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Beneficial Effect of Dexmedetomidine on Testicular Ischemia – Reperfusion Injury in Rats

Korzystny wpływ deksmedetomidyny na niedokrwienie jąder – uszkodzenie reperfuzyjne u szczurów

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Abstract

Background/Objectives. The present study was designed to determine the beneficial effect of dexmedetomidine (Dex) on torsion-detorsion-induced histopathological changes in experimental testicular ischemia/reperfusion (I-R) injury in rats.
Material and Methods. Twenty-one male Sprague-Dawley rats were separated into three groups of seven rats each. A sham operation was performed in group 1 (control). In group 2 (I-R/Untreated), unilateral testicular torsion was performed for 6 h followed by 1 h of detorsion of the testis. In group 3 (I-R/Dex), after performing the same procedures as in group 2, dexmedetomidine was given intravenously. Ipsilateral orchidectomies were performed in all experimental rats for histological examination. The levels of MDA and activities of SOD and CAT were measured in the testicular tissue.
Results. MDA levels were higher in group 2 than in group 1 rats and lower in group 3 than in group 2. SOD and CAT activities were higher in group 3 than in group 2 rats. Histopathologically, in the group 2 rats the lesions varied between grades III and IV and edema, congestion, hemorrhage between seminiferous tubules, and necrosis of the germinal cells were predominant features in sections. However, most of the specimens in the dexmedetomidine-treated group 3 showed grades I and II injury. The testicular injury score was also lower in group 3 rats than in group 2.
Conclusions. The results show that dexmedetomidine may play a protective role in reducing injury caused by I-R (**Adv Clin Exp Med 2008, 17, 5, 513–518**).

Key words: testicular torsion, ischemia-reperfusion, dexmedetomidine, rat.

Streszczenie

Wprowadzenie/Cel pracy. Ocena korzystnego wpływu deksmedetomidyny *(Dex)* na zmiany histopatologiczne w wyniku skręcenia jąder w eksperymentalnym niedokrwieniu – uszkodzeniu reperfuzyjnym (I-R) u szczurów.
Materiał i metody. 21 szczurów szczepu Sprague-Dawley płci męskiej podzielono na 3 grupy po 7 osobników. W grupie I (kontrolnej) przeprowadzono operację pozorną. W grupie 2 (I-R/bez leczenia) uwalniano skręt jądra na godzinę. W grupie 3 (I-R/Dex) po przeprowadzeniu takiej samej operacji jak w grupie 2 podawano deksmedetomidynę dożylnie. U wszystkich szczurów doświadczalnych przeprowadzono jednostronną orchidektomię w celu przeprowadzenia badań histologicznych. W tkance jądra badano stężenie MDA i aktywność SOD i CAT.
Wyniki. Stężenie MDA było większe w grupie 2 niż w 1. W grupie 3 stężenie MDA było mniejsze niż w grupie 2. Aktywność SOD i CAT była większa w grupie 3 niż w grupie 2. W grupie 2 wykryto zmiany histopatologiczne III–IV stopnia. W badanych preparatach dominowały: obrzęk, przekrwienie, zmiany krwotoczne oraz martwica komórek zarodkowych. Chociaż większość próbek z grupy 3 leczonej deksmedetomidyną wykazała zmiany I–II stopnia, to wynik oceny punktowej uszkodzenia jąder był niższy w grupie 3 niż w grupie 2.
Wnioski. Badania pokazały, że deksmedetomidyna może odgrywać rolę ochronną w zmniejszaniu uszkodzeń spowodowanych przez I-R (**Adv Clin Exp Med 2008, 17, 5, 513–518**).

Słowa kluczowe: skręcenie jąder, niedokrwienie – reperfuzja, deksmedetomidyna, szczur.

Torsion of the spermatic cord, which compresses the spermatic vessels, reduces or halts testicular blood flow and induces testicular ischemia [1]. A testicular atrophy rate of 68% after testicular ischemia has been reported [2]. Spermatic cord torsion is characterized by tissue hypoxia and eventually by the necrosis of germinal cells, which give rise to subfertility or infertility. Therefore, surgical intervention is frequently mandatory [3]. It is known that the major part of the damage occurs during the reperfusion period and that reactive oxygen species (ROS) are responsible for the tissue injury. Previous studies in rats have demonstrated that with the resumption of blood flow xanthine oxidase converts hypoxanthine to uric acid and produces large quantities of superoxide radicals, which are responsible for reperfusion injury [3, 4]. These free radicals react with lipids in the cell and mitochondrial membranes, changing their permeability and disrupting cell integrity [5, 6].

Dexmedetomidine, a selective α_2-adrenoceptor agonist, was approved by the US Food and Drug Administration in 1999 for the sedation of patients hospitalized in intensive care units, after which a great number of research articles have emerged reporting further potential indications, such as regional [7] and general [8] anesthesia. Dexmedetomidine was reported to be effective in protecting against focal ischemia in rabbits [9] and in incomplete forebrain ischemia in rats [10]. Additionally, dexmedetomidine may reduce the excessive release of noradrenaline induced by ischemia by the activation of presynaptic α_2-adrenoceptors [11, 12]. This could attenuate the detrimental effects of metabolizing excessive noradrenaline, which can lead to the formation of free radicals [13].

Despite its increased clinical use, often in critically ill patients, the effect of dexmedetomidine on testicular ischemia/reperfusion (I/R) injury has not yet been investigated [14].

The aim of the present study was to evaluate, in an experimental model of testicular I/R, the effects of dexmedetomidine on histopathology in testes after unilateral testicular torsion and detorsion.

Material and Methods

The experiment was conducted at the Health Research Center of Abant Izzet Baysal University. All animals were housed in a temperature- and light-controlled room with *ad libitum* access to water and rat chow. The Animal Care Committee of Abant Izzet Baysal University Medical School approved all experimental procedures and all experimental protocols were performed according to the guidelines for the ethical treatment of experimental animals.

Twenty-one male Sprague-Dawley rats (body weight: 160–180 g) were randomly separated into three groups, each containing seven rats. All surgical procedures were performed under phenobarbital anesthesia (2.4 mg/100 g i.p.) by employing a sterile technique. The left femoral vein was cannulated for administration of drugs and saline. The testes were exposed through identically opened and closed right-sided midscrotal vertical incisions. Torsion was created by rotating ipsilateral testes 720 in a clockwise direction for 6 h and maintained by fixing the testes medially and laterally to the scrotum with a 6/0 silk suture. After six hours of torsion, one-hour detorsion of the testes was performed. A sham operation was performed in group 1 (Sham-control). The testes were brought through the incision and then replaced with a fixation to the scrotum. In group 2 (I-R/Untreated), following 6 h of unilateral testicular torsion, one-hour detorsion of the testis was performed. No drug was given. In group 3 (I-R/ /Dex), after performing the same surgical procedure as in group 2, a selective and potent α_2-adrenoceptor agonist dexmedetomidine (Dexmedetomidine hydrochloride 100 mcg/kg i.v; Precedex 100 mcg/2 ml, Abbott, USA) was given intravenously at the starting time of reperfusion. At the end of the study the animals were killed and the testes were removed for biochemical and histological analysis.

Biochemical Analysis

At the end of ischemia-reperfusion period, the samples were kept at –70°C until the day of assessment. After weighing the testicular tissue it was homogenized in five volumes of ice-cold tris-HCl buffer (50 mM, pH 7.4) containing 0.50 ml/1 Triton x-100; homogenization (homogenizer: IKA Ultra Turrax T 8, IKA Labortechnic, Staufen, Germany) was carried out for 2 min at 13,000 rpm. All procedures were performed at 4°C. Homogenate, supernatant, and extracted samples were prepared and the determinations described below were made on the samples using commercial chemicals supplied by Sigma (St. Louis, MO, USA). Protein measurements were made in the samples according to a method explained elsewhere [15].

Determination of MDA levels was based on the coupling of MDA with thiobarbituric acid at 95°C [16]. Tissue SOD activity was determined using the nitroblue tetrazolium (NBT) method described by Sun et al. [17] and modified by Durak et al. [18]. In this method, NBT is reduced to blue formazan by superoxide (O_2^-), which has a strong absorbance at 560 nm. One unit (U) of SOD is defined as the amount of protein that

Table 1. Histological grading system developed by Cosentino et al. [20]

Tabela 1. System oceny histologicznej opracowany przez Cosentino et al. [20]

Grade I	Showed normal testicular architecture with an orderly arrangement of germinal cells
Grade II	Injury showed less orderly, noncohesive germinal cells and closely packed seminiferous tubules
Grade III	Injury exhibited disordered sloughed germinal cells with shrunken pyknotic nuclei and less distinct seminiferous tubule borders
Grade IV	Injury defined, seminiferous tubules that were closely packed with coagulative necrosis of the germinal cells

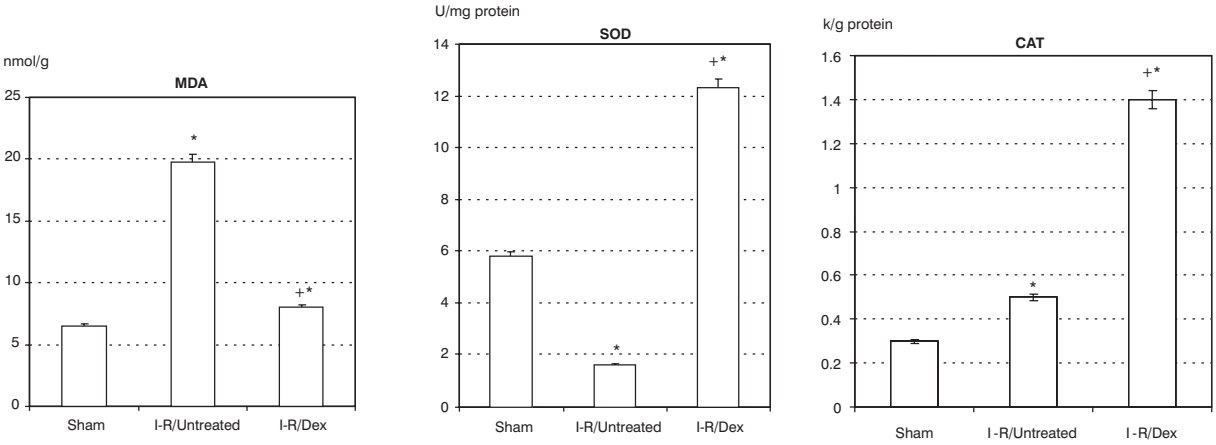

Fig. 1. Effects of ischemia/reperfusion and dexmedetomidine on the MDA, SOD, and CAT levels in testicular tissue. *$p < 0.05$ compared with sham group. †$p < 0.05$ compared with I-R/Untreated group. The values are the mean ± *SEM*. MDA, malondialdehyde; SOD, superoxide dismutase; CAT, catalase

Ryc. 1. Wpływ niedokrwienia/reperfuzji i deksmedetomidyny na stężenie MDA, SOD i CAT w tkance jąder: *$p < 0,05$ w porównaniu z operacją pozorną †$p < 0,05$ w porównaniu z grupą I-R/nieleczoną. Wartości są wyrażone jako wartość średnia ± *SEM. MDA* – malonodwualdehyd, SOD – dysmutaza ponadtlenkowa, CAT – katalaza

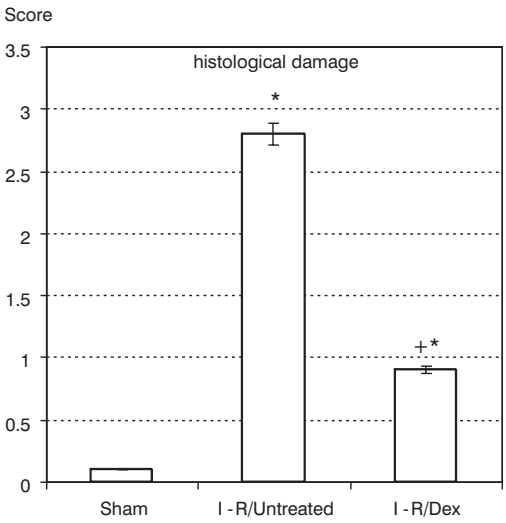

Fig. 2. Comparative histological score measurements of the groups. *$p < 0.05$ compared with sham group. †$p < 0.05$ compared with I-R/Untreated group. Values are mean ± *SEM*

Ryc. 2. Porównanie oceny histologicznej grup: *p < 0,05 w porównaniu z operacją pozorną †p < 0,05 w porównaniu z grupą I-R/nieleczoną. Wartości są wyrażone jako wartość średnia ± SEM

inhibits the rate of NBT reduction by 50%. The calculated SOD activity is expressed as U/mg of protein. Catalase (CAT, EC 1.11.1.6) activity was determined according to Aebi's method [19]. The principle of the assay is based on determination of the rate constant k (s^{-1}) of H_2O_2 decomposition at 240 nm. Results were expressed as k (rate constant) per gram of protein.

Histological Examination

The extracted testes were immediately placed into 10% formalin solution. The tissue specimens were placed in paraffin blocks, sectioned at 5 μm, and stained with Hematoxylene & Eosine. The sections were examined under a light microscope by two investigators in a blinded manner. The histological parameters was scored by the Cosentino et al. classification [20] (Table 1).

Statistical Analysis

All data are expressed as the median ± standard error of the mean (*SEM*). Significance of differences was evaluated using the Mann-Whitney *U* test. The level of statistical significance was accepted as *P* less than 0.5.

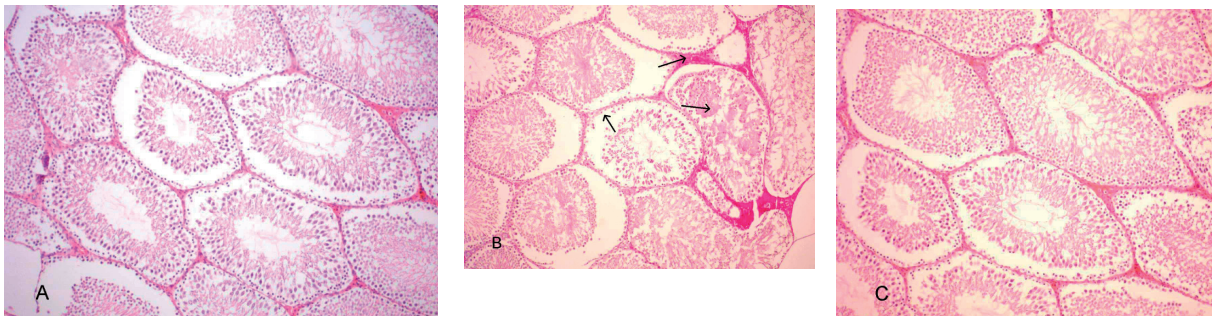

Fig. 3. The rats in the sham-control group had essentially normal testicular architecture, H&E, ×200 (A); for the group 2 rats, the lesions varied between grade III and grade IV. Arrows indicate the presence of interstitial edema, congestion, and hemorrhage between seminiferous tubules, H&E, ×200 (B); For the dexmedetomidine-treated group, most of the specimens showed a reduction in both interstitial edema and hemorrhage, H&E, ×200 (C)

Ryc. 3. Budowa tkanki jąder szczurów w grupie z operacją pozorną była prawidłowa, H&E, 200× (A); w grupie 2 wykryto zmiany III–IV stopnia, strzałki wskazują śródmiąższowy obrzęk i zmiany krwotoczne w kanalikach nasienych, H&E, 200× (B); w grupie leczonej deksmedetomidyną przeważająca liczba preparatów wykazała zmniejszenie obrzęku śródmiąższowego oraz zmian krwotocznych, H&E, 200× (C)

Results

The MDA, SOD, and CAT values for the different groups are shown in Figs. 1a, b, and c. The MDA level was significantly higher in group 2 than in group 1 ($p = 0.05$). The MDA level increase was prevented significantly by dexmedetomidine treatment when comparing groups 2 and 3 ($p = 0.05$). SOD and CAT activity were significantly lower in group 2 than in group 1 ($p < 0.05$ in both cases). Additionally, SOD and CAT activities were significantly higher in group 3 than in group 2 rates ($p < 0.05$ in both cases).

The testicular injury score significantly higher in the group 2 and 3 rats than in group 1 ($p < 0.05$ in both cases). However, this increase was lower in group 3 rats than in group 2 ($p < 0.05$) (Fig. 2).

Figure 3a shows the normal histology of the right testis. Seminiferous tubules, germ cells, and Sertoli and Leydig cells appear complete, without infiltrations or hemorrhagic signs. In contrast, light microscopy showed in group 2 rats that the right testis torsion caused interstitial space dilatation and the presence of edema, hemorrhage, and necrosis of the germinal cells (Fig. 3b). Dexmedetomidine administration markedly reduced testicular damage such as interstitial edema and hemorrhage lesions and alterations (Fig. 3c).

Discussion

Testicular torsion compromises testicular blood flow [21, 22] and induces I/R injury to the testis, which results in germ cell apoptosis [23, 24], testicular atrophy [25], and loss of spermatogenesis [24, 26]. In ischemia-reperfusion injury, over-generation of reactive oxygen species (ROS) can cause tissue damage through cell membrane lipid peroxidation, protein denaturation, and DNA impairment [27, 28]. Under these conditions, the defense system, which includes such antioxidant enzymes as SOD and CAT, has a crucial role in resisting ROS-induced cell death [29]. ROS scavengers can convert toxic ROS into water and oxygen [28]. SOD specifically detoxifies O_2^- to H_2O_2, which is then scavenged by peroxisomal catalase [30]. In short, during I/R, H_2O_2 cannot be readily scavenged because of low activities of SOD and CAT [29]. MDA is one of the most sensitive indicators of lipid peroxidation [31]. As long as fatty acids, O_2, and metal catalysts (Fe^{+2}, Cu^+) are present, lipid peroxidation leads to the formation of new free radicals. Therefore, the period of reperfusion is highly suitable for lipid peroxidation [32]. Increased lipid peroxidation can also result in the release of proteolytic lysosomal enzymes and mitochondrial matrix enzymes into the cytoplasm, which gives rise to intracellular proteolysis and cellular destruction [32].

Dexmedetomidine, an extremely potent and selective α_2-adrenoreceptor agonist, has been extensively investigated in a variety of cerebral ischemia models and results have shown that in some models it partially decreases ischemic damage. The responses to activation of the receptors include decreased contraction of vascular and other smooth muscle [33]. It has been reported to protect against incomplete ischemia in rats [34, 35] and focal ischemia in rabbits [36]. Decreased sympathetic tone was believed to mediate the reduction of necrotic cell death [37]. Additionally, dexmedetomidine increased the concentration of the anti-apoptotic proteins Bcl-2 and Mdm-2 [37]. In a recent study, Eser et al. [38] showed that dexmedetomidine has a neuroprotective effect and that dexmedetomidine may cause inhibi-

tion of lipid peroxidation, an increase in endogenous antioxidant defense enzymes, and a reduction in tissue NO formation. In the present study, SOD and CAT activities were decreased significantly in group 2 compared with group 1. The tissue malondialdehyde level in ipsilateral testes was increased significantly in group 2 compared with group 1. In group 3, MDA levels were decreased significantly compared with group 2. In addition to these data, the significant increases in SOD and CAT activities in group 3 compared with group 2 point to possible protective effects of dexmedetomidine. According to the observations of this study, the histopathological injury score was significantly decreased in group 3 compared with that of group 2. In the dexmedetomidine-treated group, histopathological features such as edema, congestion, hemorrhage, and necrosis of the germinal cells were markedly less than in group 2.

In the present study it was observed that dexmedetomidine has a protective effect on testicular injury induced by I/R. The effects may be explained by the above-mentioned roles of dexmedetomidine, such as a reduction of ROS generation, decreased contraction of vascular and other smooth muscle, and an increased concentration of anti-apoptotic proteins. The present results, which will be supported by additional experimental studies, may help in better understanding the exact mechanism of dexmedetomidine's efficacy.

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