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Research Article
Ameliorative Effect of Galantamine on Doxorubicin-Induced Cardiotoxicity and Hypothyroidism

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Abstract

Background and Objective: Doxorubicin (DXR) is used to treat cancer patients, although it has been linked to hypothyroidism and cardiotoxicity. Few research studies have examined how cholinergic activity can protect against hypothyroidism and cardiotoxicity, despite DXR destroying the cholinergic system. Neuroprotective qualities are seen in the acetylcholinesterase inhibitor galantamine (GLN). The current research investigated the mechanisms linked to DXR-induced hypothyroidism and cardiotoxicity, as well as the possible protective effect of GLN in avoiding hypothyroidism and cardiotoxicity. **Materials and Methods:** Female Wistar rats were categorized as either controls, DXRs, GLNs or DXR+GLNs. The rats were divided into two groups: One received DXR (5 mg kg^{-1} intraperitoneally twice weekly for two weeks), while the other received GLN (2.5 mg kg^{-1} via oral gavage once daily for 15 days). The DXR+GLN group received both GLN (twice weekly) and DXR (daily) at the same time. Biochemical calculation of cardiotoxicity biomarkers troponin I, CK and CK-MB in rat blood serum was performed, together with biochemical estimation of thyroid hormone TSH, T3, FT3, T4, FT4 and T4. **Results:** The DXR decreased T3, FT3, T4 and FT4 levels, co-treatment with GLN enhanced this decrease. In addition, DXR raised Troponin I, CK and CK-MB levels, while co-treatment with GLN (DXR+GLN) reduced those elevations. The DXR-treated rats had significantly lower T4, FT4, T3 and FT3 levels, but GLN had no effect. **Conclusion:** The GLN showed promise as a neuroprotective drug against DXR-induced hypothyroidism and cardiotoxicity in rats.

Key words: Doxorubicin, galantamine, acetylcholinesterase inhibitor, hypothyroidism and cardiotoxicity

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

INTRODUCTION

Cancer, a formidable affliction, stands as a prominent contributor to global mortality, claiming the lives of an estimated 10 million individuals in the year 2020, thus solidifying its position as a leading cause of death[1]. Even though there has been an increase in the number of deaths caused by cancer, the survival rate of patients in developing nations has improved thanks to improvements in early identification and treatment[2]. The most significant drawbacks of chemotherapy are its potential for harm and the development of resistance to its effects[3]. There is evidence that chemotherapy can also produce various additional harmful effects, including cardiotoxicity, hepatotoxicity, nephrotoxicity and thyroid dysfunction[4,5].

The DXR, classified as an anthracycline chemotherapy medication, is frequently administered to patients undergoing adjuvant therapy for breast cancer[6]. Two mechanisms have been shown that DXR has anticancer effects, one mechanism is intercalating DNA and other is blocking topoisomerase II[7]. Free radicals are increased by DXR, which in turn causes damage to cellular membranes, DNA and proteins[8]. Previous research conducted by our team found that DXR has the potential to cause neurotoxicity and inflammation[9,10]. On the other hand, relatively few medications have been shown to lower the toxicity of DXR[9,10]. Acetylcholine is an essential neurotransmitter for memory function and cholinergic neurons are the cells in the brain that create it[11]. The innervation of cholinergic nerves extends to a wide range of central and peripheral tissues, encompassing vital organs such as the heart and thyroid gland. Upon activation, these tissues respond to the binding of acetylcholine to either nicotinic or muscarinic receptors[12]. Cholinergic nerves innervate the majority of central and peripheral tissues[13]. It has been observed that chemotherapy causes a decrease in acetylcholine levels, which may have an effect on the activities of both the heart and the thyroid[14].

As a treatment for Alzheimer's disease, the acetylcholinesterase inhibitor GLN is administered to the patient[15]. The GLN does not treat Alzheimer's disease but has been shown to increase both acetylcholine levels and cognitive performance[16]. The GLN exerts inhibitory effects on the enzymatic degradation of acetylcholine, while concurrently promoting the release of acetylcholine from presynaptic neurons. Furthermore, GLN plays a pivotal role in modulating the activity of both nicotinic and muscarinic receptors[17]. The neuroprotective impact of GLN and its ability to increase cognitive performance has been demonstrated in both clinical and preclinical research[18].

Moreover, acetylcholinesterase inhibitors like donepezil were shown to improve heart function after treatment with doxorubicin[19]. Furthermore, DXR has been linked to the development of hypothyroidism, a condition that can severely impact cardiac function[20]. A recent study found that doxorubicin can impact cardiac function by causing hypothyroidism but that treatment with thyroxine can ameliorate this dysfunction[21]. As a result, the purpose of this study was to test a hypothesis regarding hypothyroidism and the potential protective influence of galantamine to reverse the effects of the condition on heart and thyroid functions.

There are quite a few studies evidencing the relation between DXR and cardiotoxicity, the knowledge is still limited about DXR and hypothyroidism in breast cancer patients[22]. Hence, it is of considerable interest to explore the impact of DXR-induced cardiotoxicity and hypothyroidism in female rats, as well as the potential mitigation thereof through the administration of GLN. Moreover, the outcomes of this investigation aim to elicit a comprehensive comprehension of the fundamental mechanisms involved in chemotherapy-induced cardiotoxicity and hypothyroidism, thereby offering an experimental instrument for exploring potential interventions that foster improved lifestyles in individuals who have survived cancer by alleviating the toxicity associated with anticancer medications.

MATERIALS AND METHODS

Study area: The study conducted between 1st to 30th May, 2023 at the College of Pharmacy, Qassim University in the Kingdom of Saudi Arabia.

Chemicals: The DXR was obtained from EBEWE Pharma Company (Attersee, Austria), while GLN hydrochloride was obtained from Sigma-Aldrich (USA).

Animals and drug administration: Forty female rats (weighing 150-250 g) obtained from the College of Pharmacy, Qassim University were housed individually in plastic cages. The animals were maintained under standard laboratory conditions under a light and dark cycle of 12 hrs each and at a temperature of 25°C. They were given free access to food and water. The rats were separated into four groups, control (saline 0.1 mL/100 g, i.p., twice weekly for two weeks), DXR, GLN and DXR+GLN. Rats in the DXR groups were administered an intraperitoneal injection of 5 mg kg^{-1} DXR twice weekly for 2 weeks (total dose: 20 mg kg^{-1}). The GLN was administered to the GLN groups dissolved in the rats' drinking water at a 2.5 mg kg^{-1} concentration. The DXR+GLN was administered GLN daily on the same day as DXR treatment.

Electrochemiluminescence immunoassays analysis: On day 14, after administering the last drug dose, animals were sacrificed by cervical decapitation under CO_2 anesthesia. Blood was promptly collected into EDTA tubes from the four groups (controls, GLN, DXR and DXR+GLN) and the vials of the samples were centrifuged at 12,000×g for 10 min. The plasma was collected, transferred to 2 mL vials and stored at -80°C. Subsequently, the samples were collected and analyzed using a fully automated analyzer that utilizes a patented Electrochemiluminescence (ECL) technology for immunoassay analysis of TSH, T4, FT4, T3, FT3, troponin I, CK and CK-MB. The ECL technology method employed the COBAS INTEGRA 400 plus system following the manufacturer's instructions (Roche Diagnostics, Germany). The obtained data were subjected to statistical analysis.

Statistical analysis: The data obtained from the experiment were subjected to analysis using GraphPad Prism 10.0.0.153 software, developed by GraphPad in Boston, Massachusetts, USA. The results were expressed as Means±Standard Error of the Mean. The ECL results for each group were subjected to a One-way Analysis of Variance (ANOVA), followed by Dunnett's analysis for further examination. The data pertaining to all treatment groups were subjected to comparative analysis in relation to the control data. A p-value below the threshold of 0.05 was deemed to possess statistical significance.

RESULTS

Effects of DXR and GLN on cardiotoxicity: Analysis revealed no significant differences in troponin I levels between the groups. However, there was a slight increase in troponin I level in the DXR group relative to the control group (Fig. 1). The DXR therapy (20 mg kg^{-1}, intraperitoneal administration) caused a substantial increase in troponin I, CK and CK-MB levels, which was partially (but not fully) reversed by DXR+GLN co-treatment (Fig. 1a-c).

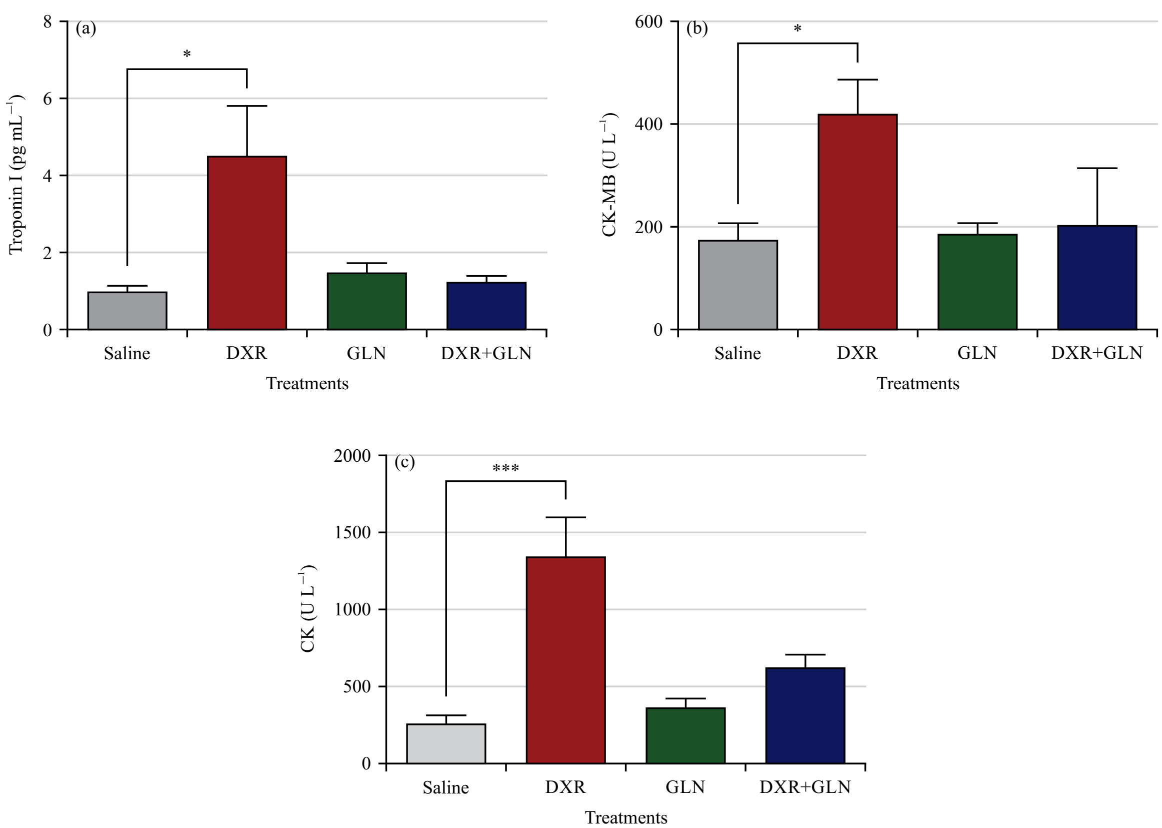

Fig. 1(a-c): Effects of DXR, GLN and combination on (a) Troponin I, (b) CK-MB and (c) CK levels

Results were presented using the Standard Error of the Mean (SEM) and comparisons to the control group were done using one-way ANOVA, as respect to the control rats (*p<0.05)

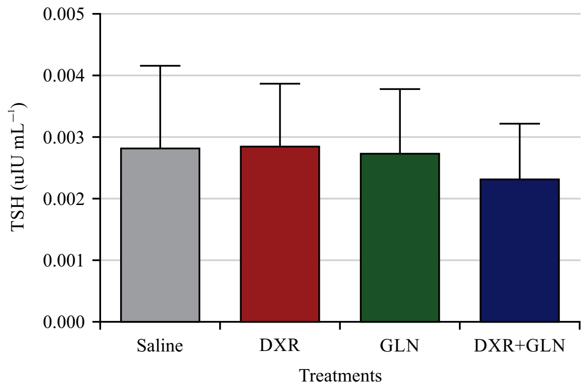

Fig. 2: Effects of DXR, GLN and combination on TSH levels

DXR, GLN and combination treatments (20 mg kg^{-1}, intraperitoneal injection and GLN orally) did not alter the TSH levels

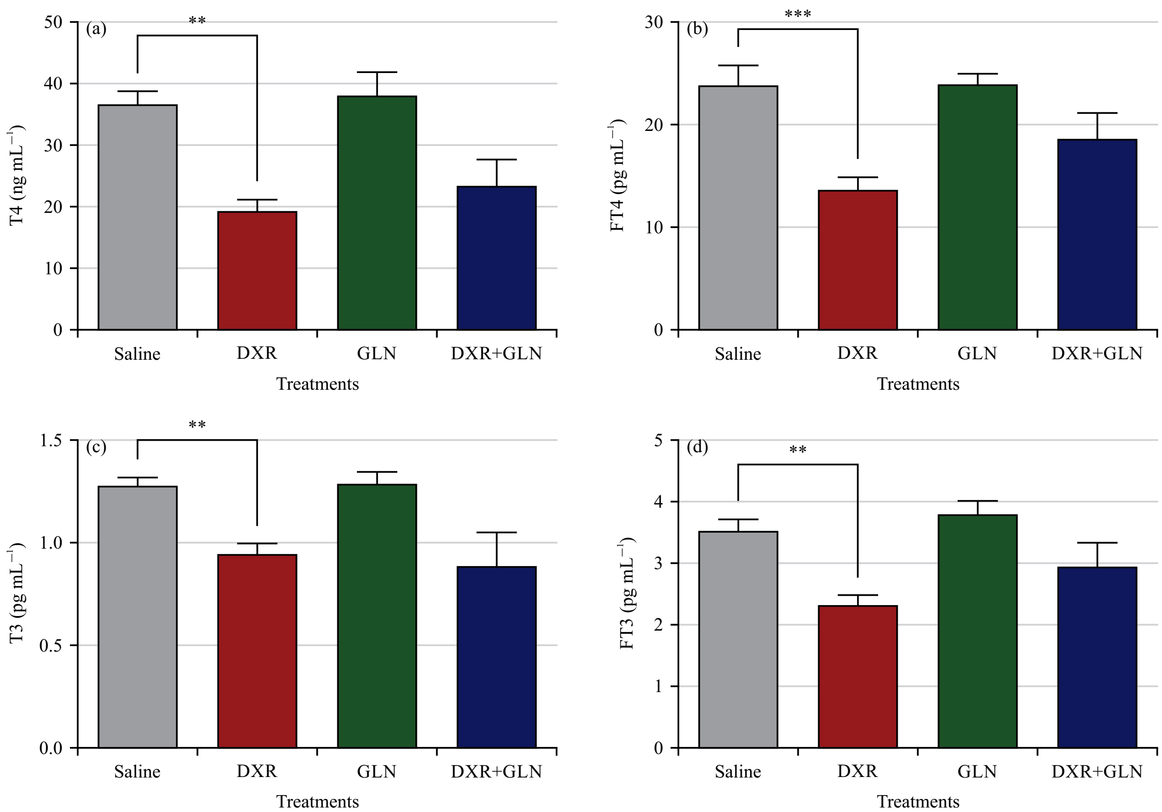

Fig. 3(a-d): Effects of DOX, GLN and combination on (a) T4, (b) FT4, (c) T3 and (d) FT3 levels

DXR treatment (20 mg kg^{-1}, intraperitoneal injection) significantly decreased the T3 and FT3 levels related to the control group, but GLN treatment did not alter the T3 and FT3 levels. DXR+GLN co-treatment showed improved T3 and FT3 levels compared to the DXR-only treatment, but this effect was not significant. The expression of data is as SEM for seven rats in each rat group (**$p<0.01$) and (***$p<0.001$) related to the control rats

Effects of DXR and GLN on TSH levels: The ECL analysis showed no significant differences in the TSH levels among the control, DXR, GLN and DXR+GLN groups, while it showed a significant decrease in free and total (T3 and T4) among the DXR group, indicating that neither DXR nor GLN treatments impacted TSH levels (Fig. 2).

Effects of DXR and GLN on free and total (T3 and T4) levels: The ECL analysis revealed that free and total T4 and T3 levels were significantly decreased in the DXR and DXR+GLN groups compared with the control group. However, co-administration of GLN mitigate this decrease in the free and total T4 and T3, which indicated GLN's ability to mitigate the toxic effect of DXR (Fig. 3a-d).

DISCUSSION

In the current investigation, plasma concentrations of Thyroid Stimulating Hormone (TSH), Thyroxine (T4), Free Thyroxine (FT4), Free Thyroxine (FT3), troponin I and creatine kinase (CK), as well as CK-MB were measured in rat models that had been treated with doxorubicin (DXR). This allowed the researchers to investigate the impact of DXR on thyroid and heart function. Furthermore, the potential protective impact of GLN, which has been found to improve thyroid and heart function, was also studied as it pertains to DXR's induction of hypothyroidism and cardiotoxicity.

Clinical and experimental research has shown that DXR can affect thyroid and heart function[23,24]. According to the current study's findings, DXR does indeed increase heart toxicity markers (troponin I, CK and CK-MB) and decreases thyroid hormone levels, corroborating those of the earlier studies. Since thyroid hormone receptors are highly expressed in the brain and heart[25], a decrease in thyroid hormones can alter the activity of these receptors and cause changes in heart and brain function. Accordingly, hypothyroidism has been linked to both mental and cardiac complications[26]. Furthermore, cardiac dysfunction has been linked to hypothyroidism and has been shown to decrease blood flow and impact blood supply to the rest of the body, including the brain[27]. Therefore, it is important to research further the mechanisms by which DXR affects cardiac and thyroid function since this may lead to the discovery of therapeutic drugs that can prevent or alleviate these harmful effects of DXR.

The present investigation analyzed the effects of DXR, GLN and the combination of DXR and GLN on TSH, T4, FT4, T3 and FT3 levels. The TSH levels did not change much after DXR or GLN treatment across all groups, which was an interesting finding. Furthermore, DXR-treated rats had significantly lower T4, FT4, T3 and FT3 levels, but GLN had no effect. That is, while GLN co-treatment did result in higher levels of T4, T3, FT4 and FT3, the increase was not statistically significant. Researchers found that GLN significantly decreased FT4 levels and significantly increased TSH levels in patients with type 2 diabetes. As a result, more research is needed to confirm whether or not GLN has any ameliorative effect on DXR-induced thyroid damage.

The DXR was found to have cardiotoxic effects, as measured by markedly elevated levels of troponin I, CK and CK-MB compared to the control group. In addition, GLN was found to reverse these effects partially. However, GLN's positive effects were consistent with those that have been documented in the past. One animal study has shown that GLN could prevent DXR's cardiotoxicity. Another study showed that GLN improved heart function in those with type 2 diabetes mellitus. Although promising, these results need to be confirmed because GLN has also been observed to worsen DXR-induced cardiomyopathy.

The present study has limitations due to its *in vivo* nature. Confirming the results in future *in vitro* investigations and clinical trials will be necessary. The mechanisms by which DXR and GLN affect thyroid and heart function were also not investigated. The GLN, for instance, has been shown to ameliorate diabetic cardiomyopathy in a rat model by decreasing cardiac CaMKII/NF-B signaling and increasing PPAR- expression. Thyroid hormone receptors (THRs) are intriguing because of their potential impact on thyroid function, THR1 is primarily located in cardiac and skeletal muscle, whereas THR2 is primarily found in the liver, kidneys and brain.

CONCLUSION

It is found that GLN may offer protection against DXR-induced toxicities in rat models, confirming prior findings that DXR therapy might produce hypothyroidism and cardiotoxicity. Future therapeutic methods against DXR-induced toxicities may benefit from verifying these findings through research that additionally studies related processes.

SIGNIFICANCE STATEMENT

The current investigation aims to assess the ameliorative effect of galantamine on doxorubicin-induced cardiotoxicity and hypothyroidism in experimental rat models. Female rats were administered with doxorubicin intraperitoneal and galantamine orally. The biochemical assessment involved the measurement of serum troponin I, CK, CK-MB, TSH, T3, FT3, T4 and FT4 levels. Rats treated with doxorubicin demonstrated a notable elevation in troponin I, CK and CK-MB levels and a reduction in T3, FT3, T4 and FT4 levels to a significant degree. The findings indicate that the administration of doxorubicin induces cardiotoxicity and hypothyroidism and galantamine improves these effects. Eventually, it is worth noting that galantamine exhibits an ameliorative effect over doxorubicin-induced cardiotoxicity and hypothyroidism.

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