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Protective effects of N-acetylcysteine and taurine on oxidative stress induced by chronic acetaldehyde administration in rat liver and brain tissues

Kronik asetaldehit uygulaması ile uyarılan oksidatif streste sıçan karaciğerinde ve beyin dokularında N-asetilsistein ve taurinin koruyucu etkileri

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Abstract

Aim: Acetaldehyde (AA) is one of the main products of alcohol metabolism. Exposure to AA can occur through ingestion of several dietary products, inhalation of cigarette smoke/automobile exhausts, or contact with cosmetics. AA accumulation causes oxidative stress. The aim of this study was to investigate the prooxidant/antioxidant status in rats chronically exposed to AA, and to evaluate the effects of N-acetylcysteine (NAC) and taurine (TAU) on prooxidant/antioxidant balance.
Methods: Sprague Dawley rats were divided in the following groups (n=8; each): Control, AA, AA+NAC, AA+TAU. Reactive oxygen species (ROS), diene conjugate (DC), malondialdehyde (MDA), protein carbonyl (PC), ferric reducing antioxidant power (FRAP) and glutathione (GSH) levels as well as superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) activities were determined in liver and brain tissues.
Results: AA treatment in drinking water was detected to induce prooxidant state in both liver and brain of rats. NAC treatment decreased AA-induced prooxidant status in both tissues. Although TAU treatment diminished ROS levels, MDA and PC levels remained unchanged in examined tissues of AA-treated rats. NAC and TAU elevated liver and brain GSH levels in AA-treated rats.
Conclusion: Chronic AA administration has created a prooxidant condition, and NAC/TAU appears to be useful in suppression of the developed oxidative stress.

Keywords: Acetaldehyde, oxidative stress, N-acetylcysteine, taurine, liver, brain.

Öz

Amaç: Asetaldehit (AA), alkol metabolizmasının ana ürünlerinden biridir. AA'e maruz kalma birçok diyet ürününün yenmesi, sigara dumanı/otomobil egzozlarının solunması veya kozmetik ürünlerle temas yoluyla oluşabilir. AA birikimi oksidatif strese neden olur. Bu çalışmanın amacı kronik AA'e maruz kalan sıçanlarda prooksidant/antioksidan durumunu araştırmak ve N-asetil sistein (NAC) ve taurinin (TAU) proksidant/antioksidan dengesi üzerindeki etkilerini değerlendirmektir.
Yöntemler: Sprague Dawley sıçanlar aşağıdaki gruplara ayrıldı (n = 8; her biri): Kontrol, AA, AA+NAC, AA+TAU. Karaciğer ve beyin dokularında reaktif oksijen türleri (ROS), dien konjugatları (DC), malondialdehit (MDA), protein karbonil (PC), ferrik indirgeyici antioksidan güç (FRAP) ve glutatyon (GSH) düzeyleri ve ayrıca süperoksit dismutaz (SOD) ve glutatyon peroksidaz (GSH-Px) aktiviteleri incelendi.
Bulgular: İçme suyu ile AA uygulanan sıçanların karaciğer ve beyin dokularında prooksidan bir durum oluştuğu saptandı. NAC uygulaması her iki dokuda AA'e bağlı prooksidan durumu azalttı. TAU incelenen dokularda ROS oluşumunu azaltmasına rağmen, MDA ve PC düzeyleri değişmedi. NAC and TAU AA uygulanan sıçanların karaciğer ve beyinlerinde GSH düzeylerini arttırdı.
Sonuç: Kronik AA uygulamasının proksidant bir durum yarattığını, NAC/TAU uygulamalarının AA ile uyarılan oksidatif stresin baskılamada yararlı olabildiği görülmektedir.

Anahtar Kelimeler: Asetaldehit, oksidatif stres, N-asetilsistein, taurin, karaciğer, beyin.

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Introduction

Acetaldehyde (AA), an organic aldehyde, is a highly reactive compound and the first oxidation product of ethanol metabolism. Ingested ethanol is absorbed from the upper gastrointestinal tract and transported to the liver. Then, it is mainly metabolize into AA by alcohol dehydrogenase-1B and detoxified to acetic acid by aldehyde dehydrogenase-2. Although the liver is the primary site of ethanol oxidation, other organs in gastrointestinal system, heart and brain may also participate in the formation of AA from ethanol [1]. Therefore, many of the toxic effects of ethanol consumption is suggested to be related to AA formation in the liver and other tissues [2, 3].

On the other hand, AA is used as an additive and a flavoring substance in the production of many foods. Therefore, several dietary products such as milk, yogurt, cottage cheese, bread, roasted coffee beans, instant tea, coffee, alcoholic and non-alcoholic beverages contain significant and detectable amounts of AA. AA is widely used in the chemical industry for production of cosmetics, dye, plastics, adhesives, disinfectants and pesticides and is also found in cigarette smoke and automobile exhausts. AA may naturally be formed in small amounts in human body during threonine catabolism [4]. In addition, significant extrahepatic formation of AA takes place in the gastrointestinal system via alcohol dehydrogenase during ethanol oxidation. Therefore, marked amounts of AA may be supplied from dietary sources and generated through extrahepatic metabolism of ethanol [2, 3].

Even though AA is short-lived, prior to its breakdown into acetate, it can cause cellular and tissue injury. Lipid peroxidation, together with the covalent binding of AA to lipids and proteins, is considered a critical process underlying AA-induced toxicity. AA may react with amino, hydroxyl and sulfhydryl groups and modify the structure and function of macromolecules such as DNA, proteins and enzymes [1-3]. In addition, AA induces apoptosis and increases the formation of inflammatory mediators [1, 5, 6]. Findings related to AA toxicity were usually obtained from in vitro experiments with AA [6, 7] or from animals treated with ethanol plus an inhibitor of AA dehydrogenase [8, 9] and transgenic mice [10, 11]. These studies showed that oxidative stress plays an important role in AA-induced toxicity. Therefore, antioxidant therapies may be useful to prevent AA-induced oxidative stress and tissue damage.

N-acetylcysteine (NAC) and taurine (TAU) are well-known sulfur-containing antioxidant molecules [12-15]. NAC is a derivative of cysteine. It acts as free radical scavenger and stimulates GSH synthesis [12, 13]. TAU is important for many physiological functions such as detoxification, membrane stabilization and osmoregulation. It decreases tissue lipid peroxidation by scavenging or quenching ROS or binding free metal ions such as Fe2+ or Cu+ via its sulfonic acid group [14, 15]. Therefore, NAC and TAU treatments were suggested to be useful in oxidative stress-induced pathologies [12-15] such as diabetes mellitus, cancer and various intoxications including ethanol toxicity [16-19], as a result of these properties.

Studies about the effect of in vivo AA treatment are restricted because of its unstable structure and rapid metabolism. In addition, there is no study investigating the effect of in vivo AA treatment on prooxidant-antioxidant balance in hepatic and extrahepatic tissues. Therefore, this study was planned to understand the direct toxic effect of AA from exogeneous sources and the efficacy of NAC and TAU treatments against on AA- toxicity. For this reason, reactive oxygen species formation (ROS), oxidative changes that occur in lipids and proteins as well as antioxidant parameters in liver and brain tissues of rats that were treated chronically with AA along with NAC and TAU were investigated.

Material and methods

Chemicals

AA, NAC, TAU and other chemicals were supplied from Sigma-Aldrich (St. Louis, MO, USA).

Animals and treatments

Male Sprague Dawley rats weighting 240-260 g, were obtained from the Istanbul University Aziz Sancar Institute of Experimental Medicine, Rats were housed in a light- and temperature-controlled room on a 12/12 hours light/dark cycle. The experimental procedure used in this study met the guidelines of the Animal Care and Use Committee of Istanbul University (Project No: 2013/45).

Animals were divided randomly into four groups. Body weights and drinking and feeding habits were taken into account during experimental period for 8 months.

1) Control (n=8): Rats in this group were fed with a standard pellet lab chow.

2) AA group (n=8): Rats were fed with normal commercial food and treated with AA in the drinking water with increasing concentrations [0.7% (v/v) for the first 4 months, 1.05% for the following 2 months and 1.4% for the last 2 months] to ensure adaptation of rats. The daily consumption of AA was calculated as 400 mg/kg body weight (BW) for 4 months, 600 mg/kg BW for 2 months and 800 mg/kg BW for 2 months. In this period, water containers containing AA were stored in the cold and changed every 2-3 days to prevent evaporation of AA as previously reported [20, 21].

3) AA+NAC group (n=8): Rats were given AA in drinking water and received a normal commercial rat chow containing 1% (w/w) NAC for 8 months. The consumption of NAC was roughly equivalent to 500 mg/kg BW/day.

4) AA+TAU group (n=8): Rats received AA in drinking water and a normal commercial rat chow containing 2.5% (w/w) TAU for 8 months. The consumption of TAU was roughly equivalent to 1.25 g/kg BW/day.

At the end of the treatment period, all rats were anesthetized with sodium thiopental (50 mg/kg, intraperitoneal) and sacrificed by collecting the blood into dry tubes by intracardiac puncture. Serum was obtained by centrifugation at 1,500 × g for 10 min. Liver and brain tissues were rapidly removed, washed in ice-cold saline and stored at -80 ºC until they were needed for analysis. Tissues were homogenized in ice-cold 0.15 M potassium chloride (KCl) (10%; w/v) and homogenates were centrifuged at 600 g for 10 min and obtained postnuclear fractions were used biochemical determinations in tissues. Superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) activities were determined in the postmitochondrial fraction of tissues. To obtain this fraction, postnuclear fractions were recentrifuged at 10,000 g for 20 min at 4oC and supernatants were collected. All weight determinations were performed on an EK-i/EW-I scale (A&D Co., Japan).

Determinations in serum

Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) measurements were performed on Cobas Integra 800 autoanalyzer (Roche Diagnostics, Mannheim, Germany).

Determinations of ROS formation, lipid and protein oxidation products

ROS formation was assayed fluorometrically as described previously [22]. Homogenates were incubated with 100 μM 2, 7-dichlorodihydrofluorescein diacetate (DCFH-DA) at 37 °C for 30 min. The fluorescence of 2, 7-dichlorofluorescein

was determined using a microplate fluorometer (Fluoroskan Ascent FL, Thermo Scientific Inc, USA) with an excitation of 485 nm and emission of 538 nm. Results were expressed as relative fluorescence units (RFU).

Lipid peroxidation was determined by measuring dien conjugate (DC) and malondialdehyde (MDA) levels in the liver and brain homogenates [18, 23]. Results were expressed as µmol/g tissue and nmol/g tissue, respectively.

The oxidative protein damage was measured by the quantification of carbonyl groups based on their reaction with 2, 4-dinitrophenylhydrazine (DNPH) to form protein hydrazones. Protein carbonyl (PC) results were calculated from the maximum absorbance (360 nm) using a molar absorption coefficient of 22,000 M^{-1} cm^{-1} and expressed as nmol carbonyl per mg protein [24].

Determinations of non-enzymatic and enzymatic antioxidants

Total antioxidant status was evaluated using ferric reducing antioxidant power (FRAP) assay [25]. In this assay, at low pH, a ferric- tripyridyltriazine (Fe^{3+}-TPTZ) complex is reduced to the ferrous form, which can be monitored by measuring the change in absorbance at 593 nm. Results were expressed as nmol/mg protein. Glutathione (GSH) levels were measured with 5, 5-dithiobis-(2-nitrobenzoate) at 412 nm and were expressed as µmol/g tissue [26].

SOD activity was assayed by its ability to increase the effect of riboflavin-sensitized photooxidation of o-dianisidine and results were given as U/mg protein [27]. GSH-Px activity was measured using cumene hydroperoxide as substrate and results were expressed as nmol/min/mg protein [28]. Protein levels were determined using bicinchoninic acid [29].

Statistical analysis

All statistical analyses were performed with IBM SPSS statistics for Windows (version 21; SPSS Inc., Chicago, IL, USA). The results were expressed as mean ± SEM. Experimental groups were compared using Kruskal–Wallis (post hoc Mann-Whitney U) tests. A p value < 0.05 was considered to be statistically significant.

Results

There were no significant differences in final body weights and liver and brain weights between groups. However, body weight gain during 8 months was found to decrease in comparison with the control group. Liver index (liver weight/BW) increased in treated groups. Chronically AA administration with or without NAC and TAU did not cause significant changes in serum ALT and AST activities (data not shown).

Figure 1 demonstrates the changes in ROS, DC, MDA and PC levels. According to this;

a) AA treatment resulted in significant increases in ROS formation in the liver and brain ($p<0.01$, $p<0.001$). NAC and TAU caused significant decreases in AA-induced ROS formation in the liver ($p<0.001$, $p<0.001$) and brain ($p<0.001$, $p<0.001$) tissues.

b) Hepatic ($p<0.05$) and brain MDA levels increased due to AA treatment, but increases in brain MDA levels were not significant. NAC treatment decreased MDA ($p<0.05$) levels in brain, but not in liver of AA-treated rats. However, there were no changes in hepatic and brain MDA levels of AA-treated rats due to TAU treatment.

c) DC levels in liver and brain tissues remained unchanged.

d) Liver PC levels remained unchanged, but brain PC ($p<0.001$) levels were found to increase in AA-treated rats. NAC treatment diminished liver ($p<0.01$) and brain PC ($p<0.05$) levels in AA-treated rats as compared to AA group, but these levels did not alter due to TAU treatment.

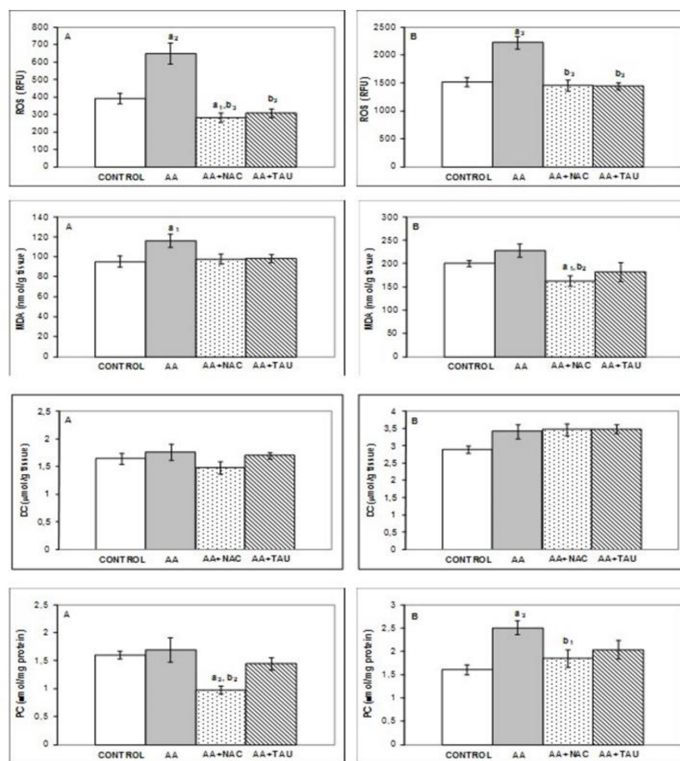

Figure 1: The effects of N-acetylcysteine (NAC) and taurine (TAU) on liver (A) and brain (B) reactive oxygen species (ROS), malondialdehyde (MDA), dien conjugate (DC), and protein carbonyl (PC) levels (Mean ± SEM, n=8 each) a1 $p<0.05$; a2 $p<0.01$; a3 $p<0.001$ according to control group; b1 $p<0.05$; b2 $p<0.01$; b3 $p<0.001$ according to AA group.

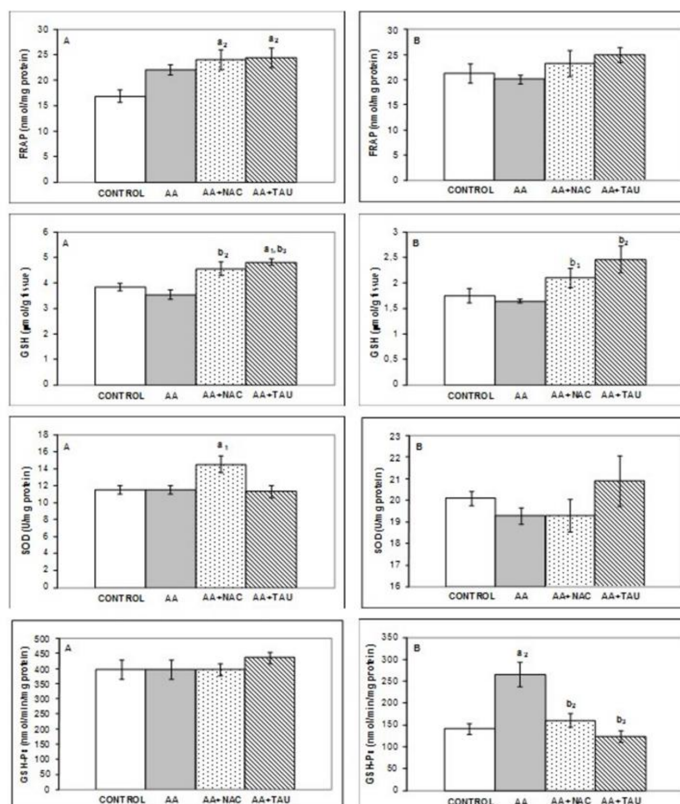

Figure 2: The effects of N-acetylcysteine (NAC) and taurine (TAU) on liver (A) and brain (B) ferric reducing antioxidant power (FRAP), glutathione (GSH) levels, and superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) activities (Mean ±SEM, n= 8 each)

a1 $p<0.05$; a2 $p<0.01$ according to control group; b1 $p<0.05$; b2 $p<0.01$; b3 $p<0.001$ according to AA group.

Figure 2 demonstrates the changes in antioxidant parameters. According to this;

a) Hepatic and brain FRAP levels were detected not to alter in AA-treated rats. Hepatic FRAP values were higher in AA+NAC ($p<0.01$) and AA+TAU ($p<0.01$) groups than control group.

b) There was no significant changes in hepatic and brain GSH levels of AA-treated rats as compared to controls. However, NAC and TAU treatments significantly increased hepatic ($p<0.01$, $p<0.001$) and brain ($p<0.05$, $p<0.01$) GSH levels as compared to AA group.

c) There were no changes in liver and brain SOD activities following AA treatment. In AA+NAC group, liver SOD ($p<0.05$) activity increased as compared to control values.

d) Liver GSH-Px activity did not alter in groups. However, significant increase in brain GSH-Px ($p<0.01$) activity was found in AA-treated rats. NAC and TAU treatments decreased brain GSH-Px ($p<0.01$, $p<0.001$) activity in AA-treated rats.

Discussion

Several factors including oxidative stress are implicated in AA-induced toxicity [5, 6]. It has been demonstrated that AA leads to accumulation of ROS through induction of aldehyde oxidase and xanthine oxidase and decreases GSH levels isolated hepatocytes [6, 30]. AA was detected to be 10-30 times more toxic than ethanol, when their LD50 doses were compared [31]. The increasing effect of AA on lipid peroxidation was reported to be more prominent than ethanol [8, 32]. Indeed, lipid peroxide levels were found to increase in hepatic mitochondrial and microsomal fractions in acute ethanol- (5 g/kg; i.p.) and AA- (500 mg/kg; i.p.) treated rats and the effect of AA was more marked in the mitochondrial fraction [33]. Increased hepatic lipid peroxide levels was also detected after acute AA (0.3 g/kg; per oral) administration [34]. Increases in serum ALT, AST and γ-glutamyl transpeptidase activities and decreases in free and protein- bound sulfhydryl groups in plasma, liver and brain were detected in rats after 4 weeks of AA (0.25 g/kg/day, per oral) treatment [35]. Some investigators have also reported that administration of AA for 11 weeks in drinking water was reported to cause steatosis, inflammation and protein-AA adducts in the liver [20, 21]. These authors have pointed that AA delivered via the digestive tract was to be more hepatotoxic than AA formed during ethanol oxidation within the liver. When AA is given in drinking water, it accumulates in the gastrointestinal tract, and even though some amounts are metabolized to acetate by intestinal bacteria, significant amounts of AA arrive to the liver via vena porta, and join to systemic circulation. Therefore, it has been reported that the use of AA in drinking water may be a suitable method to investigate the toxic effects of AA with extrahepatic origin [20, 21].

For this reason, in the current study the effect of long-term AA treatment in drinking water on prooxidant and antioxidant balance were investigated in liver and brain tissues of rats. AA treatment was detected to induce prooxidant state in both liver and brain of rats without any change in antioxidant parameters. Only, brain GSH-Px activity was found to increase significantly in AA-treated rats. This increase may be related to adaptive change against oxidative stress and may prevent further increases in prooxidant status in the brain. The results reported here agree with previous in vitro [6, 30] and in vivo [33, 34] studies showing that AA produces a prooxidant state in rats.

In the literature, there are some in vitro studies investigating the effect of NAC and TAU on AA-toxicity [36-38]. NAC was reported to prevent AA-related toxicity in embryo cell cultures [36]. It has been demonstrated that AA caused increases in ROS generation, mitochondrial dysfunction and apoptosis in cell cultures and that AA-induced toxic effects were averted by NAC [37]. TAU may also have a beneficial effect against aldehyde toxicity by forming conjugates with these compounds such as glucose, AA and MDA via its amino group [38]. However, there is no published in vivo study investigating the effects of NAC and TAU on the direct toxicity of AA.

In the present study, NAC treatment decreased AA-induced prooxidant status in both liver and brain. Although TAU treatment diminished ROS levels, MDA and PC levels remained unchanged in examined tissues of AA-treated rats. NAC and TAU elevated liver and brain GSH levels in AA-treated rats. These results can be attributed to their direct antioxidant properties such as scavenging free radicals and chelating metals together with their stimulating effect on GSH synthesis. Limitation of this study was the lack of histopathological analysis.

In conclusion, our results may indicate that NAC and TAU were found to decrease prooxidant status generated by in vivo AA-treatment and that NAC was more effective than TAU.

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