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Protective Effects of cAMP and Coenzyme Q Against Cisplatin-Induced Liver Injury

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Abstract

Objective: This study aimed to investigate the effects of cyclic adenosine monophosphate (cAMP) and coenzyme Q (CoQ), administered individually or in combination, on the hepatic antioxidant defense system and oxidative damage markers in a cisplatin (Cis)-induced hepatotoxicity model.

Methods: Wistar albino rats bred at the Ondokuz Mayıs University Experimental Animal Research Center were divided into eight groups: control, Cis, CoQ, cAMP, CoQ+cAMP, Cis+CoQ, Cis+cAMP, and Cis+CoQ+cAMP. Superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) activities as well as malondialdehyde (MDA) levels were measured in the liver tissues obtained from experimental groups. Data were analyzed using the Mann-Whitney U test.

Results: Cis administration caused time-dependent fluctuations in SOD, CAT, and GPx activities, along with an increase in MDA levels. CoQ administration significantly reduced MDA levels at all time points and improved antioxidant enzyme activities. cAMP administration markedly decreased MDA levels, particularly in the early phase (4–12 h), and modulated SOD and CAT activities. The combined administration of cAMP and CoQ enhanced GPx activity in the late phase (24–48 h) and exerted the strongest suppression of MDA levels.

Conclusion: The findings indicate that cAMP is as effective as CoQ in attenuating cisplatin-induced oxidative stress. Both cAMP and CoQ exhibited hepatoprotective effects individually, while their combination produced a synergistic effect, achieving the highest degree of protection. These results may contribute to the development of novel pharmacological strategies to mitigate cisplatin-associated hepatotoxicity.

Keywords: Cisplatin; Liver Injury; Oxidative Stress; cAMP; Coenzyme Q; Antioxidant Enzymes; Protective Effect

1. Introduction

Cisplatin (Cis) is a broad-spectrum chemotherapeutic agent widely used in the treatment of solid tumors. Despite its efficacy, one of the most significant limiting factors in clinical applications is the severe toxicities it induces in various organs [1]. Hepatotoxicity is a critical adverse effect of Cis that can lead to considerable morbidity in clinical practice [2]. As the liver plays a central role in drug biotransformation, it is particularly vulnerable to oxidative stress–mediated injury [3].

The underlying mechanism of Cis-induced hepatotoxicity is associated with increased production of reactive oxygen species (ROS), elevated lipid peroxidation, and imbalance in the antioxidant defense system [4,5]. Functional alterations of enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) play a pivotal role in this process. In particular, ROS overproduction results in the oxidative degradation of membrane lipids, leading to malondialdehyde (MDA) accumulation, which serves as a hallmark of cellular damage [5].

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Recent studies have demonstrated that oxidative stress is not only limited to classical cellular injury but also triggers programmed cellular processes such as ferroptosis and endoplasmic reticulum (ER) stress [6]. Therefore, protective strategies against Cis-induced hepatotoxicity are suggested to involve agents that target multiple pathways, including antioxidants and intracellular signaling regulators [6,7].

In this context, coenzyme Q (CoQ) and cyclic adenosine monophosphate (cAMP) stand out as noteworthy molecules. CoQ is an endogenous antioxidant that plays a crucial role in the mitochondrial electron transport chain and has been shown to attenuate oxidative stress–related liver injury in various experimental models [7,8]. On the other hand, elevation of intracellular cAMP levels provides hepatoprotective effects by activating CREB-mediated antioxidant gene expression and suppressing inflammation [9]. Recent studies have reported that cAMP-enhancing agents, such as phosphodiesterase-3 (PDE3) inhibitors, alleviate Cis-induced liver injury [10].

Therefore, investigating the protective effects of cAMP and CoQ, both individually and in combination, in a Cis-induced hepatotoxicity model is of considerable importance for elucidating the mechanistic aspects of oxidative stress and guiding the development of novel pharmacological strategies.

2. Materials and Methods

In the study approved by the Ondokuz Mayıs University Ethics Committee with the decision numbered HEK/28, Wistar albino rats weighing 250-300 g, bred in the Ondokuz Mayıs University Experimental Animal Research Center (DEHAM), were used.

2.1. Experimental Groups

Eight groups were formed as follows:

Control group (no intervention), 2. Cis group, 3. CoQ group, 4. cAMP group,5. CoQ + cAMP group, 6. Cis + CoQ group, 7. Cis + cAMP group, 8. Cis + CoQ + cAMP group.

Each group consisted of 5 rats. Injections were administered between 08:00 and 09:00 a.m. Following injection, animals were sacrificed by cervical dislocation at 4, 8, 12, 24, and 48 hours. After perfusion with 0.9% NaCl, the livers were excised and stored in 0.25 M sucrose solution at –80 °C until analysis.

2.2. Administered Substances

Cis was used at a dose of 10 mg/kg (commercial preparation, 100 mg/100 mL) [11]. cAMP, obtained from Calbiochem, was administered at a dose of 15 mg/kg [12], and CoQ, obtained from Sigma (London, England), was administered at a dose of 371 mg/kg [13].

Determination of Enzyme Activities and MDA Levels

- Protein concentration was determined by the method of Lowry et al. [14].
- CAT activity was measured according to the method of Lück [15].
- SOD activity was determined by the method of McCord and Fridovich [16] and further validated by the method of Flohé and Otting [17].
- GPx activity was measured as described by Lawrence and Burk [18].
- MDA levels were assessed using the method of Draper and Hadley [19], in addition to the thiobarbituric acid (TBA) assay described by Hommouda et al. [20].

Statistical Analysis; Data were analyzed using the Mann-Whitney U test, and $p < 0.05$ was considered statistically significant.

3. Results

SOD Activity: When the effect of Cis on total hepatic SOD activity was compared with the control group, inhibition was observed within the first 8 hours, while at the 12th hour, a 45% activation was detected. This activation decreased at the 24th hour and returned to nearly control levels at the 48th hour ($p > 0.05$). However, when the enzymatic activity changes induced by Cis were compared across different time points, significant differences were observed ($p < 0.05$).

cAMP administration resulted in significant inhibition at all time points ($p < 0.05$). Similarly, CoQ administration caused statistically significant inhibition across all time points ($p < 0.05$). In the Cis+cAMP group, compared with the control, the 45% activation observed with Cis alone at the 12th hour increased to 80% with the addition of cAMP ($p < 0.05$). In the Cis+CoQ group, this activation reached 66% with CoQ supplementation ($p < 0.05$). In the cAMP+CoQ group, 40% inhibition was observed at the 4th hour and 56.8% at the 8th hour. At the 12th hour, inhibition decreased to 10.9%, which shifted to 1.6% activation at the 24th hour and reached 45% activation at the 48th hour. These enzyme activity changes were statistically significant across time points ($p < 0.05$).

In the Cis+cAMP+CoQ group, 22% inhibition was observed at the 4th hour and 35.8% at the 8th hour, followed by 33.5% activation at the 12th hour. At the 24th hour, 46% inhibition was recorded, while at the 48th hour, 31.8% activation was noted. The inhibition observed at the 8th hour was statistically significant ($p < 0.05$). When compared across different time points, significant differences were observed between the 4th and 48th hours ($p = 0.028$) and the 8th and 48th hours ($p = 0.028$) ($p < 0.05$) (Figure 1).

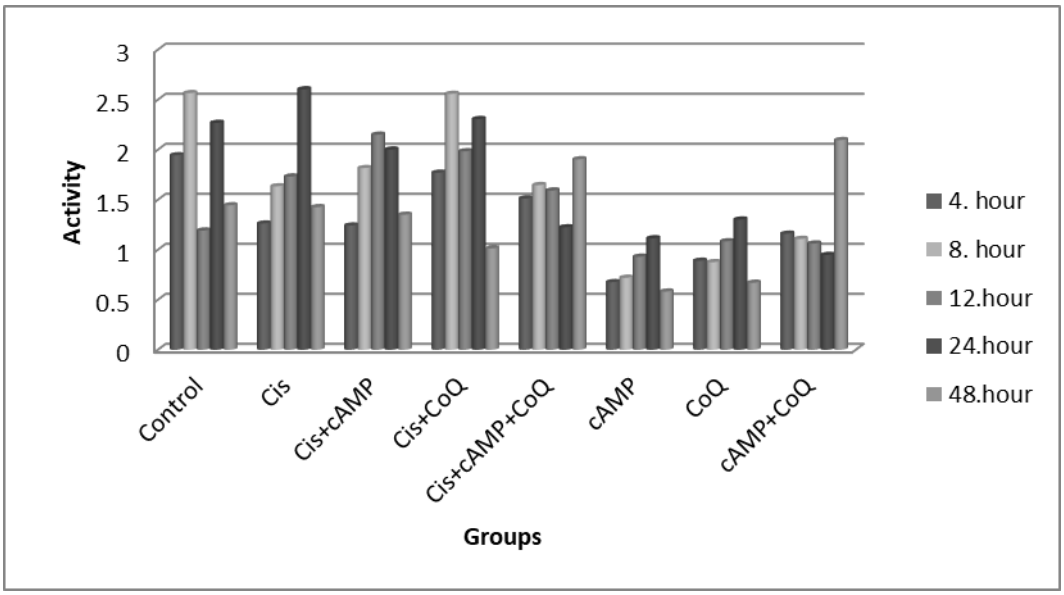

Figure 1 Time-dependent change of SOD activity according to experimental groups

CAT Activity: Compared with the control group, Cis administration caused 13.6% and 18.5% inhibition in hepatic CAT activity at the 4th and 8th hours, respectively. At the 12th hour, 31% activation was detected, which decreased to 20% at the 24th hour and returned to near-control levels at the 48th hour. Significant differences were observed among time points ($p < 0.05$).

In the cAMP group, compared with the control, CAT activity showed 5.7% inhibition at the 4th hour and 30.9% at the 8th hour, while 19.6% activation was observed at the 12th hour. No difference was noted at the 24th hour, whereas 36% activation occurred at the 48th hour. The changes in CAT activity were statistically significant at the 8th ($p = 0.028$) and 12th hours ($p = 0.009$).

In the CoQ group, inhibition was observed at the 4th (2%) and 8th (24%) hours. This inhibition was 15.7% at the 12th hour and 18.9% at the 24th hour, followed by 12.7% activation at the 48th hour. These changes were statistically significant ($p < 0.05$).

In the Cis+cAMP group, CAT activity showed 30.9% inhibition at the 4th hour, which decreased to 20% at the 8th hour, and shifted to 35.7% activation at the 12th hour. At the 24th and 48th hours, 20% inhibition was observed. The differences at the 24th and 48th hours compared with the control were statistically significant ($p < 0.05$).

In the Cis+CoQ group, no difference was observed at the 4th hour, while 21% inhibition occurred at the 8th hour. At the 12th hour, inhibition was 2%, followed by 15% activation at the 24th hour and 36% inhibition at the 48th hour. The difference at the 48th hour was statistically significant ($p < 0.05$).

In the Cis+cAMP+CoQ group, no differences were noted at the 4th hour, while inhibition of 10% and 15% occurred at the 8th and 12th hours, respectively. At the 24th hour, 15% activation was recorded, followed by 31% inhibition at the 48th hour. The difference at the 48th hour was statistically significant ($p < 0.05$). Differences among time points were also significant ($p < 0.05$) (Figure 2).

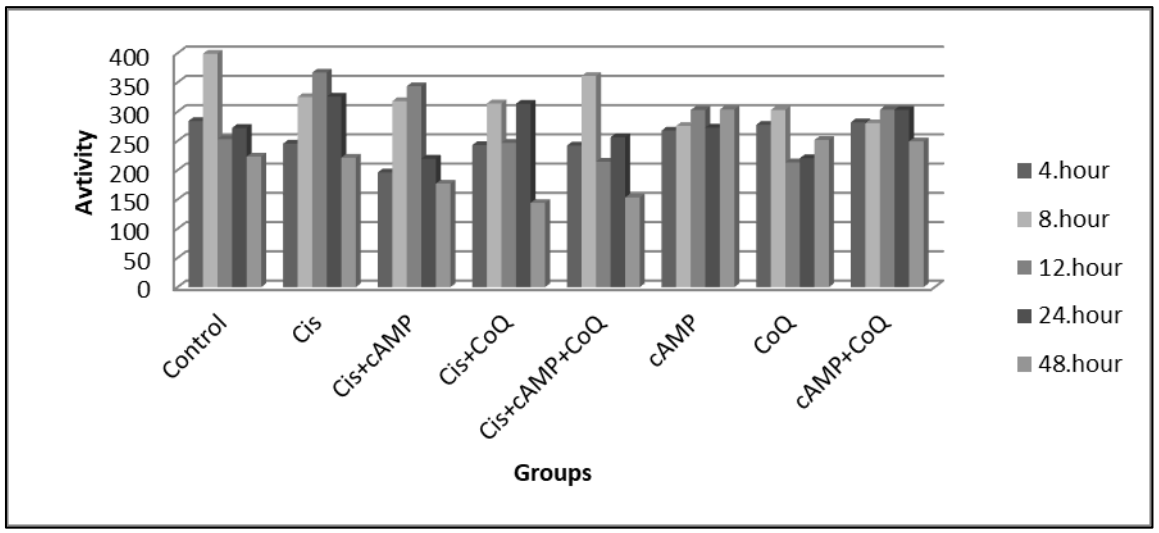

Figure 2 Time-dependent change of CAT activity according to experimental groups

GPx Activity: In the Cis group, GPx activity showed 37% inhibition at the 4th hour compared with the control group, while no differences were observed at the 8th and 12th hours. At the 24th hour, 26% activation was noted, which increased to 33% at the 48th hour. The inhibition observed at the 4th hour was statistically significant ($p < 0.05$).

In the cAMP group, GPx activity showed 84% inhibition at the 4th hour and 51% at the 8th hour compared with the control. At the 12th hour, 3% activation was recorded, followed by no difference at the 24th hour and 4% inhibition at the 48th hour. Inhibition at the 4th hour was statistically significant ($p < 0.05$).

In the CoQ group, GPx activity showed 85% inhibition at the 4th hour and 24% inhibition at the 8th hour. At the 12th hour, 30% activation was observed, which decreased to 6% at the 24th hour and increased to 37% at the 48th hour. Inhibition at the 4th hour and activation at the 48th hour were statistically significant ($p < 0.05$).

In the Cis+cAMP group, GPx activity showed 48% and 34% inhibition at the 4th and 8th hours, respectively. At the 12th hour, 45% activation was noted. At the 24th and 48th hours, 23% inhibition and 22% activation were observed, respectively. The inhibition at the 4th hour was statistically significant ($p < 0.05$).

In the Cis+CoQ group, GPx activity showed 41% inhibition at the 4th hour, followed by 22% activation at the 8th hour. At the 12th hour, 39% inhibition was recorded, followed by 40% activation at the 24th hour and 15% inhibition at the 48th hour. The inhibition at the 4th hour was statistically significant ($p < 0.05$).

In the cAMP+CoQ group, GPx activity showed 40% inhibition at the 4th hour, 46% inhibition at the 8th hour, and 42% inhibition at the 12th hour. At the 24th hour, 37% activation was recorded, which markedly increased to 130% at the 48th hour. Differences across time points were statistically significant ($p < 0.05$).

In the Cis+cAMP+CoQ group, GPx activity showed 44% inhibition at the 4th hour and 46% inhibition at the 8th hour, which decreased to 13% at the 12th hour. At the 24th hour, 103% activation was observed, followed by 44% inhibition at the 48th hour. These differences were statistically significant ($p < 0.05$) (Figure 3).

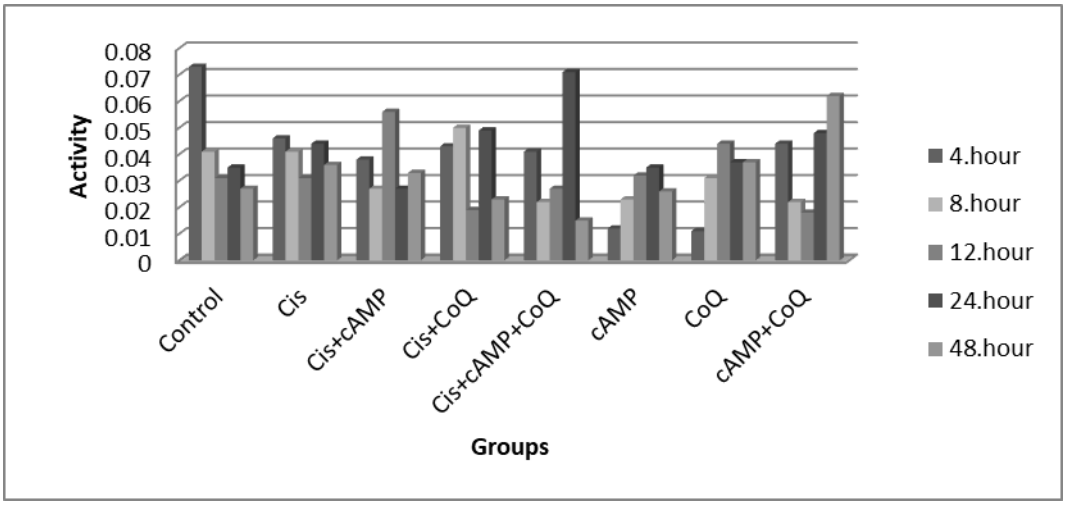

Figure 3 Time-dependent change of GPx activity according to experimental groups

MDA Levels: In the Cis group, hepatic MDA levels were 7% lower than the control at the 4th hour but increased by 20% at the 8th hour and 15% at the 12th hour. At the 24th and 48th hours, MDA levels were 4% and 34% higher, respectively. Although Cis administration led to an overall increase in MDA levels after the 4th hour, these increases were not statistically significant ($p > 0.05$). However, differences among time points were statistically significant ($p < 0.05$).

In the cAMP group, hepatic MDA levels were reduced by 84%, 83%, 68%, 75%, and 72% at the 4th, 8th, 12th, 24th, and 48th hours, respectively, compared with the control. These reductions were statistically significant at all time points ($p < 0.05$).

In the CoQ group, hepatic MDA levels were 81%, 77%, 75%, 85%, and 89% lower at the 4th, 8th, 12th, 24th, and 48th hours, respectively, compared with the control. All reductions were statistically significant ($p < 0.05$).

In the cAMP+CoQ group, MDA levels were reduced by 92%, 76%, 85%, 92%, and 84% at the 4th, 8th, 12th, 24th, and 48th hours, respectively. These reductions were statistically significant at all time points ($p < 0.05$).

In the Cis+cAMP group, MDA levels were 9% and 1% higher at the 4th and 8th hours, respectively, compared with the control, and 30% higher at the 12th hour. At the 24th and 48th hours, MDA levels were 28.7% and 17% lower, respectively. While these changes were not statistically significant compared with the control ($p > 0.05$), differences across time points were significant ($p < 0.05$).

In the Cis+CoQ group, MDA levels were 28% higher at the 4th hour compared with the control, 15% lower at the 8th hour, 48% higher at the 12th hour, 35% higher at the 24th hour, and 3% lower at the 48th hour. These differences were not statistically significant ($p > 0.05$). However, comparisons across time points revealed significant differences ($p < 0.05$).

In the Cis+cAMP+CoQ group, MDA levels were 9% higher at the 4th hour, nearly equal (1% higher) to control at the 8th hour, and 30% higher at the 12th hour. At the 24th hour, MDA levels were 29% lower, while at the 48th hour, they were 10% higher compared with the control. Although differences with the control were generally not significant, MDA levels at the 12th hour were significantly higher ($p < 0.05$). Comparisons across time points showed significant differences between the 4th and 48th hours, as well as between the 8th and 48th hours ($p < 0.05$) (Figure 4).

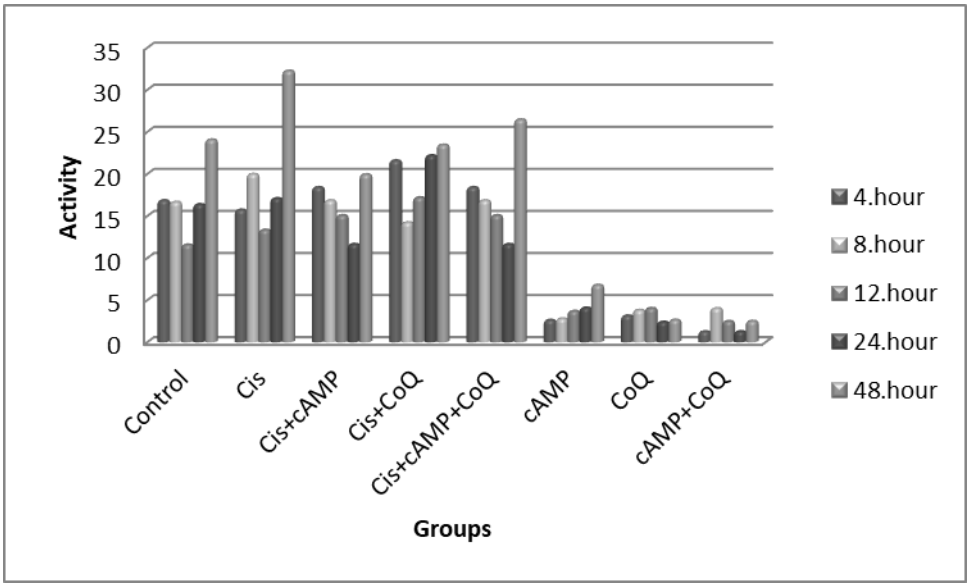

Figure 4 Change in MDA amount over time according to experimental groups

4. Discussion

The primary mechanism of tissue injury caused by reactive oxygen species (ROS) is lipid peroxidation of cell membranes. While lipid peroxidation occurs at very low levels in healthy tissues, its increase can be considered an indicator of ROS-mediated tissue damage. One of the degradation products of lipid peroxidation is malondialdehyde (MDA), and the measurement of MDA levels is widely accepted as a biomarker of in vivo ROS-mediated injury [21].

In this study, the effects of coenzyme Q10 (CoQ), an antioxidant, and cyclic adenosine monophosphate (cAMP), a secondary messenger regulating various cellular functions, were investigated in a cisplatin (Cis)-induced hepatotoxicity model. Specifically, we examined their impact on hepatic radical-scavenging enzyme activities and MDA formation.

Our results demonstrated that Cis administration altered SOD, CAT, and GPx activities and increased MDA levels. Türkmen et al. [22] reported that in a Cis-induced cardiotoxicity model, activities of SOD, GPx, CAT, and total glutathione levels decreased significantly. Similarly, Taghizadeh [23] showed that MDA levels, hepatic injury enzymes (ALT, AST, ALP), and caspase-3 immunoreactivity increased in the liver tissue of Cis-injected mice. Doğan et al. [24] also reported that Cis markedly elevated MDA and 8-OHdG levels in kidney and liver tissues.

In our study, administration of CoQ alone significantly reduced MDA levels at all time points. When CoQ was co-administered with Cis, it attenuated Cis-induced MDA elevation, particularly at the 8th and 48th hours. Sunar [25] demonstrated that CoQ supplementation suppressed MDA production, thereby preventing Cis-induced histopathological retinal injury. Hormozi et al. [26] also showed that CoQ effectively reduced MDA levels and improved antioxidant enzyme activity in cadmium-exposed rat livers.

Our findings indicate that Cis triggers time-dependent dynamic changes in antioxidant enzyme activities. SOD and CAT inhibition in the early phase (4–8 h), followed by reactivation at 12–24 h, reflects an adaptive stress response in hepatocytes. Similarly, the marked GPx increase at 24–48 h is consistent with a late-phase activation of the NRF2-ARE pathway, a critical defense axis against oxidative stress [27]. These data support the notion that different biomarkers vary in their sensitivity and timing in response to oxidative injury [5]. The increase in MDA levels observed in our study also suggests that Cis not only induces classical oxidative stress but may also trigger ferroptosis, a lipid peroxidation–driven form of programmed cell death. Previous studies emphasized the critical role of GPx4 and the NRF2 pathway in ferroptosis regulation, highlighting GPx activity as an adaptive response to suppress ferroptosis [4,27].

One of the most important findings of our study is that cAMP demonstrated antioxidant effects comparable to CoQ. Particularly in the early phase (4–12 h), cAMP administration significantly reduced MDA levels and modulated SOD and CAT activities. These results can be explained by the activation of the cAMP/CREB signaling pathway, which induces antioxidant gene expression and suppresses inflammation. In line with our findings, several studies have reported that elevation of intracellular cAMP attenuates oxidative stress and inflammation while improving mitochondrial functions,

thereby exerting hepatoprotective effects [9,10,29,30]. Although CoQ provided a more stable and sustained antioxidant response, the early protective effect of cAMP suggests that it may represent a valuable therapeutic candidate against Cis-induced hepatotoxicity.

CoQ treatment consistently suppressed MDA levels and improved antioxidant enzyme activities at all examined time points. This is in agreement with previous reports showing the protective effects of CoQ against oxidative stress–mediated damage in multiple tissues, including the retina, kidney, and liver [8,25,26]. Furthermore, studies have suggested that CoQ exerts synergistic antioxidant effects when combined with other agents [28]. The enhanced late-phase hepatoprotection observed in the cAMP+CoQ group in our study further supports the therapeutic potential of combination strategies.

Finally, recent studies have demonstrated that ER stress and activation of the PERK/ATF4/CHOP axis play important roles in Cis-induced hepatotoxicity [2,6]. The reduction in MDA levels and improvement in antioxidant enzyme activities observed in our study may be associated with alleviation of these stress responses. Taken together, our findings highlight that both cAMP and CoQ mitigate Cis-induced hepatotoxicity through multiple mechanisms, including modulation of oxidative stress, ferroptosis, and ER stress pathways.

Our study demonstrated that cisplatin induces time-dependent oxidative stress in the liver, during which different components of the antioxidant defense system are activated at distinct time intervals. The findings revealed that SOD and CAT activities were suppressed in the early phase, whereas GPx activity was markedly increased in the late phase. This observation is consistent with the dynamic activation patterns of the NRF2-ARE pathway described in the literature [27]. Moreover, the increase in MDA levels suggests that cisplatin may trigger not only classical oxidative stress but also lipid peroxidation–driven cell death pathways (ferroptosis) [4].

With respect to pharmacological interventions, cAMP administration significantly reduced MDA levels and modulated SOD and CAT activities. These findings are in line with current evidence indicating that the cAMP/CREB pathway suppresses oxidative stress and inflammation [9,10,29,30]. CoQ administration, on the other hand, consistently decreased MDA levels and improved antioxidant enzyme activities. This outcome parallels previous studies reporting the protective effects of CoQ against oxidative stress–mediated damage in various tissues [7,8,25,26].

Another noteworthy finding was the synergistic effect observed with the combined administration of cAMP and CoQ. This combination particularly enhanced GPx activity in the late phase and exerted the most pronounced suppression of MDA levels. Such results are consistent with recent literature highlighting the therapeutic potential of antioxidant combination strategies [28].

5. Conclusion

This study demonstrated that cisplatin induces time-dependent oxidative stress in the liver, during which different components of the antioxidant defense system are activated at distinct time intervals. The findings revealed that SOD and CAT activities were suppressed in the early phase, whereas GPx activity was markedly increased in the late phase. Furthermore, the elevation of MDA levels indicated that cisplatin triggers not only classical oxidative stress but also lipid peroxidation–driven cell death pathways (ferroptosis).

In conclusion, the data obtained demonstrate that in the cisplatin-induced hepatotoxicity model, cAMP exhibits antioxidant effects comparable to those of CoQ, with both agents providing significant protective roles. Notably, their combined administration achieved the greatest benefit by suppressing oxidative stress and enhancing antioxidant defense. These findings highlight the potential of cAMP and CoQ as promising candidates for the development of novel neuroprotective and anticancer adjuvant strategies aimed at mitigating cisplatin-associated hepatotoxicity.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

This study was approved by the Ondokuz Mayıs University Animal Ethics Committee decision numbered HEK/28.

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