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Research Article
Comparative Investigation of the Effects of Adenosine Triphosphate and Agomelatine Against Acrolein-Induced Oxidative and Inflammatory Lung Injury in Rats

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Abstract

Background and Objective: Acrolein-induced tissue damage has been attributed to oxidative stress and inflammation. This study aimed to determine the effects of adenosine triphosphate (ATP) and agomelatine, two substances known to have antioxidant and anti-inflammatory effects, separately and in combination, on possible acrolein-induced lung damage in rats. **Materials and Methods:** There were 30 albino Wistar rats divided into five groups of six: Healthy (HG), acrolein (AC), ATP+acrolein (ATAC), agomelatine+acrolein (AGAC) and ATP+agomelatine+acrolein (AAAC). The dose of ATP administered intraperitoneally was 4 mg/kg and the dose of agomelatine administered orally was 25 mg/kg. An oral dose of acrolein 3 mg/kg was given 1 hr following the administration of ATP and agomelatine. For 30 days, the treatment protocol was followed once a day. Afterwards, the rats were euthanized and their lungs were removed. Oxidants, antioxidants and pro-inflammatory cytokines were measured in lung tissues. **Results:** In lung tissues, acrolein increased malondialdehyde, nuclear factor kappa, tumor necrosis factor-alpha, interleukin-1beta and interleukin-6 levels and decreased total glutathione, superoxide dismutase and catalase levels ($p<0.001$). The ATP+agomelatine, ATP and agomelatine treatments were the most effective at preventing these biochemical changes, respectively ($p<0.001$). As a result, the biochemical data of the HG and AAAC groups were similar ($p>0.05$). **Conclusion:** It could be suggested that both ATP and agomelatine might be effective against the pneumotoxic effects of acrolein, though a combination therapy would be more effective.

Key words: Acrolein, adenosine triphosphate, agomelatine, pneumotoxicity, oxidative damage

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

As a highly reactive aldehyde, acrolein poses a serious threat to human health and life[1]. It is possible for humans to be exposed to acrolein through both dietary and endogenous sources[2]. The majority of dietary acrolein is produced by heat treatment of lipid-rich foods, such as frying and barbecuing[3]. Acrolein is also found in alcoholic beverages such as beer, wine and brandy, in addition to fats and lipid-rich foods[3]. As well as dietary sources, acrolein can also be ingested through environmental sources, such as tobacco smoke and incomplete combustion of plastics, wood and gasoline[4]. The human body can also produce acrolein endogenously through polyamine catabolism and lipid oxidation, which may contribute to many diseases[2]. Acrolein exposure from dietary and environmental sources has been reported to accelerate the onset and spread of many pathological conditions[5]. Exogenous acrolein exposure has been linked to multiple sclerosis, neurodegenerative diseases, cardiovascular diseases, diabetes, asthma, chronic obstructive pulmonary disease and even respiratory cancer[1]. There is evidence that acrolein is more toxic than reactive oxygen species (ROS) and that it causes changes to the structure of proteins[6]. Additionally, acrolein has been reported to be a primary source of ROS and to play a significant role in lung disease pathogenesis[1]. Acrolein consumption has been shown to result in a decrease in intracellular adenosine triphosphate (ATP) concentrations[7]. Based on the information obtained from the literature, it is possible that acrolein-induced oxidative lung injury occurs as a result of a reduction in intracellular ATP levels.

In this study, acrolein was tested for its ability to prevent lung damage in rats and ATP is a nucleoside triphosphate consisting of adenine, ribose and three phosphates[8]. Cellular ATP is known to play a role in the synthesis of ROS scavenging and scavenging antioxidants, as well as to provide energy for the synthesis of antioxidants[9,10]. Furthermore, it has been found that ATP inhibits the increase of malondialdehyde (MDA), Tumor Necrosis Factor-α (TNF-α) and Nuclear Factor-κB (NF-κB) levels in tissues and organs as well as the decrease of antioxidant Total Glutathione (tGSH) levels[11].

In this study, acrolein was also tested against its possible pulmonary toxicity with agomelatine, a melatonin receptor agonist (MT_1 and MT_2)[12]. Despite not being approved for marketing by the US Food and Drug Administration, agomelatine is widely used throughout the world[13]. Agomelatine was originally investigated as a chronobiotic; however, following the discovery of its 5-HT2c antagonist activity, interest shifted to its anxiolytic and antidepressant properties[12]. As reported, agomelatine reduces lipid peroxidation (LPO) levels, protects neurons from cytosolic ROS damage and increases endogenous Glutathione (GSH) levels[14]. It is reported in the literature that agomelatine protects brain tissue from stress-induced oxidant and proinflammatory cytokine (TNF-α, Interleukin-6 (IL-6), Interleukin-1beta (IL-1β)) damage[15]. In the literature, no studies have investigated the effects of antioxidants such as ATP and agomelatine against acrolein-induced lung injury. Therefore, the purpose of this study was to examine and compare the effects of ATP, agomelatine and their combination on acrolein-induced lung injury in rats.

MATERIALS AND METHODS

Study area: Animal experiments of the study were carried out in February-March, 2024 at Erzincan Binali Yıldırım University Experimental Animals Application and Research Centre.

Animals: Thirty male albino Wistar rats (280-292 g) were obtained from Erzincan Binali Yıldırım University Experimental Animal Research and Application Center. Before the procedure, animals were fed *ad libitum* in groups of 6 (n = 6) at 21±2°C temperature in a 12 hrs light-dark cycle. The experimental process was endorsed by Erzincan Binali Yıldırım University Experimental Animals Local Ethics Committee (Date: 28.12.2023, No: 43).

Chemical substances: Acrolein (50 mg vial) was obtained from Sigma Aldrich, ATP from Zdorove Narodu (Kharkiv, Ukraine), Agomelatine from Servier (Istanbul, Turkey), Thiopental Sodium from IE Ulagay (Istanbul, Turkey).

Experimental groups: The rats were divided into 5 groups, each consisting of six rats: Healthy (HG), acrolein alone (AC), ATP+acrolein (ATAC), agomelatine+acrolein (AGAC) and ATP+agomelatin+acrolein (AAAC).

Experimental procedure: The ATAC group was first injected with ATP intraperitoneally (i.p.) at a dose of 4 mg/kg. In the AGAC group, agomelatine was given orally via gavage at a dosage of 25 mg/kg. A combination of ATP and agomelatine was administered to the AAAC group at the above-mentioned dose and method. During this period, both the HG and AC groups received the same amount of saline (0.9% NaCl) orally. Acrolein was administered orally by gavage to rats in the AC, ATAC, AGAC and AAAC groups 1 hr after ATP and agomelatine administration[16]. This treatment was repeated once a day for 30 days. After 30 days, the animals were

killed with 50 mg/kg intraperitoneal thiopental sodium and their lungs were removed. The oxidant antioxidant and proinflammatory cytokine levels including MDA, tGSH, superoxide dismutase (SOD), catalase (CAT), NF-κB, TNF-α, IL-1β and IL-6 were measured in the excised lung tissues.

Biochemical analyses

Analysis of MDA, GSH, SOD and CAT in lung tissue: In order to determine MDA, GSH and SOD levels in lung tissues, Enzyme-Linked Immunosorbent Assays (ELISAs) kits were used and the assays were conducted according to the instructions provided by the kit (Cat No. 10009055, 703002 and 706002, Cayman Chemical Company, Michigan, USA, respectively). The CAT determination was performed in accordance with the method described by Góth[17].

Analysis of NF-κB, TNF-α, IL-1β and IL-6 in lung tissue: In lung tissues, NF-κB levels were measured using ELISA rat kits obtained from SUNREDBIO (Shanghai, China) and TNF-α, IL-1β and IL-6 levels were measured using ELISA rat kits obtained from Eastbiopharm (Hangzhou, China) and the kit procedures were followed for the analysis.

Statistical analysis: The statistical analysis was conducted using SPSS statistical software version 22.0 (IBM, Armonk, New York, USA). The data were presented in the form of a mean and a standard deviation. A Shapiro-Wilk's test was conducted on the data and it was determined that they were normally distributed. As a result, one-way ANOVA was used for the analysis. Depending on the results of Levene's test, Tukey's or Games-Howell's tests were performed as *post hoc*. The p-values below 0.05 were considered significant.

RESULTS

MDA, tGSH, SOD and CAT analysis results: When MDA levels were measured between the rat groups as presented in Fig. 1a and Table 1, it was observed that MDA levels were

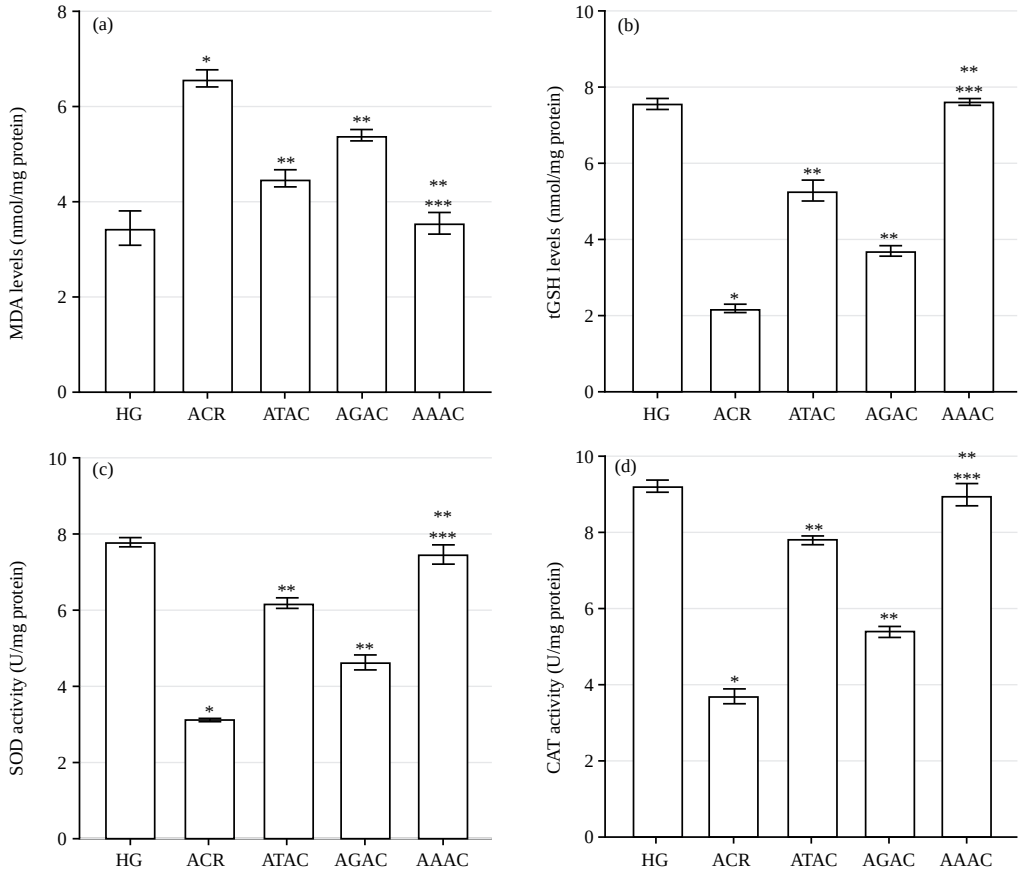

Fig. 1(a-d): Analysis results of oxidants and antioxidants in lung tissues

*p<0.001 vs. HG, **p<0.001 vs. ACR, ***p>0.05 vs. HG, MDA: Malondialdehyde, tGSH: Total Glutathione, SOD: Superoxide dismutase, CAT: Catalase, HG: Healthy, AC: Acrolein, ATAC: ATP+acrolein, AGAC: Agomelatine+acrolein and AAAC: ATP+agomelatine+acrolein

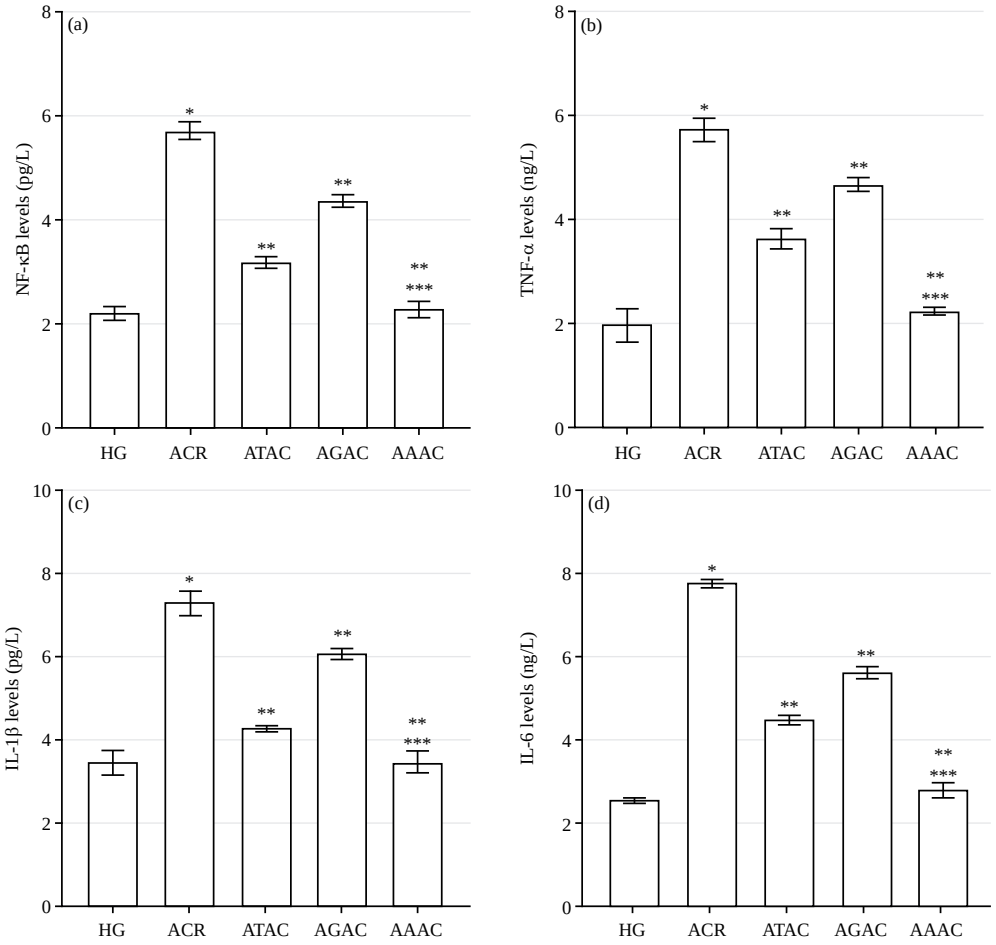

Fig. 2(a-d): Analysis results of pro-inflammatory cytokines in lung tissues

*p<0.001 vs. HG, **p<0.001 vs. ACR, ***p>0.05 vs. HG, MDA: Malondialdehyde, tGSH: Total glutathione, SOD: Superoxide dismutase, CAT: Catalase TNF-α: Tumor Necrosis Factor-alpha, IL-1β: Interleukin 1β, IL-6: Interleukin-6, HG: Healthy, AC: Acrolein, ATAC: ATP+acrolein, AGAC: Agomelatin+acrolein and AAAC: ATP+agomelatin+acrolein

Table 1: Results of biochemical analyses of lung tissues

	Experimental groups (Mean±Standard deviation)				
Biochemical parameter	HG	AC	ATAC	AGAC	AAAC
MDA (nmol/mg protein)	3.45±0.35	6.58±0.19*	4.50±0.16**	5.40±0.10**	3.56±0.21**,***
tGSH (nmol/mg protein)	7.55±0.15	2.21±0.09*	5.31±0.29**	3.71±0.16**	7.61±0.09**,***
SOD (U/mg protein)	7.82±0.10	3.14±0.05*	6.19±0.13**	4.63±0.17**	7.48±0.25**,***
CAT (U/mg protein)	9.19±0.15	3.70±0.20*	7.80±0.11**	5.40±0.17**	9.00±0.31**,***
NF-κB (pg/L)	2.24±0.13	5.75±0.15*	3.21±0.08**	4.41±0.13**	2.30±0.15**,***
TNF-α (ng/L)	1.96±0.31	5.70±0.22*	3.62±0.18**	4.64±0.14**	2.21±077**,***
IL-1β (pg/L)	3.45±0.29	7.35±0.29*	4.32±0.05**	6.12±0.12**	3.52±0.26**,***
IL-6 (ng/L)	2.55±0.15	7.75±0.20*	4.48±0.24**	5.61±0.30**	2.81±0.42**,***

*p<0.001 vs. HG, **p<0.001 vs. ACR, ***p>0.05 vs. HG, MDA: Malondialdehyde, tGSH; Total Glutathione, SOD: Superoxide dismutase, CAT: Catalase, TNF-α: Tumor Necrosis Factor-alpha, IL-1β: Interleukin 1β, IL-6: Interleukin-6, HG: Healthy, AC: Acrolein, ATAC: ATP+acrolein, AGAC: Agomelatine+acrolein, AAAC: ATP+agomelatine+acrolein. Statistical analysis was done with one way ANOVA and Games-Howell test or Tukey's HSD was applied as *post hoc*

elevated in the acrolein group compared to the healthy group (p<0.001). The ATP+agomelatine and ATP and agomelatine were the most effective suppressors of acrolein-induced MDA increases, respectively (p<0.001). The MDA levels were similar between rats that received ATP+agomelatine and rats in the HG (p = 0.963).

The results of antioxidant analysis in lung tissues revealed a reduction in tGSH, SOD and CAT levels in rats in the AC group ($p<0.001$). This decrease was determined to be suppressed in rats receiving ATP, agomelatine and combination therapy with acrolein ($p<0.001$). The ATP+agomelatine was the most effective treatment in maintaining antioxidant levels and tGSH, SOD and CAT data were similar in AAAC and HG groups ($p>0.05$) Fig. 1(b-d) and Table 1.

NF-κB, TNF-α, IL-1β and IL-6 analysis results: Lung tissues were also analyzed for the levels of NF-κB, TNF-α, IL-1β and IL-6. As seen in Fig. 2(a-d) and Table 1, the analysis results revealed that NF-κB, TNF-α, IL-1β and IL-6 levels were increased in the AC group treated with acrolein alone compared to the HG group ($p<0.001$). The acrolein-induced increase in NF-κB, TNF-α, IL-1β and IL-6 levels was best prevented by ATP+agomelatine, ATP and agomelatine treatments, respectively ($p<0.001$). The levels of NF-κB, TNF-α, IL-1β and IL-6 in the lungs of the AAAC and HG groups were similar ($p>0.05$).

DISCUSSION

As part of this study, ATP, agomelatine and their combination were investigated biochemically against the possible toxicity of acrolein on the lungs. Acrolein is a ubiquitous toxic chemical that is also produced by cellular metabolism[18]. However, due to the presence of acrolein in tobacco smoke, the lungs are a prime target for acrolein toxicity[19]. There is evidence that various mechanisms such as oxidative stress, inflammation and altered immune responses are involved in the pathogenesis of acrolein toxicity[18]. Acrolein, which is both a product and an initiator of oxidative damage, is reported to activate intracellular pathways that release ROS in the literature[19,20]. When excess ROS are produced, they react with polyunsaturated fatty acids in cell membranes, resulting in LPO and an increase in MDA levels[21,22]. Following LPO, MDA plays an important role in continuing oxidative cellular damage[23]. The biochemical results of our experiment indicated that MDA levels increased in the lung tissues of rats exposed to acrolein, similar to the findings of Rashad *et al.*[21]. In this study, it was found that ATP suppressed the increase in MDA in the presence of acrolein. There is evidence in the literature that acrolein disrupts mitochondrial respiration, decreasing ATP production[24]. The effects of ATP treatment on oxidative lung damage have not been investigated in any studies. However, it has previously been shown that exogenous ATP treatment decreased the increase in MDA observed in the presence of oxidative cardiac injury[11]. Despite agomelatine's ineffectiveness compared to ATP in this study, it was significantly effective in preventing the increase in MDA induced by acrolein. Agomelatine has also been tested in patients with methotrexate-induced lung injury and it has been shown to inhibit the increase in MDA levels and protect the lungs from damage caused by oxidative and inflammatory processes[25]. Furthermore, although ATP and agomelatine inhibited the increase in MDA levels, the lowest MDA levels were found in the combination of ATP and agomelatine.

Based on our biochemical analysis, we found that tGSH levels were lower in the acrolein group compared to the groups that had increased MDA levels. As an endogenous antioxidant, GSH provides cellular protection against reactive oxygen species (ROS)[26]. The GSH conjugation is the primary metabolic pathway of acrolein. If acrolein is not conjugated and removed from the system, cellular antioxidative defense is impaired, leading to a reduction in GSH levels and a decrease in the activity of antioxidant enzymes[27]. In human bronchial epithelial cell cultures, Nardini *et al.*[28] reported significant decreases in GSH levels after exposure to acrolein at varying times. As reported in another study, acrolein induces GSH depletion and is pneumotoxic[29]. As a result of our biochemical analysis, acrolein administration to rats resulted in a decrease in the activities of SOD and CAT enzymes, as well as the levels of tGSH in lung tissues. It is important to note that SOD and CAT are enzymes that function in coordination as endogenous antioxidants. In addition to catalyzing the dismutation of superoxide into hydrogen peroxide and molecular oxygen, SOD is a metalloenzyme in the first line of defense against reactive oxygen species. By converting hydrogen peroxide into oxygen and water, CAT detoxifies the hydrogen peroxide formed[30,31]. According to a previous study, the level of CAT activity in rat lungs decreased after 4 hrs of exposure to acrolein vapor in a dose-dependent manner, while the level of SOD activity increased[29]. In another study, it was reported that exposure to acrolein caused severe cytotoxicity and decreased SOD activity, GSH and ATP levels in human lung fibroblast cell cultures[32]. The ATP treatment significantly prevented the acrolein-induced decline in tGSH, SOD and CAT levels in this study. Exogenous administration of ATP, which is implicated in the production of antioxidants, has previously been shown to protect heart, skin and bone tissues from oxidative damage and to prevent the reduction of tGSH, SOD and CAT[11,23,33]. Agomelatine was also found to contribute to the maintenance of antioxidant levels in this study.

According to Kamel *et al.*[25] agomelatine significantly prevented methotrexate-induced decreases in GSH and SOD in lung tissues. During the literature review, no studies comparing the antioxidative effects of ATP and melatonin were found. In spite of this, our study results revealed that despite agomelatine's ability to increase ATP levels, it demonstrated a lower antioxidant effect than exogenously administered ATP[34]. In contrast, ATP+agomelatine combination was the most effective treatment for preventing acrolein-induced oxidant increase and antioxidant decrease.

The oxidative damage caused by acrolein in the lungs leads to inflammation of the tissues. Inflammation further contributes to the destruction of respiratory tract tissues[21]. Alternatively, inflammation contributes to an imbalance in the lungs' redox system by generating ROS[35]. Therefore, NF-κB, TNF-α, IL-1β and IL-6 amount were also investigated in rat lung tissues in our study. Current experimental results revealed that acrolein treatment increased both NF-κB and TNF-α, IL-6 and IL-1β levels in lung tissues. The NF-κB has been proposed as a transcription factor implicated in recognizing oxidative stress[20]. There were conflicting findings in the literature regarding the effect of acrolein on NF-κB. In addition to its immunosuppressive effect through suppression of NF-κB, acrolein is also reported to exert a proinflammatory effect by release of inflammatory mediators such as IL-1β, IL-6, IL-8 and TNF-α through activation of NF-κB expression[1]. It has been suggested that the different effects of acrolein on NF-κB may be cell-type specific and may be affected by various regulatory mechanisms including GSH depletion[36]. Current findings showed an increase in NF-κB, TNF-α, IL-6 and IL-1β levels following acrolein treatment. Similarly, Sun *et al.*[19] reported an increase in activated macrophages in the lungs, NF-κB induction and increased production of proinflammatory cytokines by intranasal acrolein exposure in rats. Liu *et al.*[37] showed that NF-κB expression increased in lung epithelial cells of rats exposed to acrolein. In addition, inflammatory cells and TNF-α, IL-8 and IL-1β were found to increase in bronchoalveolar lavage fluids. In another study, it was found that acrolein administration increased NF-κB, TNF-α, IL-6 and IL-1β levels in rat lungs[27]. Current experimental results revealed that the increase in inflammatory markers was inhibited by ATP pretreatment. Various studies have reported that ATP treatment has a decreasing effect on proinflammatory cytokine levels such as NF-κB, TNF-α and IL-6[11,25,38]. In the agomelatine group, NF-κB, TNF-α, IL-1β and IL-6 were lower than that of acrolein group and higher than that of the ATP group. The anti-inflammatory activity of agomelatine was attributed to NF-κB inhibition and this inhibition was believed to decrease the levels of proinflammatory cytokines. Kamel *et al.*[25] and Kose *et al.*[39] studies also revealed that agomelatine decreased the expression of NF-κB, TNF-α and IL-6 in lung injury induced by different factors in rats. In the literature, there were no studies investigating the combination of ATP and agomelatine in terms of anti-inflammatory activity.

Analyzing the histopathology of lung tissues is also important when investigating acrolein-induced lung injury and possible treatments.

CONCLUSION

In the current study, biochemical analyses were conducted to investigate the effects of ATP, agomelatine and ATP+agomelatine combination treatments on possible lung damage caused by acrolein. Our experimental results revealed that acrolein induced upregulation of oxidants (MDA) and proinflammatory cytokines (NF-κB, TNF-α, IL-1β and IL-6) and downregulation of antioxidants (tGSH, SOD and CAT) in rat lung tissue. In terms of preventing these changes, the ATP+agomelatine, ATP and agomelatine treatments performed the best, respectively. The results of the ATP and agomelatine combination treatment group were almost identical to those of the healthy group.

SIGNIFICANCE STATEMENT

Acrolein-induced toxicity may result from dietary sources and environmental exposure as well as endogenous sources. In the literature, it has been reported that acrolein exposure can accelerate the initiation and spread of many pathological conditions and therefore it is important to eliminate the adverse effects of toxicity. In the present study, the capacity of ATP and agomelatine to prevent acrolein-induced lung injury was investigated. Current results suggest that both ATP and agomelatine can be used to counteract the pneumotoxic effects of acrolein; however, combination therapy may prove to be more effective.

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