Effects of Levothyroxine and Liothyronine on Cirrhotic Cardiomyopathy in Rats

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Abstract- In liver cirrhosis, there is low T3 syndrome associated with a decrease in total triiodothyronine (T3) and free T3 concentrations and cirrhotic cardiomyopathy (CCM) with chronotropic incompetence. Thus, we aimed to investigate the effects of eliminating T3 and thyroxine (T4) deficiencies on cardiac chronotropic dysfunction. Bile duct ligation (BDL) was used to induce cirrhosis in male Wistar rats. The chronotropic responses were studied through the Power Lab system in sham/saline, sham/T3T4, BDL/saline, and BDL/T3T4 groups. The serum T3 and T4, and T3 resin uptake (T3RU) levels were assessed. The atrial T3 receptor expression was investigated through a real-time polymerase chain reaction (Real-time PCR). The chronotropic responses were decreased in the BDL/saline group and raised in the BDL/T3T4 group. The serum T3 levels decreased in the BDL/saline group compared to sham group, but increased in the BDL/T3T4 group compared to the BDL/saline group. The serum T4 level increased in the BDL/saline and decreased in the BDL/T3T4 group. The serum T3RU level decreased in the BDL/saline and increased in the BDL/T3T4 group. The T3 receptor expression in atria increased in the BDL/saline group, nonetheless, it did not change in the BDL/T3T4 group compared to the sham/saline and the BDL/saline groups. T3T4 treatment did not increase the chronotropic response in the control group but the treatment improved the chronotropic hyporesponsiveness, and serum T4 and T3 RU abnormalities in cirrhosis, however, it is not related to the atrial T3 receptor expression.

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Introduction

Liver cirrhosis is defined by fibrosis with recurrent nodules (1-3). It has severe morbidity and mortality and if remain untreated the patients undergo liver transplantation. The accumulation of extracellular matrix in cirrhosis is the main cause of tissue scarring, liver parenchyma destruction (4), portal hypertension, and end-stage liver disease (5). Liver cirrhosis leads to CCM characterized by systolic, diastolic, and electrophysiological abnormalities. The systolic dysfunction in CCM is related to rises in endogenous cannabinoids, inflammatory cytokines, and nitric oxide (NO) levels, and a fall in β-adrenoreceptors expression. The diastolic abnormality is caused by the activation of the renin-angiotensin system and cardiac hypertrophy. The electrophysiological dysfunction is attributed to the defects in ion channels and membrane fluidity (6).

The thyroid hormones (THs) exerts transcriptional genomic, thermogenic, and hemodynamic effects on the

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heart. The genomic effect is caused by the activation of the genes like α-myosin heavy chain, β-1 adrenergic receptors (β1ARs), Na^+/K^+ ATPase, and voltage-gated K^+ channels or repression of genes like β-myosin heavy chain, thyroid nuclear receptors α-1, Na^+/Ca^{2+} exchanger, and THs transporters. The thermogenic effect is related to a decrease in vascular resistance. The hemodynamic effect of THs is attributed to the positive chronotropic effect (7).

The liver is involved in the conjugation and excretion of THs (8). In Liver cirrhosis, the low T3 syndrome is associated with a decrease in total T3 or free T3 concentrations (8,9). The low T3 syndrome in cirrhosis may be due to decreased liver uptake of T4, lowered hepatocellular function to convert T4 to T3, or decreased caloric intake of hepatocytes (10).

Till now, several studies have shown that hyperthyroidism leads to increased chronotropic and ionotropic responses (11,12). Hypothyroidism was also showed to decrease the heart rate, increase the systolic and decrease the diastolic time (12). To our understanding, the studies on the effect of THs on low T3 syndrome related chronotropic hypo-responsiveness in cirrhosis and its relation with T3 receptor expression are deficient, that is why our present study is designed. Therefore, our experiment aimed to investigate the hypothesis that THs treatment in BDL-induced CCM may treat chronotropic dysfunction; and if so, then maybe related to T3 receptor expression in the cirrhotic hearts.

Materials and Methods

Animals

A total of 48 Male Wistar rats (*Rattus norvegicus*), 250-280 g, were obtained from the Department of Pharmacology, Tehran University of Medical Sciences, Tehran, Iran. The animals were kept under standard laboratory conditions by providing standard rodent chow and free access to water. The light and dark cycles provided were 12 hours and temperature of 22° C. For the care and use of laboratory animals, the guidelines of the National Institutes of Health (NIH), US Publication No. 8023, and revised 1978 were strictly followed during the experimentations. All the procedures performed on animals were approved by the animal ethical committee of the institute.

The rats (n=48) were divided randomly into four groups: sham/saline, sham/T3T4, BDL/saline, and BDL/T3T4. In each experimental group, a total of 12 rats were used, out of which 6 rats were used for serum analysis and in vitro study while the other 6 rats were used for Real-Time PCR.

Induction of cirrhosis

The cirrhosis was induced through BDL as previously described (13). In short, general anesthesia was induced through intraperitoneal injection (i.p.) of ketamine (ketamine hydrochloride=50 mg/kg body weight) and xylazine (xylazine hydrochloride=10 mg/kg body weight). The laparotomy was performed, and the common bile duct was cut between the ligatures and the abdominal wall was closed in two layers. For sham-operated groups, the same procedure was used except the bile duct was inspected visually without ligation and cutting. The consecutive studies were carried out on day 29^{th} of the surgeries.

Treatment protocols

On day 2^{th} post-surgery, saline or T3T4 [T3=Liothyronine at 2 μg/100g/day; T4=Levothyroxine at 8 μg/100g/day; equal to amount of daily T3 and T4 released in healthy rats, both obtained from Iran Hormone Inc., Tehran, Iran] was administered to respective groups by oral gavage (p.o.) for 27 consecutive days (14). The subsequent studies were carried out on day 28^{th} post-treatment.

Chronotropic study

For the chronotropic study, the atria with spontaneous beating were isolated in a cold physiological salt solution (PSS) with a supply of carbogen gas (a mixture of 95% O_2 and 5% CO_2). Under an isometric tension force of 1g, 37.0±1° C temperature, 7.4 pH and a rich carbogen gas supply, the atria were dipped in an isolated organ bath of the tissue bath with 20 mL of PSS (15). The PSS was of the following composition: NaCl=112 mM, KCl=5 mM, $CaCl_2$=1.8 mM, $MgCl_2$=1 mM, NaH_2PO_4=0.5 mM, KH_2PO_4=0.5 mM, $NaHCO_3$=25 mM, glucose=10 mM and EDTA=0.004 mM. Through the Power Lab system (AD Instrument, Australia), the beating rates of the atria were measured after stimulation with 10^{-10} to 10^{-5} M concentrations of a isoproterenol, a non-selective β adrenergic receptor agonist (15,16).

Serum T3 and T4 measurements

The serum T3 and T4 levels were determined through individual ELISA (Cusabio, China) kits as previously described (17). In short, the blood samples were collected from the heart directly after deep anesthesia with ketamine and diazepam. The sera were collected after centrifugation at 3000 rpm for 10 minutes at 4° C and were stored at -20° C for future analysis. The antibody's-

coated wells were poured 100 µl serum sample and standard T3 and T4 solutions which were later followed by the addition of 50 µl horseradish peroxidase conjugate, color solution, and stop solution, and the absorbance was read at 450 nm by the ELISA reader.

Serum T3RU measurement

The serum T3RU level was determined by the Amersham/Searle competitive binding assay (18). In short, the serum samples were collected for T3 and T4 assays as described. The serum sample and the standard serum were poured into a vial having adsorbent granules, labeled liothyronine, and a buffer solution. The unbound labeled liothyronine was bound to the granules by displacing the labeled liothyronine from the thyroxine-binding proteins by the serum T3. Finally, the supernatant was collected, the radioactivity was counted for T3RU and compared to the standard sera.

Atrial T3 receptor mRNA expression

Real-time PCR was used for the quantification of atrial T3 receptor mRNA expression in the heart atria. RNeasy Fibrous Tissue Mini Kit (QIAGEN, Germany) was used for the total RNA extraction as per manufacturer instructions. DNase (Promega) was used for the removal of genomic DNA. RNA treated with deoxyribonuclease, ribonuclease free water, and hexamer primer was used for making the complementary DNA (cDNA) strand, and was added the deoxy nucleoside triphosphates, reverse transcriptase, and ribonuclease inhibitor and incubated at 42° C for 1h. For PCR of rat 18S ribosomal RNA (rRNA) and thyroid receptors beta 1 (TR-β1), the oligonucleotide primers used were (16,19):

Rat 18S rRNA (product size: 109) forward: 5′-ATCACCTTTCGATGGTAGTCG-3′; Reverse: 5′-TCCTTGATGTGGTAGCC-3′

Rat TR-β1, Forward: 5′-CACCTGGATCCTGACGATGT-3′; Reverse: 5′-ACAGGTGATGCAGCGATAGT-3′

Rotor-Gene machine was used for Real-time PCR. The reaction mixture (20 µL) was comprised of cDNA template (1 µL), forward and reverse oligonucleotide primers (10 pmol each), and optimized PCR master mix (10 µL). To normalize the Real-time PCR, an internal control gene of 18S rRNA was used. The TR-β1 RNA was adjusted to18S rRNA and the data were analyzed by the competitive critical threshold method (19).

Statistical analysis

The results obtained were mentioned as mean±SEM. One-way analysis of variance (ANOVA) was used for the comparison of two variables. For the comparison of multiple groups, the Bonferroni post-test was applied. The *P* less than 0.05 was considered statistically significant. For statistical analysis, the GraphPad Prism 5.0 software was used.

Results

The cirrhotic animals showed signs of dark yellow urine, jaundice, and ascites. Moreover, the spleen weight was significantly increased (3.10±0.13 g) compared to the sham (1.71±0.06 g), $P<0.01$. These pathological simptoms together with the clinical symptoms in this model indicates the liver cirrhosis.

Chronotropic responses

The chronotropic responses were evaluated for both sham and BDL rats after using different concentrations of isoproterenol, Figure 1. The chronotropic and the maximum responses were decreased significantly ($P<0.05$) in BDL/saline group as compared to the sham/saline group, (Figure 1a), while no significant difference for isoproterenol effective concentration 50 (EC50) (log-EC50=8.51±0.08 vs. log-EC50=8.89±0.04) was observed. In the BDL/T3T4 group, the chronotropic responses were increased significantly ($P<0.01$) than the BDL/saline group, (Figure 1b). No significant difference ($P>0.05$) was observed in the chronotropic responses of the BDL/T3T4 group and the sham/saline group (Figure 1c), while a significant increase ($P<0.05$) in the chronotropic responses was observed in the BDL/T3T4 group compared to the sham/T3T4 group (Figure 1d).

Serum T3 and T4 levels

The data regarding the serum T3 and T4 levels in the sham/saline, sham/T3T4, BDL/saline, and BDL/T3T4 are shown in Figure 2. In the sham/T3T4 and BDL/saline groups, the serum T3 levels were decreased significantly ($P<0.05$) as compared to the sham/saline group (Figure 2a). In the BDL/T3T4 group, the serum T3 level was increased significantly as compared to the BDL/saline and the sham/T3T4 groups ($P<0.05$). T3T4 treatment could not increase T3 serum level in the sham group (Figure 2a).

In comparison to the sham/saline group, the serum T4 levels were increased significantly ($P<0/05$) in BDL/saline groups compared to sham/saline (Figure 2b). The T3T4 treatment decreased significantly ($P<0.001$) the serum T4 levels in BDL animals as compared to the BDL/saline group (Figure 2b).

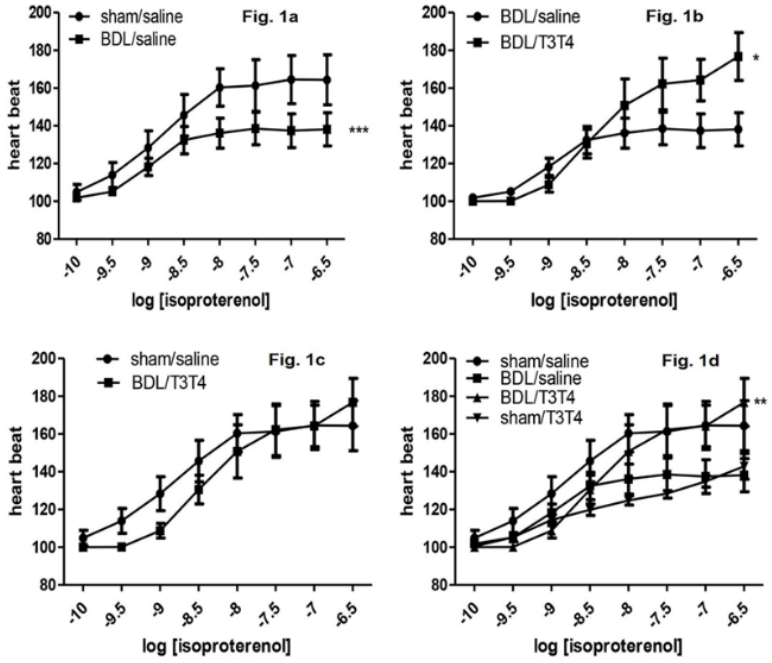

Figure 1. Isoproterenol-stimulated chronotropic responses in the sham/saline, sham/T3T4, BDL/saline and BDL/T3T4 groups. The respective groups were treated with saline or T3T4 (T3=2 μg/100 g/day, T4=8 μg/100 g/day) for 27 days. Different concentrations of isoproterenol-induced significant differences in chronotropic responses (Bonferroni post-test). The data are presented as mean±SEM. In each experimental group, 6 rats were used. (1a) ****P*<0.05 [BDL/saline group compared to sham/saline group]; (1b) **P*<0.01 [BDL/T3T4 group compared to BDL/saline group]; (1c) *P*>0.05 [BDL/T3T4 group compared to sham/saline group]; (1d) ***P*<0.05 [BDL/T3T4 group compared to Sham/T3T4 group]

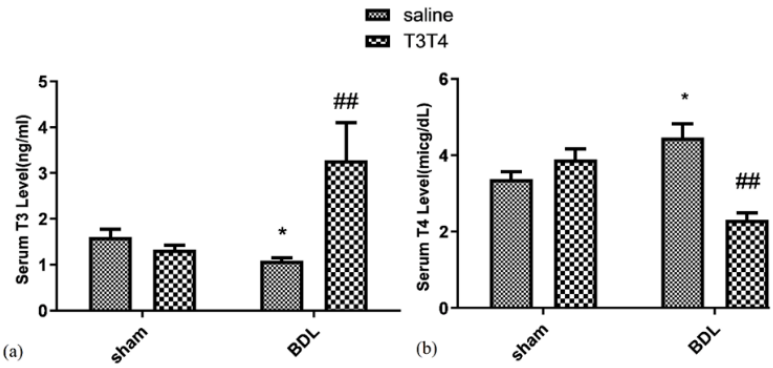

Figure 2. Serum T3 and T4 levels in sham/saline, sham/T3T4, BDL/saline, and BDL/T3T4 groups. The respective groups were treated with saline or T3T4 (T3=2 μg/100g/day, T4=8 μg/100g/day) for 27 days. The data are presented as mean±SEM. In each experimental group, 6 rats were used. **P*<0.05 [sham/saline group compared to BDL/saline group], ##*P*<0.01 [BDL/T3T4 group compared to BDL/saline group]

Serum T3RU level

The serum T3RU levels were measured for both sham and BDL rats and are shown in Figure 3. The serum T3RU level was decreased significantly (*P*<0.05) in BDL/saline group as compared to the sham/saline group. In BDL/T3/T4 group, the serum T3RU level was increased significantly (*P*<0.05) as compared to BDL/saline group.

Atrial T3 receptor mRNA expression

The T3 receptor mRNA expressions in sham and BDL groups are shown in Figure 4. The atrial T3 receptor

mRNA expression was increased non-significantly (P>0.05) in the sham/T3T4 group than the sham/saline group. In BDL/saline group, the atrial T3 receptor mRNA expression was increased significantly (P<0.05) as compared to the sham/saline group. The T3 receptor mRNA expression was increased non-significantly (P>0.05) in BDL/T3T4 group than BDL/saline and sham/T3T4 groups.

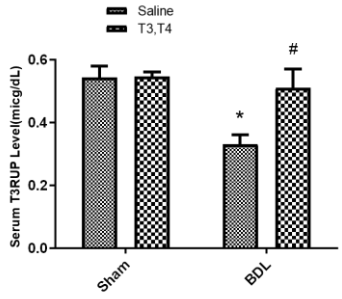

Figure 3. Serum T3RU levels in sham/saline, sham/T3T4, BDL/saline, and BDL/T3T4 groups. The respective groups were treated with saline or T3T4 (T3=2 µg/100g/day, T4=8 µg/100g/day) for 27 days. The data are presented as mean±SEM. In each experimental group, 6 rats were used. *P<0.05 [BDL/saline group compared to sham/saline group], #P<0.05 [BDL/saline group compared to BDL/T3T4 group]

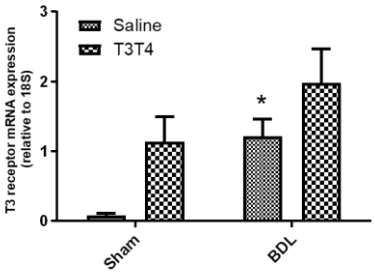

Figure 4. T3 receptors mRNA expression in rat's atria of sham/saline, sham/T3T4, BDL/saline, and BDL/T3T4 groups. The respective groups were treated with saline or T3T4 (T3=2 µg/100g/day, T4=8 µg/100g/day) for 27 days. The data are presented as mean±SEM. In each experimental group, 6 rats were used. *P<0.05 [BDL/saline group compared to sham/saline group]

Discussion

The current study investigated the effect of a long-term THs treatment on chronotropic dysfunction in CCM and atrial T3 receptor expression in the cirrhotic hearts. It is well established that in cirrhosis, the heart rate is not increased by physical stimulation (15,20), and this derangement occurs due to CCM (20). The latest studies had shown that cirrhotic hearts have lower chronotropic responses (15,20). Hyperthyroidism leads to increased chronotropic and ionotropic responses (11,12).

Our study showed that the chronotropic responses decreased in BDL/saline group and increased in BDL/T3T4 group. Houdijk *et al*., showed that both the heart rate and blood pressure were decreased in BDL animals as compared to sham animals (21). The studies on the effect of THs on chronotropic responses in cirrhosis are deficient. Vargas-Uricoechea *et al*., showed that hypothyroidism leads to low chronotropic and ionotropic responses while hyperthyroidism caused an increase in chronotropic, ionotropic, stroke volume, and ejection fraction (12). The results of these studies are quite comparable to our present study.

We mentioned that the serum T3 level did not decrease in BDL/saline group while it increased significantly in BDL/T3T4 group. Vincken *et al*., showed that cirrhotic patients had a significantly lowered level of free triiodothyronine (fT3). An inverse relation was seen between the fT3 level and the Child-Pugh score (22). We also found the same relation between cirrhosis and serum T3 level which can be related to the failure of the liver to convert T4 to T3. Chi *et al*., stated that THs control the cell growth in hepatocellular carcinoma, increase the fats metabolism in hepatic steatosis and decrease liver inflammation during injury (23). In our present study, the T3T4 treatment in cirrhosis increased the serum T3 level in the BDL/T3T4 group which may be attributed to a decrease in liver inflammation to enable the liver to convert T4 to T3. After long-term treatment of cirrhotic rats with T3T4, T3 level got elevated to the degree that T3 deficiency was compensated and also the level of T3 in BDL/T3T4 did not cause tachycardia at the beginning of the study. TSH levels were not measurable in BDL/T3T4 group on day 28th, it showed that the thyroid gland had no role in the measured T3 and T4 levels in BDL/T3T4 group.

After long-term treatment of cirrhotic rats with T3T4, T3 level got elevated to the degree that T3 deficiency was compensated and the level of T3 in BDL/T3T4 did not cause tachycardia at the beginning of the study.

In our present experimentation, the serum T4 level in BDL/saline group was increased significantly and decreased significantly in the BDL/T3T4 group. Hegedus showed that the serum levels of free thyroxine (fT4), thyroxine-binding globulin (TBG), and T4 were significantly increased in acute viral hepatitis than after recovery (24). Borzio *et al*., also found that in cirrhotic patients, the level of thyrotropin, TBG, and fT4 were significantly higher than in healthy controls (25). The results of these studies are like our findings. We also found that the serum T4 level was decreased significantly

in BDL/T3T4 group. The reason for this was presented by Dong *et al*., and mentioned that the THs decrease the liver inflammation and regulate the liver function to convert T4 into T3 (26).

We showed that the serum T3RU level was decreased significantly in BDL/saline group and increased significantly in BDL/T3T4 group. Hegedus, in acute viral hepatitis, showed a significant decrease in T3RU level during the disease (24). In our current study, the T3RU was also found lowered in BDL animals which can be related to the lowered production of T3 in the cirrhotic liver. An increase in the T3RU level in the BDL/T3T4 group also may be attributed to a decrease in liver inflammation in cirrhosis by the T3T4 treatment to rise the serum T3 level by the conversion of T4 to T3 (23).

In the present study, the T3 receptor mRNA expression in rat's atria was increased significantly in the BDL/saline group. Our results regarding the increase in atrial T3 receptor mRNA expression in BDL-induced CCM and by the T3T4 treatment are new additions to the previous studies. Chamba *et al*., found no changes in the expression of thyroid receptors alpha 1 (TR-α1) and TR-β1 proteins in normal and diseased liver. Also, hepatocellular expression of these mRNAs is maintained in chronic liver disease despite a marked reduction in circulating T3 concentrations (27). The results of this study in the liver are different from our results in the heart which may be related to the differences in different species and organs. Kahaly and Dillmann showed that TR-α1 and TR-β1 in the heart have 40% T3 binding and THs cause a negative regulation of the TR-α1 nuclear receptors proteins (28). The reason for the difference was presented by Peliciari-Garcia *et al*., and mentioned that the oscillations of the myocardial processes are dependent on the circadian clock, the T3 sensitivity, and the T3 mediated core clock components (29).

We mentioned that in the sham/T3T4 group, the chronotropic responses were decreased while the T3 receptor mRNA expression increased non-significantly. We also found that the T3 receptor mRNA expression was increased in the BDL/saline group while the chronotropic responses diminished in this group. The reason for this was presented by Bachman *et al*., and stated that the chronic T3 treatment leads to cardiomyopathy due to increased beta-adrenergic receptor transcription (30). As a consequence, It has been suggested that this lack of myocardial hemodynamic response to isoproterenol in rats with cirrhosis is due to a down-regulation of β1ARs (31).

Our present study revealed that BDL-induced cirrhosis in rats alters the chronotropic responses, serum THs levels, and atrial T3 receptor expression in the heart. The long-term THs treatment restored the chronotropic hypo-responsiveness in CCM but seems not to be related to the atrial T3 receptors expression in the heart. The T3 level increment in THs-treated BDL rats can be related to the improvement of atrial beat response. Changes in T3RU levels in cirrhotic rats may be related to low T3 production or abnormal serum protein pattern in cirrhosis. The administration of thyroid hormones in patients with liver cirrhosis may delay or improve cirrhotic cardiomyopathy, which requires clinical studies to prove.

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