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The Effect of N-Acetylcysteine on Oxidant/Antioxidant Status in Irradiated Rats

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Summary: N-Acetylcysteine (NAC) is both a strong antioxidant and a glutathione precursor. The effect of NAC on the oxidant/antioxidant status of some tissues of the irradiated rats was investigated. Twenty one rats were assigned to 3 groups; the control group, the irradiation group, for which physiological saline solution was administered as i.p. for three days and then, 9 Gy gamma irradiation was applied, and 3rd irradiation + NAC group for which NAC was administered as i.p. for three days as 300 mg/kg body weight and then the same dose of irradiation was applied. Upon irradiation, the increase determined in malondialdehyde (MDA) was significant in the liver, kidney, and brain tissues of the rats (P<0.05). While glutathione peroxidase (GSH-Px) activity decreased in all of the tissues and superoxide dismutase (SOD) activity only in the liver (P<0.01), glutathione (GSH) levels significantly increased in the kidney and ovarium tissues (P<0.001). While NAC administration returned the increased MDA levels in the kidney and brain as a result of irradiation to normal levels (P<0.05), it was determined that it did not return the increased MDA levels in the liver tissue to the normal level (P<0.001). While NAC addition led to a significant increase in GSH levels of the liver, heart, spleen, brain and ovarium tissues compared to both control and irradiation groups, it caused a significant decrease in the kidney tissue compared to irradiation group (P<0.001). As a result of NAC addition, a significant decrease was determined in spleen GSH-Px activity, heart and ovarium SOD activity compared to control and irradiation groups (P<0.05). It can be asserted that GSH increasing by the addition of NAC is the main antioxidant that has a role in decreasing oxidative stress occurring as a result of irradiation. In the examination of MDA values, it was found that the addition of NAC protected the kidney and brain against the oxidative damage induced by irradiation but NAC addition could remain insufficient for the liver.
Key words: Irradiation, N-Acetylcysteine, oxidative stress

Radyasyona Maruz Kalan Ratlarda Oksidan/Antioksidan Durum Üzerine N-Asetilsistein'in Etkisi

Özet: N-Asetilsistein (NAC) hem güçlü bir antioksidan, hemde glutatyon prekürsörüdür. Radyasyona maruz kalan ratların bazı dokularındaki oksidan/antioksidan durum üzerine NAC'ın etkisi araştırıldı. Yirmi bir rat üç gruba bölündü; 1. grup kontrol grubu. 2. grup radyasyon grubu; serum fizyolojik üç gün i.p. verildikden sonra 9 Gy gamma radyasyon uygulandı. Üçüncü grup radyasyon + NAC grubu; NAC, 300 mg/kg canlı ağırlık i.p. olarak üç gün süreyle verildi ve sonra aynı dozda radyasyon uygulandı. Radyasyon sonucu, ratların karaciğer, böbrek ve beyin dokularında malondialdehit (MDA)'de önemli artış saptandı (P<0.05). Tüm dokulardaki glutatyon peroksidaz (GSH-Px) aktivitesi ve sadece karaciğer süperoksit dismutaz (SOD) aktivitesi azaldı (P<0.01), böbrek ve ovaryum dokularında glutatyon (GSH) düzeyleri önemli olarak arttı (P< 0.001). N-Asetilsistein ilavesinin radyasyon sonucu böbrek ve beyindeki artmış MDA seviyelerini normal seviyeye ulaştırırken (P<0.05), karaciğer dokusunda artan MDA seviyelerini normal seviyeye (P<0001) getiremediği belirlendi. N-Asetilsistein ilavesi hem kontrol hemde radyasyon uygulanan gruba gore; karaciğer, kalp, dalak, beyin ve ovaryum dokularının GSH seviyelerinde önemli artışa, böbrek dokusunda radyasyon uygulanan gruba göre önemli azalmaya sebep oldu (P<0.001). N-Asetilsistein ilavesiyle dalak GSH-Px aktivitesinde, kalp ve ovaryum SOD aktivitesinde kontrol ve radyasyon uygulanan gruba göre önemli azalma tespit edildi (P<0.05). N-Asetilsistein ilavesiyle artan GSH'un radyasyon sonucu oluşan oksidatif stresi azaltmada rol alan ana antioksidan olduğu söylenebilir. Doku MDA değerleri incelendiğinde, NAC ilavesinin böbrek ve beyini radyasyonun neden olduğu oksidatif hasardan korumasına rağmen, karaciğer için yetersiz kalabileceği düşünülebilir.
Anahtar kelimeler: N-Asetilsistein, oksidatif stres, radyasyon

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Introduction

The wide use area of radiation includes radiotherapy, medical diagnosis, dental radiography, and several imaging protocols and also its exposure is seen in

accidental radiation releases (Radwan and Mohamed, 2018). A detrimental effect of irradiation is the production of reactive oxygen species (ROS), which includes superoxide anion radical ($\cdot O_2^-$), hydrogen peroxide (H_2O_2), and hydroxyl radical ($^{\cdot}OH$). ROS are highly reactive and could diffuse to vital cellular targets like DNA, proteins and membrane, ultimately leading to cell death (Kilciksiz et al., 2008; Mansour et al., 2008).

Cells possess an important antioxidant defense against ROS. The antioxidant system consists of low molecular weight antioxidant molecules, such as GSH and of various antioxidant enzymes; for instance SOD, GSH-Px). When there is an imbalance between formation of ROS and antioxidant defense, this can lead to oxidative stress, associated with deficiencies of antioxidants and/or rised production of ROS (Sies, 1993).

It is reported that a number of dietary antioxidants decrease free radical attacks towards biomolecules (Duthie et al., 1996). N-Acetylcysteine is a natural compound found in several vegetables such as garlic, onion, peppers, and asparagus (Demirkol et al., 2004; Hsu et al., 2004). N-Acetylcysteine has multiple biological activities including antioxidant, anticarcinogenic, and antiangiogenic properties (Kilciksiz et al., 2008; Mansour et al., 2008; Tosetti et al., 2002). Being a strong antioxidant and a GSH precursor NAC directly destroys ROS (Liu et al., 2007). Many studies have revealed that NAC has an ability to decrease chemically created oxidative stress and DNA damage (Kilciksiz et al., 2008; Liu et al., 2007; Mansour et al., 2008; Neal et al., 2003). Moreover, NAC has been used clinically for decades in order to treat numerous illnesses (Thomas, 1993).

It is known that exposure to γ-radiation causes liver damage (Kilciksiz et al., 2008; Mansour et al., 2008; Radwan and Mohamed, 2018). Antioxidant supplements reduce side effects of the radiation treatment by inhibiting the oxidative damage to normal cells (Lawenda et al., 2008). In the present study, the effect of irradiation on oxidative stress parameters (MDA, SOD, GSH, GSH-Px) of the liver, kidney, heart, spleen, brain and ovarium tissue and the presence of a protective effect of NAC that is an antioxidant on these tissues were investigated.

Material and Methods

Animals

Twenty one, female fertile Wistar albino rats (200 ± 10 g) aged between 4–5 months were supplied from the Animal Care Unit of Fırat University and were kept in plastic cages with stainless-steel grid tops. The experimental conditions were environmentally controlled in terms of temperature (23±2 °C), humidity (50±5%), and light (12 h of light and dark cycle). The animals were fed with pellet diet and water ad libitum. Three rats were kept together in polypropylene cages containing sterile husk bedding during the experiment. The experiments were carried out after the approval of the Local Ethics Committee of the Veterinary Research Institute (Official form date and number: 18.04.2013 and 2013/4-1) in Elazıg.

Irradiation of the rats

A γ-ray source was used to perform whole-body irradiation. The animals were placed in Plexiglass^R cages and irradiated in groups of seven rats, simultaneously. The source-to-skin distance was 291 cm with a dose of 0.0233 Gy/s (Benkovica et al., 2008) and absorbed dose of 9 Gy. They were irradiated by a 160 MLC LINAC (Siemens Artiste linear accelerator, using 6 MV photons). The rats were irradiated under continuous isoflurane anesthesia in a specially fabricated plexiglas chamber radiating out from the center.

Experimental design

The rats were seperated into three groups including 7 rats in each.

Control group; rats did not receive any treatment.

Irradiation group; rats were treated with intraperitoneal injection (i.p.) containing a physiologic saline solution for three days. All the rats in this group were irradiated with gamma-rays at dose of 9 Gy.

Irradiation + NAC group; the rats were treated with i.p. injection containing NAC at dose of 300 mg/ kg body weight (Kilciksiz et al., 2008) for 3 consecutive days. Then, all the rats were irradiated with gama-rays at dose of 9 Gy.

Ketamine (ketamine hydrochloride, 50 mg/kg [Ketalar® 5%, Parke-Davis] and xylazine 8 mg/kg [Rompun® 2%, Bayer]) mixture was done intraperitoneally in order to anesthetize the rats. All the rats were sacrificed at 24th hour after irradiation exposure. After decapitation, whole liver, spleen, kidney, brain, heart and ovarium tissues were rapidly resected. The tissues were stored at -80°C.

Biochemical analyses in tissues

The tissues were homogenized by using a Teflon-glass homogenizer with 1.15% KCl in order to obtain 1:10 (w /v) homogenate. Malondialdehyde and GSH levels of tissue homogenates were determined spectrophotometrically according to the methods of Placer et al. (1966) and Sedlak et al. (1968), respectively. GSH-Px and SOD activities were measured spectrophotometrically according to the methods of Lawrance and Burk (1976) and Sun et al. (1988), respectively. Homogenate protein levels were performed

based on the method of Lowry et al. (1951).

Statistical analysis

The SPSS statistical software (SPSS for windows, version 22.0) was used for all statistical analyses. All the data were presented in mean (±) and standard error (SE). Analysis of variance (ANOVA) followed by Duncan test was used to determine whether there were significant differences among the groups. The 5% level of significance was used to establish differences.

Results

As a result of irradiation, a significant increase was determined in MDA of liver, kidney (P<0.001), and brain (P<0.05) tissues of the rats. Also, there was a significant decrease in GSH-Px activity of all the tissues and SOD activity in the liver (P<0.01). On the other hand, GSH level increased significantly in the kidney and ovarian tissues (P<0.001) (Table 1).

While NAC administration return the MDA levels, increasing in the kidney (P<0.001) and brain (P<0.05) as a result of the irradiation, to normal levels, it was found that there was a significant decrease in MDA levels increasing in the liver tissue (P<0.001), but, it could not significantly bring them to the control level. Malondialdehyde values of heart, spleen and ovarium tissues significantly decreased as a result of the addition of NAC compared to both control and irradiation groups (P<0.001) (Table 1).

While NAC addition led to a significant increase in GSH levels of the liver, heart, spleen, brain and ovarium tissues compared to both control and irradiation groups, it caused a significant decrease in the kidney tissue compared to irradiation group (P<0.001). As a result of NAC addition, a significant decrease was determined in spleen GSH-Px activity and heart and ovarium SOD activity compared to control and irradiation groups (P<0.05) (Table 1).

Table 1. The effect of N-acetylcysteine on oxidant/antioxidant status in the tissues of irradiated rats

	Control	Irradiation	Irradiation + NAC	P
		LIVER		
MDA (nmol/g prot)	4.56 ± 0.38^{c}	12.57 ± 0.56^{a}	8.93±0.74^{b}	***
GSH-Px (U/g prot)	2.12± 0.33^{a}	0.75 ± 0.16^{b}	0.6 ± 0.10^{b}	***
GSH (nmol/g prot)	0.59 ± 0.05^{b}	0.35 ± 0.04^{b}	2.13 ± 0.11^{a}	***
SOD (U/g prot)	1.8 ± 0.19^{a}	1.12± 0.04^{b}	1.31± 0.07^{b}	**
		KIDNEY		
MDA (nmol/g prot)	9.10 ± 0.42^{b}	22.57 ± 2.86^{a}	14.48± 1.45^{b}	***
GSH-Px (U/g prot)	2.54 ± 0.27 ^{a}	1.10 ± 0.17 ^{b}	0.92 ± 0.30 ^{b}	***
GSH (nmol/g prot)	0.41 ± 0.02^{b}	1.92 ± 0.43^{a}	0.53 ± 0.03^{b}	***
SOD (U/g prot)	1.52 ± 0.11	1.63 ± 0.09	1.45 ± 0.12	NS
		HEART		
MDA (nmol/g prot)	12.24 ± 0.98 ^{a}	15.02 ± 1.37 ^{a}	6.68 ± 1.23 ^{b}	*
GSH-Px (U/g prot)	45.29 ± 1.58^{a}	22.61 ± 1.56^{b}	13.95 ± 3.17^{b}	***
GSH (nmol/g prot)	0.73 ± 0.06^{b}	0.82 ± 0.09^{b}	2.31 ± 0.20^{a}	***
SOD (U/g prot)	3.36 ± 0.33^{a}	2.76 ± 0.24^{ab}	2.00 ± 0.26^{b}	*
		SPLEEN		
MDA (nmol/g prot)	14.09 ± 1.15^{a}	16.76 ± 0.70^{a}	7.64 ± 0.93^{b}	***
GSH-Px (U/g prot)	18.35 ± 1.12^{a}	11.23 ± 1.11^{b}	5.75 ± 1.72^{c}	***
GSH (nmol/g prot)	0.41 ± 0.01^{b}	0.55 ± 0.05^{b}	2.21 ± 0.19^{a}	***
SOD (U/g prot)	1.4 ± 0.05	1.5 ± 0.13	1.30 ± 0.14	NS
		BRAIN		
MDA (nmol/g prot)	13.07 ± 0.86^{b}	21.65 ± 2.02^{a}	18.79 ± 2.49^{ab}	*
GSH-Px (U/g prot)	38.41 ± 1.98^{a}	21.36 ± 1.77^{b}	20.94 ± 4.45^{b}	***
GSH (nmol/g prot)	0.5 ± 0.1^{b}	0.67 ± 0.04^{b}	2.13 ± 0.02^{a}	***
SOD (U/g prot)	1.97 ± 0.14	1.97 ± 0.11	1.79± 0.22	NS
		OVARIUM		
MDA (nmol/g prot)	12.93 ± 0.82^{a}	14.64 ± 1.4^{a}	6.56 ± 1.31^{b}	***
GSH-Px (U/g prot)	57.76 ± 2.99^{a}	38.74± 0.97^{b}	29.93 ± 1.69^{b}	**
GSH (nmol/g prot)	0.82 ± 0.02^{c}	1.33 ± 0.15^{b}	2.49 ± 0.29^{a}	***
SOD (U/g prot)	3.78 ± 0.15^{a}	4.01 ± 0.24^{a}	3.06 ± 0.11^{b}	**

P<0.05, **P<0.01, ***P<0.001,* ***NS:* *No Significant*
^{abc}*Mean values with different superscripts within a row were significantly different.*

Discussion

Comprehensive evidence has revealed that irradiation causes intracellular generation of ROS (Kilciksiz et al., 2008; Liu et al., 2007; Mansour et al., 2008). When ROS reacts with the unsaturated free fatty acids of membrane lipids, MDA levels elevate, which means the activation of lipid peroxidation. MDA has been commonly accepted as a sensitive marker for lipid peroxidation (Patton and Kurtz, 1951). Furthermore, MDA determinations ensure a good measure for peroxidation, one of the main mechanisms of cell damage causing necrosis or apoptosis (Comporti, 1985; De Ferreyra et al., 1989). It is a known fact that irradiation exposure leads to the liver damage (Khattab et al., 2017; Kilciksiz et al., 2008; Liu et al., 2007; Mansour et al., 2008). It is also stated that γ-radiation results in multiple organ dysfunction particularly in the liver and elevates MDA levels in various tissues based on the time and dose (Karami et al., 2018; Kilciksiz et al., 2008; Mansour et al., 2008; Simsek et al., 2012; Xie et al., 2014;). In this study, γ-radiation significantly increased MDA in the kidney, brain, and liver tissues but led to an insignificant increase in heart, spleen, and ovarium tissues. Irradiation is seen to result in damage in more than one tissues. Liver, which is a radiosensitive organ, has a higher susceptibility against radiation damage (Radwan and Mohamed, 2018). This situation is confirmed by the fact that the increased MDA levels in the liver was 3-fold compared to the kidney and brain (2-folds).

Enzymatic and non-enzymatic antioxidant systems allow cells protect themselves against oxidative damage. As the first-line of antioxidant defense against the detrimental effects of ROS, SOD acts to turn $\cdot O_2^-$ into H_2O_2 (Liu et al., 2007). Additionally, GSH-Px takes part significantly in the protection against oxidative damage by providing the convertion of H_2O_2 to H_2O and O_2 and using GSH as a substrate (Scibior et al., 2008). The exposure to irradiation makes changes in the balance of endogenous antioxidant enzymes. In this study, the MDA concentrations in the liver, kidney, and brain increased upon irradiation; whereas the SOD and GSH-Px activities in the liver and GSH-Px activity in the brain and kidney significantly decreased. The decreased SOD activity is associated with inhibition of the enzyme due to rised superoxide radical production or H_2O_2 increasing as a result of decreasing of GSH-Px activity, which degrades H_2O_2 (Ashry et al*.,* 2017; El-Gazzar et al*.,* 2016). There were significant decreases in the GSH-Px activity in heart, spleen, and ovarium tissues in which MDA insignificantly increased after the irradiation. Inactivation of GSH-Px activity through lipid peroxidation byproducts in irradiated rats may significantly decrease GSH-Px activity (Mansour et al., 2008). The decreased GSH-Px activity in the tissues examined after the irradiation indicated that the first enzyme affected by the irradiation was GSH-Px. Various studies revealed that irradiation decreased SOD, GSH, and GSH-Px levels in the liver (Ashry et al*.,* 2017; Khattab et al*.,* 2017; Kilciksiz et al., 2008; Mansour et al., 2008; Radwan and Mohamed, 2018). The antioxidant enzymes reduced because of the depletion of enzymes during oxidative stress caused by the irradiation (Khattab et al., 2017; Mansour et al., 2008). In contrast to studies indicating the decreased GSH in the kidney (Cosar et al., 2012; Ekici et al., 2016), the present study showed that GSH concentrations significantly increased in the kidney and ovarium as a result of γ-radiation. Being a main intracellular antioxidant, GSH takes part in the defense system of cells against oxidative damage, directly as a free radical scavenger or indirectly by repairing initial damage to macromolecules and could maintain protein and non-protein SH group in a reduced way (Scibior et al., 2008). The fact that GSH levels were observed to increase in irradiated rats may be related to the radiation adaptive response. Simsek et al. (2012) stated that irradiation did not lead to a change in the ovarium MDA but it resulted in an increase in GSH-Px and CAT activities.

It is obvious that radiation leads to oxidative stress. Exogenous antioxidants may effectively counteract the oxidative-stress state. N-Acetylcysteine was shown to scavenge oxidants directly and to increase intracellular GSH, which has a great importance in protecting from oxidative stress associated with ROS (Aruoma et al., 1989; Burgunder et al., 1989; Liu et al., 2007; Mansour et al., 2008). In this study, it was revealed that the significant increase in MDA in the kidney and brain tissues due to γ-radiation could reach the control values as a result of the addition of NAC; however, even though MDA levels in the liver significantly decreased, they could not return to the control values. This pointed out that although NAC protected the kidney and brain, NAC administration was insufficient for the liver. As a result of NAC administration, MDA significantly decreased in the heart, spleen, and ovarium tissues compared to control and radiation groups. This may be caused by strong antioxidant characteristic of NAC. In various studies, it has been determined that the addition of NAC reduces the increased MDA levels in the rat serum (Demir et al., 2011), mice and rat liver (Kilciksiz et al., 2008; Liu et al., 2007; Mansour et al., 2008) and the brain of guinea pigs (Gulbahar et al., 2009) as a result of the irradiation and also increases the decreasing antioxidant levels such as GSH-Px, SOD, GSH. NAC is both a potent antioxidant and a precursor of the reduced glutathione (GSH) (Aruoma et al., 1989; Burgunder et al., 1989; Liu et al., 2007; Mansour et al., 2008). In the present study, a significant increase was determined in the GSH concentra-

tions with the addition of NAC in all the studied tissues except for kidney compared to control and irradiation groups. N-Acetylcysteine serves as a cysteine donor and maintains or even increases the intracellular levels of glutathione, a tripeptide which protects cells from free radicals (Burgunder et al., 1989; Liu et al., 2007). Moreover, NAC is the most common intracellular antioxidant in vivo, where it scavenges ROS such as H_2O_2 and $HO^{\cdot}$ (Zafarullah et al., 2003). Decreased GSH-Px activity in the heart, spleen, and ovarium tissues and decreased SOD activity in the heart and ovarium as a result of the addition of NAC can be associated with the fact that the need for antioxidant enzymes decreased due to its direct ROS scavenging characteristic. It can be asserted that especially GSH increasing due to the effect of NAC administered was the main antioxidant taking part in reducing oxidative stress, induced by irradiation.

Consequently, in the examination of the MDA values; it was found that NAC reduced the increased MDA contents in the kidney and brain but although it decreased MDA content in the liver, it cannot return them to the control values. It was determined that NAC addition significantly increased GSH levels in the studied other tissues except for kidney. When examining its effect on liver, NAC at the dose used during radiotherapy or for reducing the oxidative damage caused by irradiation may remain insufficient. Therefore, there is a need for further studies examining different doses of NAC to reduce the effect of irradiation on liver.

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