

Investigation of the Effects of Maresin-1 on Testicular Ischemia Reperfusion Induced Oxidative Stress

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ABSTRACT

Objective: The purpose of this study is to examine the protective effects of maresin 1 on testicular injury induced by ischemia reperfusion.

Methods: 24 Sprague-Dawley male rats were divided into 3 groups. The groups are planned as follows; sham, ischemia reperfusion and ischemia reperfusion+maresin 1 groups. The spermatic cord was detected and clamped for 2 hours to establish the prompt. After 2 hours, the clamp was removed and testicular reperfusion was achieved for 2 hours. At the end of the reperfusion phase, testicular tissues were taken and total antioxidant capacity (TAC), total oxidant capacity (TOC), superoxide dismutase (SOD), malondialdehyde (MDA) and myeloperoxidase (MPO) levels were determined by spectrophotometric method.

Results: In the ischemia-reperfusion group, TOS and MDA and MPO are increased, the levels of TAS and SOD molecules are decreased. TOS and SOD levels are increased and TAS, MDA and MPO levels are decreased in the Maresin-1 treatment group.

Conclusion: These results show us that a single dose of maresin-1 application is effective against oxidative damage caused by ischemia reperfusion.

INTRODUCTION

Testicular torsion is an acute surgical condition that can result in ischemia, severe destruction of the testis and ischemia, and even infertility.^[1] It has been shown in the literature that oxidative stress is also responsible for the damage caused by detorsion after ischemia.^[2] Molecules migrating to the ischemic area with greater blood flow after deformation lead to ischemia reperfusion (I/R) damage

of the testis. Superoxide anions, hydrogen peroxide and hydroxyl radicals lead to the formation of reactive oxygen radical (ROS) and damage many components of the cell, especially the cell membrane and DNA.^[3] Changes in blood supply by I/R, excessive ROS secretion, cytokine and neutrophil migration cause changes that may lead to infertility.^[4] In rats, spermatic cord torsion causes apoptosis and inflammation-mediated damage to spermatogenesis.^[5] Antioxidant agents used today reduce the damage

by eliminating ROS in addition to the body's endogenous antioxidant defense mechanisms.^[6,7]

Maresin-1 (MaR-1) (7,14-dihydroxydocosa-4Z, 8Z, 10, 12, 16Z, 19Z hexanoic acid) is derived from docosahexaenoic acid.^[8] MaR-1 is a chemical isomer of maresin. It shows that MaR-1 inhibits ROS in cells and tissues and alleviates the inflammatory response. It was also found to suppress colonic inflammation in mice.^[9,10] MaR-1 has been shown to be an effective mediator in the stopping of polymorphonuclear infiltration and phagocytosis of macrophages.^[11] MaR-1 decreased liver steatosis in ob/ob and dietary obese mice.^[12] MaR-1 also improved microbial killing via macrophages in clinical periodontitis.^[13,14] MaR-1 demonstrated anti-inflammatory effects in a murine colitis model.^[15] MaR-1 enhanced antioxidant pathway activation in lung I/R injury.^[16] Here, it was evaluated the effects of MaR-1 against oxidant and inflammatory injuries in testicular T/D rat model.

MATERIALS AND METHODS

Experimental phase of current research was carried out at Experimental Animal Research and Application Center in our university and experiment animals were supplied by the same place. Animals were kept into standard cages in laboratory environment provided with humidity, temperature and light/dark cycle control. Animals were fed with standard pellet feed and water. Animals were fasted before the experiment for 12 hours to prevent anesthesia complications. This study was initiated with approval (2019-65) of our University Experimental Animals Local Ethics Committee. Maresin-1 was supplied by Sigma-Aldrich Co, USA.

Groups and I/R model

In our study, 24 Sprague-Dawley male rats were weighed (270 ± 15 g) and randomly divided into 3 groups. In sham group, the abdominal area was shaved and cleaned. Also, abdominal area was opened with an incision under the anesthesia and closed again without I/R model and any medication. In I/R group, immediately after anesthesia was given, the rats were fixed in the dorsal horizontal position. The incision area was cleaned with povidone iodine. Median laparotomy incision was made in 1-2 cm size. Spermatic cord was found and clamped with atraumatic microvascular clamp to create ischemia for 2 hours. The clamp was removed and testis reperfusion allowed for 2 hours. At the end of the reperfusion period, testis tissue samples were rapidly taken. I/R+MaR-1 (1 ng/0.1 mL); as a defined in the I/R group, ischemia was induced for 2 hours by clamping. MaR1 (diluted in sterile saline) was administered intraperitoneally at dose of 1 ng/0.1 mL 30 minutes before reperfusion.^[17] After 2 hours of ischemia, the clamp was removed and the reperfusion period started for 2 hours. Finally, at the end of the experiment, testes were washed and kept frozen until the biochemical analysis.

Biochemical measurements

Testis tissues were taken out of the deep freeze and weighed on the day of the analysis. A 10% homogenate was created by adding phosphate buffer on the tissues and they were homogenized (IKA, Germany) at 12.000 rpm for 1-2 min on ice. Homogenate tissue samples were centrifuged at 5000 rpm at +4°C for 30 min to obtain the supernatant. Obtained supernatants were tested for TAS, TOS, SOD, MDA, MPO. After the tissues were homogenized, all biochemical analyses were carried out in supernatants from homogenized tissues. Testis samples were processed for malondialdehyde (MDA) assay to determine lipid peroxidation status according to methods of Ohkawa et al.^[18] The results were given in $\mu\text{mol/g}$ protein. It was measured using the superoxide dismutase (SOD) activity determination protocol defined by Sun et al.^[19] The results of tissue samples were presented in U/mg protein. We also quantified testis injury by measuring tissue myeloperoxidase (MPO) activity, the activity of infiltrated neutrophils, using a protocol developed by Bradley et al.^[20] The results of MPO activity tissue samples were given in U/g protein. Total antioxidant status (TAS) value was measured with the commercially available kit (LOT: AK17081A) Rel Assay Diagnostics, Gaziantep, Turkey). Total oxidant status (TOS) measurement was made with commercially available kit (Rel Assay Diagnostics). TAS and TOS results were presented as nmol/L. The ratio of TOS to TAS was accepted as the oxidative stress index (OSI). OSI value was detected as follows: $\text{OSI} = [(\text{TOS}, \mu\text{mol H}_2\text{O}_2 \text{ equivalent/L}) / (\text{TAS}, \text{mmol Trolox equivalent/L}) \times 10]$.

Statistical analysis

One-way ANOVA with the Tukey test was used for multiple comparisons. Descriptive statistic was given as the mean \pm standard deviation (SD). The results were considered statistically significant at the level of $p < 0.05$.

RESULTS

Biochemical parameters

There was no morbidity or mortality in rats during experimental applications. In Table 1, when I/R group, compared to sham group, TAS (from 1.23 ± 0.06 to 0.67 ± 0.12 , $p < 0.001$) level decreased, whereas TOS (from 7.50 ± 0.89 to 11.96 ± 1.04 , $p < 0.001$) and OSI (from 0.61 ± 0.08 to 1.84 ± 0.46 , $p < 0.001$) levels increased. When I/R+MaR-1 group, compared to I/R group, TAS (from 0.67 ± 0.12 to 1.16 ± 0.13 , $p < 0.001$) level increased, while TOS (from 11.96 ± 1.04 to 7.80 ± 0.84 , $p < 0.001$) and OSI (from 1.84 ± 0.46 to 0.67 ± 0.09 , $p < 0.001$) levels decreased. When I/R group compared to sham group, SOD (from 359.97 ± 67.21 to 168.79 ± 19.79 , $p < 0.001$) level decreased, but MPO (from 34717.30 ± 8438.67 to 83419.38 ± 9466.95 , $p < 0.001$), MDA (from 223.99 ± 27.87 to 412.14 ± 74.02 , $p < 0.001$) levels increased. When I/R+ MaR-1 group

Table 1. Mean values of TAS, TOS, OSI, SOD, MPO and MDA parameters and comparison among sham, I/R and I/R+MaR-I groups

Experimental Groups/Parameters (n=8)	TAS (mmol/L)	TOS (μmol/L)	OSI (arbitrary unit)	SOD (U/mg protein)	MPO (U/g protein)	MDA (μmol/g protein)
Sham (I)	1.23±0.06	7.50±0.89	0.61±0.08	359.97±67.21	34717.30±8438.67	223.99±27.87
I/R (II)	0.67±0.12 ^a	11.96±1.04 ^a	1.84±0.46 ^a	168.79±19.79 ^a	83419.38±9466.95 ^a	412.14±74.02 ^a
I/R+MaR-I (III)	1.16±0.13 ^b	7.80±0.84 ^b	0.67±0.09 ^b	379.29±45.28 ^b	34203.94±7711.96 ^b	221.89±22.06 ^b

^ap<0.001 compared to sham group. ^bp<0.001 compared to I/R group. TAS: Total antioxidant status; TOS: Total oxidant status; OSI: oxidative stress index; SOD: Superoxide dismutase; MPO: Myeloperoxidase; MDA: Malondialdehyde.

compared to I/R group, while the level of SOD (from 168.79±19.79 to 379.29±45.28, p<0.001) increased, MPO (from 83419.38±9466.95 to 34203.94±7711.96, p<0.001) and MDA (from 412.14±74.02 to 221.89±22.06, p<0.001) levels decreased.

DISCUSSION

Testicular torsion is a disease caused by abnormal bending of the spermatic cord in young men.^[21] Surgical cure is achieved in 42% to 88% after torsion.^[22] Since germ cells in the testis are highly susceptible to oxidative damage, I/R damages seminiferous epithelium, germinal epithelium and Leydig cells and can lead to subfertility or infertility due to ROS overproduction.^[23-25] Studies in the literature confirm this result and have shown that sperm count decreases in male patients after torsion/detorsion (T/D).^[26] A series of cellular dysfunction after T/D causes damage to DNA, functional degradation and destruction of proteins and lipids.^[27,28] MDA indicates increased free radical formation^[29,30] and was increased by I/R in our study, which approached control values after agent administration. Protective endogenous enzymes, especially SOD, fight with the destructive effect of ROS and these molecules form TAS.^[31] In our study, TAS level and SOD were decreased in the I/R group, and this value increased again statistically with MaR-I application. The OSI, which is an indicator of oxidative stress,^[32] was increased in I/R and decreased in treatment group. MPO is determined intensively in neutrophils, and high concentration of MPO indicates neutrophil activation.^[33] MPO was increased in I/R and decreased significantly in MaR-I group.

Many MaR-I-related studies are available in the literature supporting the results of our study. In the sepsis-mouse model, MaR-I decreased ROS and improved CAT and SOD activity in mitochondria.^[11] MaR-I significantly reduced ROS and induced SOD and CAT in lung I/R injury^[16] and protected carbon tetrachloride-induced liver injury.^[34] MaR-I decreased the proinflammatory cytokines and increased interleukin-10 in lipopolysaccharide-induced lung injury models^[35,36] and decreased neutrophil infiltration and cytokines in another inflammatory respiratory experimental model.^[37] In parallel with these studies, in current study, antioxidant and anti-inflammatory properties of MaR-I have been shown in testis I/R model in rats. In the I/R group, TAS and SOD decreased while MDA, MPO, TOS, OSI levels were increased and MaR-I treatment reversed these levels.

Due to current results, reduction of MDA, MPO, TOS, OSI levels in testicular I/R model in rats by MaR-I, suggesting that MaR-I alleviated I/R-induced testis injury. We assessed oxidative stress in testis tissue to evaluate the improving effect of the MaR-I in I/R-induced testis injury and observed that oxidative stress decreased with MaR-I. The fact that there is no study related with the protective effects of MaR-I in the literature review of I/R-induced testis injury model makes this study original.

Understanding cellular damage mechanisms of I/R is important for planning new and effective treatment methods. I/R studies demonstrated that oxidative stress suppression can provide significant contributions to the I/R treatment. In this study, oxidative stress pathways were suppressed by MaR-I and this encourages hope in the treatment of I/R.

CONCLUSIONS

These results recommend that MaR-I may protect the testis by diminishing oxidative injury caused by I/R. We have indicated that treatment with MaR-I at single dose (1 ng/0.1 mL) reduces testicular damage induced by I/R in testis in experimental animals exposed to a T/D model. Part of the mechanisms of these protective effects of MaR-I may be caused from supporting the antioxidant capacities by MaR-I. Moreover, further researches are necessary to explain the other protective mechanism on I/R-induced testicular tissue damage. Current study has its own limitations. We did not find any testis study with MaR-I to compare our experiment.

Ethics Committee Approval

Experimental Animal Ethics Committee of Atatürk University (protocol number: 28.03.2019/65).

Informed Consent

Retrospective study.

Peer-review

Internally peer-reviewed.

Authorship Contributions

Concept: T.A., E.E., G.M.C., A.E.F.N., G.D.E.; Design: T.A., E.E., G.M.C., A.E.F.N., G.D.E.; Materials: T.Ö., P.E.; Data: T.Ö., P.E.; Analysis: T.Ö., P.E.; Literature Search: T.A., E.E., G.M.C., A.E.F.N., G.D.E.; Writing: T.A., E.E., G.M.C., A.E.F.N., G.D.E.; Critical Revision: T.A., E.E., G.M.C., A.E.F.N., G.D.E.

Conflict of Interest

None declared.

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Testiküler İskemi Reperfüzyon ile İndüklenen Oksidatif Strese Maresin-1'in Etkilerinin Araştırılması

Amaç: Bu araştırmanın amacı, maresin 1'in iskemi reperfüzyonun indüklediği testis hasarı üzerindeki koruyucu etkilerini incelemektir.

Gereç ve Yöntem: 24 Sprague-Dawley erkek sıçanlar 3 gruba ayrıldı. Gruplar şu şekilde planlanmıştır; sham, iskemi reperfüzyon ve iskemi reperfüzyon+ maresin 1 grupları. Spermatik kord tespit edildi ve istemi oluşturmak için 2 saat süre ile klempendi. İki saati takiben klemp çıkarıldı ve 2 saat boyunca testis reperfüzyonu sağlandı. Reperfüzyon aşamasının sonunda, testis dokuları alınarak total antioksidan kapasite (TAK), total oksidan kapasite (TOK), süperoksit dismütaz (SOD), malondialdehit (MDA) ve myeloperoksidaz (MPO) düzeyleri spektrofotometrik yöntemle belirlendi.

Bulgular: İskemi-reperfüzyon grubunda TOS ve MDA ve MPO arttı, TAS ve SOD moleküllerinin seviyeleri azaldı. Maresin-1 tedavi grubunda TOS ve SOD düzeyleri artarken ve TAS, MDA ve MPO düzeyleri azaldı.

Sonuç: Bu sonuçlar bize, tek doz maresin-1 uygulamasının, iskemi reperfüzyonunun neden olduğu oksidatif hasara karşı etkili olduğunu göstermiştir.

Anahtar Sözcükler: İnflamatuvar; maresin 1; oksidatif stres; sıçan; testiküler iskemi reperfüzyon.