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Research Article

Protective effects of CAPE against testicular damage in streptozotocin-induced diabetic rats

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Abstract

Objective: The aim of this study was to investigate the protective effect of CAPE on oxidative stress and apoptosis against streptozotocin (STZ)-induced damage in rat testis after diabetes.

Materials and methods: The rats were randomly divided into 4 groups: Control animals, Control animals given CAPE, STZ-induced diabetic animals, and STZ-induced diabetic rats given CAPE. Diabetes was induced by a single intraperitoneal injection of STZ (55 mg/kg). Testicular damage was examined by using hematoxylin and eosin staining and apoptosis was determined by Caspase-3. Potential disorders associated with seminiferous tubular sperm formation were evaluated using the Johnsen score and seminiferous tubule diameters were measured using the Leica Q Win Plus Image Analysis System.

Results: Diabetic rats showed an increase in degenerated germ cells along with a decrease in seminiferous tubule diameter. Also, Caspase-3 positive cells were significantly increased in diabetic rats compared to control rats. On the other hand, CAPE significantly reduced the damage and germ cell apoptosis in diabetic rat testis. In testis tissues samples. CAPE treatment significantly decreased the elevated tissue malondialdehyde levels, while increasing the reduced superoxide dismutase enzyme activity.

Conclusion: These results suggest that CAPE administered intraperitoneally for 20 days to diabetic rats is a potentially beneficial agent that can be used to reduce testicular damage.

Introduction

Diabetes mellitus is a disease that causes male infertility by affecting sperm quality through altered steroidogenesis characterized by hyperglycemia and endocrine disorder [1]. Various experimental and clinical observations show that hyperglycemia directly or indirectly increases free radical formation and causes oxidative stress [2,3]. Increasing oxidative stress and changes in antioxidant capacity play an important role in the pathogenesis of chronic diabetes [4]. In the current study, we used STZ-induced diabetic rats as models for type 1 diabetes [5,6]. There are experimental and clinical studies on male infertility due to diabetes [7,8]. It has been reported in studies that diabetes causes testicular damage, especially by causing cell death and apoptosis. Changes in the testicles in diabetes include atrophy in the seminiferous tubules,

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irregularity and cell loss in the germ epithelium lining the tubular wall, arrested of spermatogenesis and spermiogenesis [9] and structural and functional disorders in Leydig cells of the interstitial tissue [10].

Caffeic Acid Phenethyl Ester (CAPE), which is structurally similar to flavonoids, is an active ingredient of honey bee propolis [11]. It is known that CAPE has antitoxic, antioxidant, anti-inflammatory, antiviral, immunomodulatory, neuroprotective, and cytostatic effects [12].

This study, it was aimed to investigate the histological changes in testicular tissue in rats with diabetes and the possible protective effects of CAPE on these changes by histochemical and biochemical methods.

Materials and methods

Chemicals

STZ and CAPE were purchased from Pharmacia Company (Sigma, St. Louis, MO).

Animals

In this study, 32 Wistar albino rats were used. Rats were obtained from Inonu University Experimental Animals Research Center. The experiments were carried out in accordance with the guidelines for animal research from the National Institute of Health and were approved by the Committee on Animal Research at Inonu University, Malatya, Turkey (Ethics Approval Number: 2012/A-04).

Experimental protocol

The rats were divided into 4 groups randomly, each group including 8 animals. Group 1: Control, Group 2: CAPE, Group 3: STZ Group 4: STZ+CAPE. Experimental animals were rendered diabetic by an intraperitoneal injection of a single dose STZ (55 mg/kg) dissolved in physiological saline (0.9 % NaCl), CAPE (10 µmol/kg) was given by IP to rats for 20 days after the experimental animals were made diabetic. The plasma glucose level was measured; at the start of the experiment, 72 hours after administration of injection STZ, and after 20 days to as certain diabetic status of the animals using a glucometer.

At the end of the experiment, blood glucose levels of the animals were measured. The rats were sacrificed under ketamine/xylazine anesthesia. The testes of the animals were removed and the left testicles were taken into the deep freezer for biochemical studies, while the right testicles were fixed in 10% formalin solution for histological studies.

Histological assessment

Paraffin-embedded blocks of testicle tissue were sectioned at 5 µm thickness. Hematoxylin-Eosin (H&E) staining methods were applied to the section to observe the general histological structure and immunohistochemical staining methods were applied to the section to show the caspase-3 (Thermo Fisher Scientific, Inc., Waltham, MA, USA) activity. In this study, Johnsen's score was used to evaluate spermatogenesis [13]. In addition, the 20 most circular seminiferous tubules were randomly selected in each part of the testis in H-E stained preparations, and the diameters of these tubules were measured.

Leica DFC280 light microscope and a Leica Q Win Image Analysis system (Leica Micros Imaging Solutions Ltd., Cambridge, UK) were used for light microscopy and immunohistochemical evaluations.

Biochemical assessment

Tissue homogenate from the testis of each rat was used for analyzing oxidative stress biomarkers. Protein levels of the tissue samples were measured according to Lowry, et al. [14]. Tissue Malondialdehyde (MDA) was evaluated colorimetrically as described by Uchiyama M, Mihara M [15] to assess lipid peroxidation in the form of thiobarbituric acid reactivity substances. Measurement of reduced GSH was done using modified Elman's method [16]. Tissue Superoxide Dismutase (SOD) activity was evaluated using the method of Sun Y. [17].

Statistical analysis

A computer program (SPSS 17.0) was used to perform the statistical analysis of the study. The results were compared with Kruskal–Wallis variance analysis of variance and differences were detected between the groups. Mann–Whitney U test was used to compare group means and $p < 0.05$ values were considered statistically significant. All results were expressed as means ± Standard Error (SE).

Results

Blood glucose level

Table 1 shows the blood glucose levels of the rats in the control and experimental groups. Before diabetes induction, the blood glucose levels of all groups were similar. After Streptozotocin (STZ) injection, a significant increase was observed in the blood glucose levels of diabetic rats on day 20 compared to day 0 ($p < 0.05$). CAPE treatment produced significant changes in the blood glucose levels in nondiabetic rats ($p < 0.05$). The administration of CAPE for 20 days caused a decrease in the level of blood glucose in diabetic rats.

Histological evaluation

Evaluation of hematoxylin-eosin staining: In control (Figure 1A) and CAPE (Figure 1B) groups, testes were observed with normal histological structure. However, disorders of seminiferous tubule germinal epithelium (Figure 1C), congestion of vessels, edema in interstitial spaces (Figure 1D),

Table 1: Initial and final blood glucose levels of all group.

Parameters	Control	CAPE	STZ	STZ+CAPE
Initial blood glucose (mg/dl)	111.57 ± 5.37	96.71 ± 3.48	438.28 ± 11.41[a]	425.14 ± 9.00
Final blood glucose (mg/dl)	110.14 ± 4.83	115.14 ± 8.53	469.85 ± 26.78[a]	352.71 ± 7.93[b]

[a]Significant increase ($p = 0.0001$), *vs.* Control and CAPE group.
[b]Significant decrease ($p = 0.0001$), *vs.* STZ group.

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and desquamation of epithelial cells in the lumen were observed in diabetic rats (Figure 1E), in addition to these findings, atrophy of the tubules with varying degree of spermatogenetic arrest was detected (Figure 1F). In the CAPE-treated diabetic rats, most of the seminiferous tubules in this group were more regular. However, spermatogenic cells that have stagnated in certain stages of meiosis (Figure 1G), and congestion of vessels (Figure 1H), were found in this group. The number of tubules containing stagnated spermatogenic cells was observed less frequently than in the diabetes group. Around these tubules were intact tubules with germinative epithelium that continued to develop normally.

The mean seminiferous tubule diameter (MSTD): It was observed that the diameter of the seminiferous tubule in the STZ group was significantly reduced compared to the control group ($p = 0.001$). When the STZ+CAPE group was compared with the STZ group, there was no significant increase in this group ($p > 0.05$). In addition, when the STZ+CAPE group and the control group were compared, no statistically significant differences were found between them ($p > 0.05$). The seminiferous tubule diameter values of each group are shown in Table 2.

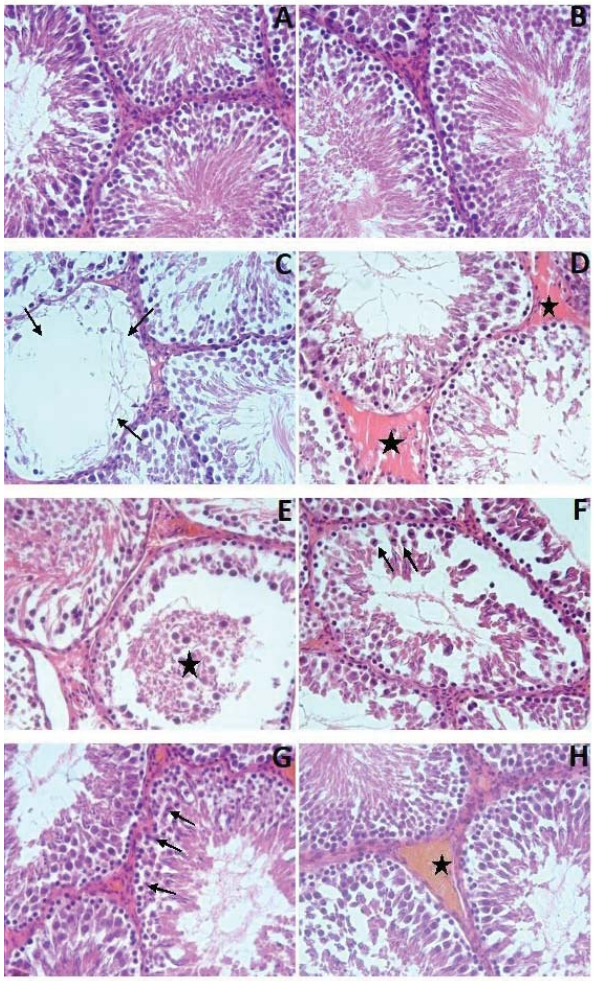

Figure 1: Control [A] and CAPE [B] groups. The seminiferous epithelium is structurally intact and shows normal association of germ cells. STZ group. Revealing disorder of seminiferous tubule germinal epithelium [arrows] [C] congestion of vessels and edema in interstitial spaces [asterisk] [D], desquamation of epithelial cells in the lumen [asterisk] [E], atrophy of the tubules with varying degree of spermatogenetic arrest [F] [arrows]. STZ+CAPE group. Revealing atrophy of the tubules with varying degree of spermatogenetic arrest [arrows] [G] and congestion of vessels and edema in interstitial spaces [asterisk] [H]. H&E x 400.

Evaluation of caspase staining: Apoptotic cells in the testis of diabetic groups were identified by caspase staining. No caspase-3 positive cells were observed in the control (Figure 2A) and CAPE groups (Figure 2B). However, the number of caspase-3 positive germ cells was found to be significantly increased in the STZ group (Figure 2C). In the STZ+CAPE group, a number of apoptotic germ cells statistically significant decrease was observed (Figure 2D). Mean histopathological scor, MSDT, and caspase (+) cells of all groups are given in Table 2.

Biochemical evaluation

STZ-induced diabetes group was compared with the control group, tissue MDA level was measured significantly increased ($p < 0.05$), while SOD activity was significantly decreased in STZ-induced diabetes ($p < 0.05$). In diabetic rats, GSH levels were upper in the testis than in control, CAPE, and CAPE-treated diabetic groups but this rise was not significant ($p > 0.05$). On the other hand, when the CAPE-treated diabetic group was examined, the MDA level was decreased in this group compared to the STZ-induced diabetes group ($p < 0.05$). Also, in the CAPE-treated diabetic group, the activity of SOD was increased compared with the diabetic group Mean tissue MDA and GSH levels and SOD activities of all groups are summarized in Table 3.

Discussion

This study demonstrated that STZ-induced diabetes in adult male rats caused testicular damage both histologically and biochemically, and CAPE administration effectively reduced this damage.

Diabetes mellitus, one of the most common metabolic diseases, represents a major concern of global health due to its serious complications [18]. There are experimental and clinical studies on diabetes-related male infertility [19,20]. Approximately 90% of diabetic patients have been reported in several studies with a decrease in sexual functions (erection, ejaculation, and libido), testicular structural and functional disorders as well as spermatogenesis disorders [21].

It has been shown in previous studies that diabetes increases oxidative stress in testicular tissue. under increased oxidative stress, reactive oxygen radicals cause cellular damage by various mechanisms including oxidative damage of DNA and proteins and membrane lipid peroxidation [22-24]. MDA levels have been widely used as a marker of lipid peroxidation products and lipid peroxidation damage in tissue and experimental studies [25,26]. In our study, while STZ increased MDA activity, SOD activity decreased significantly. The decline in the activities of these antioxidant enzymes might be due to their inactivation caused by excessive ROS production [27]. A decrease in SOD activity has been shown to increase the level of superoxide. In recent years, antioxidant usage to reduce oxidative stress-related tissue damage caused by diabetes has

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Table 2: Histopathological scor of all group.

Parameters	Control	CAPE	STZ	STZ+CAPE
Jonhsen scor	9.03 ± 0.01	9.02 ± 0.01[a]	6.96 ± 0.09[a]	7.78 ± 0.03[b]
MSTD (μm)	297.84 ± 3.15	295.51 ± 3.20	273.80 ± 3.24[a]	279.40 ± 3.60[c]
Caspase (+) cell	0.00 ± 0.00	0.00 ± 0.00	5.85 ± 0.40[d]	2.14 ± 0.26[b]

[a]Significant decrease (p = 0.0001), *vs.* Control and CAPE group
[b]Significant decrease (p = 0.0001), *vs.* STZ group
[c]Not significant change (p > 0.05), *vs.* STZ group
[d]Significant increase (p = 0.0001), *vs.* Control and CAPE group.

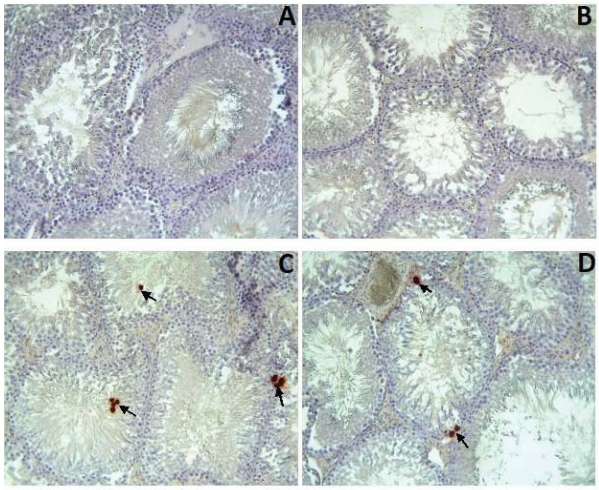

Figure 2: Control [A], CAPE [B], STZ [C], STZ+CAPE [D] The distribution of caspase positive cells in STZ [C], and STZ+CAPE group [D] [arrows] is shown. Caspase immunohistochemistry; Caspase X100.

Table 3: Biochemical results of all groups.

Parameters	Control	CAPE	STZ	STZ+CAPE
MDA nmol/mg	399.71 ± 29.4	352.57 ± 23.00	635.85 ± 49.6[a]	508.85 ± 20.70[b]
GSH nmol/mg	3.52 ± 0.13	3.66 ± 0.18	3.73 ± 0.09[c]	3.87 ± 0.03[d]
SOD U/mg	259.22 ± 13.09	262.37 ± 9.91	210.10 ± 7.44[e]	271.77 ± 13.10[f]

[a]Significant increase (p = 0.0001), *vs.* control and CAPE groups
[b]Significant decrease (p = 0.0001), *vs.* STZ group
[c]Not significant change (p > 0.05), *vs.* control and CAPE groups
[d]Not significant change (p > 0.05), *vs.* STZ group
[e]Significant decrease (p = 0.0146), *vs.* control and CAPE groups
[f]Significant increase (p = 0.0146), *vs.* STZ group.

become one of the most investigated topics. In this study, the therapeutic properties of CAPE, whose antioxidant activity is known for damage to the testicles of rats with experimental diabetes, were investigated. In our study, it was observed that CAPE treatment significantly reduced lipid peroxidation caused by diabetes. In addition, SOD activity and GSH levels increased compared to the diabetic group. But, in the CAPE-treated diabetic group, the GSH level rise was not significant.

Male fertility depends on the continuous self-renewal of spermatogonia and differentiation into spermatogenic cells. It has been reported by many researchers that diabetes causes a decrease in the diameter of the seminiferous tubules, disorganization in the germinative epithelium, and the shedding of germ cells in different stages of meiosis into the lümen [28,29] In our study, in accordance with the literature, we observed that diabetes caused atrophy in the seminiferous tubules and the immature spermatogenic cells to separate from each other and pour into the lumen. Sayım et al. reported that the separation of germinal epithelium cells and their shedding into the lumen is an indication of disruption in the connections between cells [30].

Diabetes has been suggested to cause testicular damage, cell death, and apoptosis by different mechanisms. One of the possible mechanisms is hyperglycemia. Hyperglycemia causes cell apoptosis in the testes by increasing excessive ROS production [31]. Studies have shown an increase in germ cell apoptosis in the testes of streptozotocin-induced diabetic animals [32]. Similarly, in our study, an increase in the number of apoptotic cells was found in the diabetes group. These results suggest that apoptotic cell death is an important factor in the loss of testicular function in diabetic animals. However, in the STZ+CAPE group, the number of apoptotic germ cells statistically significantly decreased was observed

Study Limitations The most important limitation of our study is that it is not supported by further immunohistochemical parameters.

In conclusion, our results suggest that the beneficial properties of CAPE treatment, via its potent antioxidants, may reduce the adverse effects of diabetes in the reproductive system in rats.

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