiation-induced oxidative stress and might preserve the integrity of tissue functions of the organs under investigations.

Keywords: Omega-3, γ-rays, rats, liver, heart, kidney.

Exposure to ionizing radiation initiates a cascade of events including oxidative damage that leads to alteration of tissue physiological function (Zhao *et al.*, 2007). Lipid peroxidation is considered to be a critical event of ionizing radiation effect (Agrawal and Kale, 2001).

Most of the toxic effects of ionizing radiation are due to generation of reactive oxygen species (ROS) by radiolysis of water which triggers formation of several reactive intermediates (Adaramoye *et al*., 2011). Therefore, to overcome this oxidant stress, the body is equipped with defence system, including enzymatic and non-enzymatic radical scavengers that can either directly detoxify ROS or indirectly regulate their levels (Sandeep and Nair, 2012). Hence, an over production of ROS leads to uncontrolled chain reactions and lipid peroxidation, resulting in various pathological conditions that may include liver injury (Kotzampassi *et al*., 2009), testicular tissues injury (Adaramoye *et al.,* 2012), lung and kidney damage (Sener *et al.*, 2006).

Omega-3 PUFAs are essential long chain polyunsaturated fatty acids of plant and marine origin. Flax seed is generally a rich source of the omega-3 PUFA alpha linolenic acid. However, docosahexaenoic acid (DHA) eicosapentaenoic acid (EPA) are the predominant omega-3 PUFAs in fish oil.

Omega-3 PUFAs play an important role in the protection of cells against ROS by increasing the activity of antioxidant enzymes (Bhattacharya *et al*., 2007). Moreover, their beneficial effects have been shown in the prevention and management of heart failure (Rupp *et al*., 2012), cardiovascular diseases (Lavie *et al.*, 2009), liver diseases (Kotzampassi1 *et al*., 2009), obesity prevention (Tai and Ding, 2010) and kidney disease (Miller *et al*., 2009). Therefore, the present study was undertaken to investigate the possible radio protective effect of omega-3 PUFAs against oxidative damage associated with some organ dysfunctions namely liver, kidney and heart.

Material and methods

Male albino rats 7± 1 weeks weighing 120-150 g were obtained from the *Egyptian Holding Company for Biological Products and Vaccine, Helwan, Cairo*. Animals were kept under good ventilation conditions and had free access to water and standard pellet concentrated diet.

Radiation facility

Whole body gamma irradiation was performed with a ventilated Canadian ^{137}Cs gamma cell-40 at the NCRRT, Cairo, Egypt at a dose rate of 0.48 Gy/ min. Rats were exposed to 4Gy delivered as a single shot dose.

Omega-3 PUFAs

Omega-3 PUFAs oil was purchased from SEDICO Pharmaceutical Co., Egypt. It was available in the form of capsules containing 1.0 g omega-3 fish oil EPA and DHA. Each rat was orally administered 0.4 g / kg body wt/ day (Erdogan *et al*., 2004) via oral gavages for 4 weeks. Higher doses were found to cause increased lipid peroxidation (Ibrahim *et al*., 2011).

Experimental design

Animals were divided into 4 equal groups each of 5 rats. Control rats; Omega-3: Rats received omega-3 daily for 4 weeks; Irradiated: Rats were whole body exposed to 4Gy γ-rays and Omega-3+ irradiation: Rats received omega-3 for 4 weeks before irradiation at 4Gy. The animals were sacrificed on the 3^{rd} and 8^{th} days post irradiation and/ or Omega-3-treatment.

Biochemical analysis

Animals were lightly anesthetized with ether and blood was collected by heart puncture. The blood content of GSH was determined as described by Beutler *et al*. (1963) whereas SOD and GPX enzyme activities were verified according to Misra and Fridovich (1972) and Paglia and Valentine (1967), respectively. Serum was separated by blood centrifugation at 3000 rpm for estimation of lipid peroxidation indicated by formation of MDA using the method described by Yoshioka *et al*. (1979). LDH and CPK activities were determined according to the method of Henderson and Moss (2001) and Rec (1977), respectively. Uric acid, creatinine and urea contents were determined according to Barham and Trinder (1972), Henry (1974) and Patton and Crouch (1977), respectively. Cholesterol, triglycerides, transaminases; ALT & AST and ALP were determined according to Richmond (1973), Fossati and Principe (1982), Reitman and Frankel (1957) and Belfield and Goldberg (1971), respectively.

Statistical analysis

The SPSS/PC 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 obtained revealed that supplementation of omega-3 PUFAs to normal rats induced a significant increase (P<0.05) of GSH content at 3 days. Irradiation provoked a significant increase (P<0.05) in serum MDA associated with a significant decrease (P<0.05) of GSH content and SOD and GPX enzyme activities, 3 and 8 days post irradiation, compared to control values. Omega- 3 supplementation before irradiation significantly lowered MDA level and increased SOD enzyme activity and GSH content, compared to their respective values in irradiated rats (Table 1).

TABLE. Effect of Omega-3 PUFAs on serum MDA level, blood GSH content, SOD and GPX enzyme activities of rats exposed to gamma irradiation (4Gy).

Groups	Days	**GSH** (mg/dl)	**MDA** (µmol/ L)	**SOD** (U/ ml)	**GPX** (U/ ml)
Control	-	37.80± 2.18^{bc}	58.86± 2.19^{cd}	13.73± 0.31^{c}	5.07± 0.26^{c}
Omega-3	3rd	46.38± 2.90^{acd}	66.24± 3.49^{c}	13.53± 0.39^{c}	4.61± 0.30
	8th	44.90± 3.53^{cd}	68.20± 4.22^{c}	13.59± 0.41^{c}	4.73± 0.35^{c}
Irradiation	3rd	28.22± 2.69^{ab}	95.56± 2.96^{abd}	8.33± 0.58^{abd}	3.86± 0.31^{a}
	8th	24.04± 3.48^{abd}	92.60± 4.73^{abd}	7.79± 0.46^{abd}	3.81± 0.31^{ab}
Omega-3+ Irradiation	3rd	35.04± 2.38^{b}	77.22± 3.60^{ac}	12.35± 0.63^{c}	4.64± 0.30
	8th	36.18± 2.66^{bc}	70.22± 5.09^{c}	12.95± 0.55^{c}	4.65± 0.32

Data are represented as means± S.E. (n= 5). [a]: Significantly different from control, [b]: Significantly different from omega-3, [c]: Significantly different from irradiated, [d]: Significantly different from omega3+ irradiation.

Irradiation induced significant increases (P< 0.05) in serum cholesterol and triglyceride levels, 3 and 8 days post irradiation. Supplementation of omega- 3 before irradiation has no significant effect on cholesterol levels, compared to irradiated values, while ameliorated triglyceride levels on the 3rd and 8th days (Table 2).

TABLE 2. Effect of Omega 3 PUFAs on serum cholesterol and triglyceride levels of rats exposed to gamma irradiation (4Gy).

Groups	Days	**Cholesterol** (mg/ dl)	**Triglycerides (**mg/ dl)
Control	-	86.20± 3.99^{cd}	87.20± 3.17^{c}
Omega-3	3rd	81.20± 3.25^{cd}	79.40± 3.46^{cd}
	8th	80.40± 3.78^{cd}	78.60± 3.71^{cd}
Irradiation	3rd	107.20± 7.55^{ab}	98.40± 4.31^{ab}
	8th	102.40± 6.77^{ab}	100.40± 4.95^{ab}
Omega-3+ Irradiation	3rd	104.80± 4.42^{ab}	92.40± 3.71^{b}
	8th	100.40± 6.36^{b}	92.60± 3.94^{b}

Legends as Table 1.

Significant increases in serum LDH and AST activities were recorded 8 days post irradiation while CPK, ALT and ALP activities showed an increase, 3 and 8 days post irradiation compared to control values. Administration of omega- 3 before irradiation reduced the increase of enzyme activities compared to irradiated values (Tables 3 & 4).

TABLE. Effect of Omega 3 PUFA on serum ALT and ALP enzyme activities of rats exposed to gamma irradiation (4Gy).

Groups	Days	**ALT** (U/ L)	**ALP** (U/ L)
Control	-	19.46± 0.81^{cd}	20.62± 1.54^{c}
Omega-3	3rd	18.96± 0.97^{cd}	20.78± 11.93^{c}
	8th	18.68± 0.80^{cd}	20.98± 1.98^{c}
Irradiation	3rd	26.64± 0.94^{abd}	29.02± 2.59^{ab}
	8th	28.00± 0.84^{abd}	30.22± 3.33^{ab}
Omega-3+ Irradiation	3rd	22.00± 1.10^{bc}	26.38± 2.46
	8th	22.60± 1.21^{abc}	25.36± 2.92

Legends as Table 1.

TABLE 4. Effect of Omega 3 PUFA on serum LDH, CPK and AST enzyme activities of rats exposed to gamma irradiation (4Gy).

Groups	Days	**LDH** (U/ ml)	**CPK** (U/ ml)	**AST** (U/ L)
Control	-	66.00± 4.43^{c}	138.40± 6.44^{cd}	62.80± 2.63^{c}
Omega-3	3rd	65.20± 4.96	135.20± 5.54^{cd}	56.40± 2.25
	8th	64.80± 5.38^{c}	133.80± 5.48^{cd}	56.40± 2.32^{c}
Irradiation	3rd	81.20± 7.11	227.40± 9.18^{abd}	64.80± 5.12
	8th	83.20± 7.96^{ab}	233.80± 8.10^{abd}	74.60± 4.34^{ab}
Omega-3+ Irradiation	3rd	72.40± 4.08	161.40± 6.82^{abc}	64.00± 3.49
	8th	72.20± 5.51	158.40± 5.94^{bc}	65.00± 2.14

Legends as Table 1.

TABLE 5. Effect of Omega 3 PUFA on serum uric acid, creatinine and urea levels of rats exposed to gamma irradiation (4Gy).

Groups	Days	**Uric acid** (mg/ dl)	**Creatinine** (mg/ dl)	**Urea** (mg/ dl)
Control	-	6.68± 0.30^{c}	1.18± 0.06^{c}	14.06± 0.73^{c}
Omega-3	3rd	6.82± 0.31^{c}	1.04± 0.08	14.88± 0.65^{c}
	8th	7.00± 0.29	1.28± 0.03	14.34± 0.52^{c}
Irradiation	3rd	8.40± 0.73^{abd}	1.03± 0.06	11.18± 0.71^{ab}
	8th	7.98± 0.32^{a}	1.41± 0.09^{a}	18.12± 1.20^{abd}
Omega-3+ Irradiation	3rd	6.70± 0.27^{c}	1.08± 0.07	13.08± 0.80
	8th	7.44± 0.40	1.25± 0.05	14.84± 0.71^{c}

Legends as Table 1.

Significant increase ($P<0.05$) in uric acid level was recorded 3 and 8 days post irradiation while urea and creatinine levels showed an increase on the 8th day post irradiation. Supplementation with omega- 3 ameliorates these increases (Table 5).

Discussion

The present study showed that exposing rats to whole body gamma irradiation (4Gy) induced oxidative stress expressed by elevation of serum MDA contents which is a one of the lipid peroxidation by-products concomitant with significant reduction in blood GSH content, SOD and GPX enzyme activities. These results are in concert with many previous studies which showed that total body irradiation induces lipid peroxidation in serum and different tissues and changes antioxidant enzyme activities (Adaramoye *et al*, 2011 & 2012). The ionizing radiation induced lipid peroxidation through the generation of ROS which attack the polyunsaturated fatty acids constituent of the cell membrane and other cell components (Zahran *et al*., 2006).

It is well documented that unchecked peroxidation decomposition of membrane lipids has severe consequences for the cell and the organism (Maurya, *et al.,* 2006). Polyunsaturated fatty acids are considered essential for the structure of cell membrane, since their central role is to maintain its structure, fluidity and function (Kotzampassi *et al.*, 2009). Attia and Nasr, (2009) recorded that an increase in saturated fatty acids or a reduction in polyunsaturated fatty acids in lipid membranes decreases the susceptibility of membranes to oxidant attack.

The omega-3 PUFAs are able to control, at least to some degree, the adverse effects of irradiation related to the inflammatory process produced where they are incorporated in the cellular membrane and modulate anti-inflammatory cytokines production (Kotzampassi *et al*., 2009), enhance resistance to free radical attack and reduce lipid peroxidation (Erdogan *et al*., 2004). The results of this study suggest that pre-treatment with omega-3 before irradiation exerts an antioxidant effect by restoring the level of MDA and GSH and antioxidant enzyme activities within the normal levels. Such results corroborate the findings of Saito and Kubo (2003).

Previous studies of (Sekine *et al*., 2006) demonstrated that tissue levels of ascorbic acid and/or glutathione increased in rats fed DHA. It was assumed that this increase would augment antioxidant potency in tissues and thus decrease lipid peroxidation. Furthermore, GSH is a necessary substrate for the antioxidant enzymes, GPX and GST. Ascorbic acid and GSH potentiate reductive recycling of vitamin E, which augments its antioxidant activity (Scarpa *et al*., 1984). In fact, omega-3 or fish oil enhance antioxidant activity in different tissues; liver (Garrel *et al*., 2012), heart (Hunkar *et al*., 2002) and kidney (Bhattecharya *et al*, 2007), suggesting that their effects are not tissue-specific and may be related to increasing mRNA expression of SOD (Kesavalu *et al.,* 2007) and GPX (Venkatraman, 1994) enzymes.

In this study, gamma irradiation induced a significant increase of total cholesterol and triglyceride levels, which runs in full agreement with the results of Ashry *et al*. (2009 & 2010). They attributed this increase to the suppression of lipoprotein lipase activity that reduces the uptake of lipids by adipose cells in addition to decreases fatty acid oxidation and increased rate of cholesterol biosynthesis in the liver and other tissues. This study, revealed that omega-3 supplementation before irradiation has a modulatory effect on lipid profile disturbance induced by gamma -irradiation. So, it could be suggested that omega-3 exert a fat-lowering effect by regulating lipid metabolism through inhibiting lipogenesis (Tai and Ding, 2010) through decreasing the expression of lipogenic genes (Nakatani *et al.,* 2003 and Xu *et al.,* 1999), enhancing lipolysis through increasing the expression of hormone sensitive lipase and decreasing the expression of perilipin (Luo *et al.,* 1998 and Wang, *et al*., 2009) and enhancing fatty acid oxidation which is mediated by increasing the oxidation-related enzyme activities (Guo *et al.,* 2005 and Ide *et al.,* 2000). In addition, omega-3PUFAs suppress pre-adipocyte differentiation and high concentration of EPA and DHA induces apoptosis of adipocytes and subsequently reduces adipogenesis (Perez-Matute *et al*., 2007 and Kim *et al.,* 2006). This apoptic effect could results in decreased adipose accumulation (Tai and Ding, 2010).

It is well known that ALP and ALT are found predominantly in the liver. Injury or diseases affecting the liver causes a release of these enzymes into the

blood stream. Radiation exposure caused damage to the cell membrane that augmented the ALP activity. The increase in ALT activity in serum reflects an increase plasma membrane permeability, which may be associated with cell death (Gharib, 2007).The fact that omega-3 PUFA could ameliorate gamma radiation –induced increase in serum ALT, AST and ALP enzyme activities point to their possible protective effect of the liver, probably mediated through reducing the levels of lipid peroxidation and improving antioxidant defence system observed in this work.

CPK, LDH and AST are important enzymes used to confirm a myocardial infarction or heart injury. The elevation in these enzyme activities after whole body gamma irradiation recorded in this study is in agreement with the previous findings of Fahim (2008) who attributed this increase to the alterations in dynamic permeability of membranes induced by ionizing radiation, allowing leaking of biological active materials out of the injured cells. The amount of these markers in plasma is directly proportional to the number of necrotic cells present in cardiac tissue (Farvin *et al.*, 2004). Omega-3 pre-treatment reduced the increase of these diagnostic marker enzymes. The protective activity of omega-3 against gamma radiation induced stress injury is due to its ability to inhibit lipid accumulation by its hypolipidaemic property (Anandan *et al*., 2007) and to prevent myocardial necrosis and restore the normalcy of the structural and functional integrity of the myocardium (Gopal *et al*., 2011). The observed increase in urea, creatinine and uric acid levels after irradiation indicates kidney injury. This injury was ameliorated by supplementation of omega-3 before irradiation as recorded in these results. Brown *et al.* (1998) recorded that dietary supplementation with omega-3 was reno-protective, preventing deterioration of renal function and preserving renal structure. It also decreases blood pressure, a known accelerant of kidney disease propagation (Fassett *et al*., 2010). According to the above results it could be concluded that oral supplementation of omega-3 before irradiation enhances antioxidant activities, decrease lipid peroxidation and regulate lipid metabolism. So, it ameliorates liver, heart and kidney dysfunctions induced by ionizing radiation.

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احماض أوميجا ٣ الدهنيه غير المشبعه تخفف من الاجهاد التأكسدى والاختلالات الوظيفيه الناجمه عن التعرض للاشعاع فى الجرذان

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تهدف هذه الدراسه الى تعيين التأثير الوقائى المحتمل لاحماض اوميجا ٣ الدهنيه غير المشبعه فى الحد من الاجهاد التأكسدى المرتبط بالاختلال الوظيفى الناجم عن التعرض للاشعاع . وقد تم تجريع الفئران الاوميجا ٣ بجرعة ٤ر. جم/كم من وزن الجسم يوميا ولمدة اربعة اسابيع قبل التعرض لاشعة جاما بجرعه قدرها ٤ جراى. وقد أدى تعرض جسم الفئران الكلى للاشعاع الى زيادة مستوى المالوندای الدهايد مصحوبا بنقص فى مستوى الجلوتاثيون والجلوتاثيون بيرواكسيديز وسوبر اكسيددیسميوتيز فى الدم بعد ثلاثه وثمانيه ايام من التعرض. وقد ارتبط بالاجهاد التأكسدى الناتج عن الاشعاع زيادة فى الانزيمات الداله على تلف وظيفة كل من القلب و الكبد (اللاكتيت ديهيدروجينيز والكرياتين فوسفو كينيز والاسبارتيت ترانس امينيز وانزيم الفوسفاتيز القاعدى والانين امينوترانسفيراز) و كذلك دلالات تلف وظيفة الكلى (اليوريا وحمض اليورك والكرياتينين) كما ادى التعرض للاشعاع الى زيادة فى مستويات كل من الكوليسترول الكلى والدهون الثلاثيه .وتشير النتائج الى ان تجريع الفئران الاوميجا ٣ قبل التعرض للاشعاع ادى الى تحفيز نظام مضادات الاكسده الطبيعيه وتخفيف الاجهاد التأكسدى والاختلالات الوظيفيه للاعضاء المختبره فى جسم الجرذان المعرضه لاشعة جاما .