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The Metabolic Effects of High-fructose Corn Syrup in Dental Tissues and Parotid Glands of Rats and the Therapeutic Effect of Alpha Lipoic Acid

Yüksek Fruktozlu Mısır Şurubunun Sıçanların Diş Dokularında ve Parotis Bezlerinde Metabolik Etkileri ve Alfa Lipoik Asitin Tedavi Edici Etkisi

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Abstract

Objective: This study aimed to examine the metabolic effects of high fructose corn syrup (HFCS) in dental tissues and parotid glands of rats and antioxidant defense of alpha-lipoic acid (ALA) in HFCS-induced effects.

Materials and Methods: Female Wistar rats (n=24) divided into three groups (group 1: negative control, group 2: positive control, and group 3: ALA) with each group consisting of 8 animals. Rats in groups 2 and 3 were subjected to HFCS for 10 weeks. ALA was given to the animals in group 3 for the last 6 weeks of the experiment. The rats were euthanized by cervical dislocation. The tissues were prepared for histopathological, and immunohistochemical [caspase-3, caspase-8 and bone moprhogenetic protein-2 (BMP-2)] evaluations. Data were analyzed by Kruskal-Wallis (non-parametric data) and one-way ANOVA tests (parametric data) ($p<0.05$).

Results: Hyperemia and neutrophil leukocyte infiltrations in dental tissues and sialadenitis characterized by severe inflammatory reactions in the parotid gland were observed in group 2. After the ALA treatment, degenerative changes were decreased in both tissues, and the gland recovered an essentially normal appearance. Group 3 exhibited significantly lower inflammatory scores than the group 2 in terms of dental pulp ($p=0.044$). Both BMP-2 values and caspase-3 cell counts of the gingival tissue were significantly lower in group 3 compared to group 2 ($p<0.01$).

Conclusion: The vascular and pulpal tissue damage caused by corn syrup was determined in this study. It was concluded that ALA could be a potential antioxidant against the harmful consequences of corn syrup consumption.

Keywords: Alpha-lipoic acid, dental pulp, high-fructose corn syrup, parotid gland, rats

Öz

Amaç: Bu çalışmanın amacı, yüksek fruktozlu mısır şurubunun (HFCS) sıçanların diş dokularında ve parotis bezlerindeki metabolik etkilerini ve alfa lipoik asitin (ALA) HFCS kaynaklı etkilerdeki antioksidan savunmasını incelemektir.

Gereç ve Yöntemler: Dişi Wistar sıçanları (n=24), her biri 8 hayvandan oluşan üç gruba (grup 1: negatif kontrol, grup 2: pozitif kontrol ve grup 3: ALA) ayrıldı. Grup 2 ve 3'teki sıçanlara 10 hafta boyunca HFCS uygulandı. Grup 3'teki hayvanlara deneyin son 6 haftasında ALA verildi. Sıçanlara servikal dislokasyon ile ötenazi uygulandı. Dokular histopatolojik ve immünohistokimyasal [kaspaz-3, kaspaz-8 ve kemik morfogenetik protein-2 (BMP-2)] değerlendirmeler için hazırlandı. Veriler Kruskal-Wallis (parametrik olmayan veriler) ve tek yönlü ANOVA testleri (parametrik veriler) ile analiz edildi ($p<0.05$).

Bulgular: Grup 2'de diş dokularında hiperemi ve nötrofil lökosit infiltrasyonları ve parotis bezinde şiddetli enflamatuar reaksiyon ile karakterize sialadenit gözlendi. ALA tedavisi sonrası her iki dokuda da dejeneratif değişiklikler azaldı ve bez normal bir görünüm kazandı. Pulpa açısından grup 3 grup 2'ye göre anlamlı olarak daha düşük enflamatuar skorlar sergiledi ($p=0,044$). Diş eti dokusunun hem BMP-2 değerleri hem de kaspaz-3 hücre sayıları grup 3'te grup 2'ye göre anlamlı derecede düşüktü ($p<0,01$).

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Sonuç: Bu çalışmada mısır şurubuna bağlı vasküler ve pulpal doku hasarlarının gerçekliği belirlendi. ALA'nın mısır şurubu tüketiminin zararlı sonuçlarına karşı potansiyel bir antioksidan olabileceği sonucuna varıldı.

Anahtar Kelimeler: Alfa-lipoik asit, pulpa, yüksek fruktozlu mısır şurubu, parotis bezi, sıçanlar

Introduction

Today, interest in the health effects of excessive high fructose corn syrup (HFCS) intake has increased due to its widespread commercial use and reporting of severe adverse metabolic effects in rodents, humans, and rats (1,2). Among these effects, oxidative stress (OS) which is observed due to HFCS-induced insulin resistance and the result of excessive production of reactive oxygen species (ROS) is an important risk factor that causes dysfunction of various tissues and organs of the body (3). However, there are hardly few studies analyzing OS and cytopathological consequences especially such as apoptosis in the salivary glands in insulin resistance (4).

Saliva has multifunctional roles, such as protecting the teeth surface and the mucous membranes of the oral cavity towards to chemical, biological, and mechanical attacks and antioxidant capacity, in maintenance of oral health (5). Therefore, saliva is considered an important element of the oral defense mechanism, as the antioxidants in saliva are the first line of defense against OS due to free radicals (6). Thus, the factors that impair the function of the salivary glands affect the oral health and quality of life negatively by changing the amount and content of saliva (7).

The dental pulp is a vascularized tissue with a dense capillary plexus and vulnerable to damage by inflammation, chemicals, and mechanical trauma (8). In an inflammatory state, odontoblasts produce copious amounts of proinflammatory mediators and various molecular and cellular signaling pathways are activated (8,9). However; OS, another consequence of a long-term inflammation, induces apoptosis of pulp cells and causes proliferation failure to replace damaged odontoblasts (10). Apoptosis markers such as caspase-3 have previously been studied in parotid gland and pulp (9,11). However, so far, no attention has been paid to their role in HFCS intake.

An alternative approach to minimize the effects caused by OS is to maintain a proper diet accompanied by regular antioxidant supplementation. It has been reported that alpha-lipoic acid (ALA), a mitochondrial coenzyme and natural antioxidant, has beneficial effects on OS parameters such as elimination of free radicals and reduction of OS in various tissues (12). It was previously reported that ALA has the ability to scavenge ROS, increase the intracellular antioxidant enzyme activity, and reduce the proinflammatory marker levels (13).

The aim of this study was to find out a) the possible metabolic effects of HFCS in parotid glands, gingiva and pulp of rats, b) the antioxidant defense of ALA in parotid glands and dental tissues of rats subjected to HFCS intake. The null hypothesis was that systemic application of ALA had no effect on the severity of inflammation induced by HFCS.

Materials and Methods

The animal experiments were approved by the Experimental Animal Committee on Animal Research of the Süleyman Demirel University, Isparta (decision no:3, date: 22.08.2013).

Female Wistar rats (n=24), weighing 250-300 g, were housed at a temperature of 21±2 °C with 60±5% humidity in a controlled room. All rats were fed with standard ad libitum chow (Korkuteli yem, Antalya, Turkey). F30 corn syrup (Toposmanoğlu, Isparta, Turkey), containing approximately 24% fructose and 28% dextrose in the syrup of 73% total solids, was prepared in 30% similar to the corresponding publications (14). The rats were randomly divided into three groups (group 1: negative control, group 2: positive control and group 3: ALA), with each group consisting of 8 animals. Standard diet and water were given only to group 1 for 10 weeks. F30 corn syrup was given to rats in group 2 and 3 within the drinking water for 10 weeks (2). ALA (100 mg/kg) (Thioctazid 600 mg tab, Meda Pharma, Turkey) was given only to rats of group 3 by oral gavage for the last 6 weeks of the experiment (14). Twenty-four hours after the last ALA application, rats were euthanized by cervical dislocation. The parotid glands were removed bilaterally. Subsequently, the jaws were defleshed and collected for histopathological examination.

During necropsy, the parotid glands, jaws were fixed in 10% buffered formalin solution (Sigma Diagnostics, St. Louis, MO, USA). After the fixation, the hemimandibulas were decalcified for 8 weeks in 18% EDTA (Cerkamed, Stalowa Wola, Poland). Five serial sections of each hemimandibula with 5 µm thickness were cut and stained with hematoxylin-eosin. Routine pathology procedures were also used for the parotid gland examined under light microscope (Olympus CX41, Tokyo, Japan). Histopathological lesions of parotid gland scored as (15);

0: Normal gland histology; 1: Only hyperemia; 2: Inflammatory cells ≤5 under a magnification of x400; 3: Inflammatory cells >6 under a magnification of x400.

For evaluating the number of polymorphonuclear leukocytes (PMNs) of the gingival junctional epithelium and connective tissue subjacent to the epithelium, an area of 0.05 mm x 0.05 mm was examined and counted under a magnification of x400 for each rats (16). Semi-quantitative histological scoring of pulp was performed according to the McClanahan criteria for histopathology (17).

Selected jaw tissue sections were immunostained for caspase-3 [Anti-caspase-3 antibody (ab4051), Abcam, Cambridge, UK] to demonstrate the apoptotic activity and bone morphogenetic proteins-2 (BMP-2) [(Anti-BMP2 antibody [65529.111] ab6285), Abcam, Cambridge, UK], parotid section was immunostained by caspase-3 and caspase-8 [Anti-Caspase-8 (ab25901), Abcam, Cambridge, UK] by routine streptavidin-biotin peroxidase technique. Tissues were counterstained with Harris hematoxylin. All slides were analyzed for immunopositivity, and a semi-quantitative analysis was carried out. The average percentages of both epithelial and submucosal immunopositive cells were then calculated. Morphometric evaluation was performed using the database manual cell sens life science imaging software system (Olympus Corporation, Tokyo, Japan).

Statistical Analysis

Statistical analysis was carried out using SPSS 13.0 software program pack (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to establish the normal distribution of variables. The histopathological scores of the groups were compared with the non-parametric Kruskal-Wallis test. The immunohistochemical data were analyzed using a parametric one-way analysis of variance (ANOVA) test. Statistical significance was determined at $p<0.05$.

Results

No pathological changes were observed in gingival tissue and dental pulp of the group 1 (Figure 1A). Increased vessel count, hyperemia and neutrophil leukocyte infiltrations were observed in gingival tissue of group 2. The PMN infiltrations were increased in both gingival epithelium and submucosa of group 2 compared to the group 1 (Figure 1B).

As a result of histopathological evaluation of the pulp, group 3 exhibited significantly lower inflammatory scores than group 2 ($p=0.044$, Table 1), while group 3 and group 1 exhibited statistically similar inflammatory scores ($p=1.000$, Table 1).

The number of caspase-3 + cells of gingiva in group 3 were significantly lower than group 2 ($p<0.05$, Table 1). Similarly, BMP-2 immunoreaction was increased by HFCS-treated rats in group 2 and significantly decreased with ALA treatment in group 3 (Table 1). Caspase-3 immunoreaction of gingiva in the groups was demonstrated in Figure 1D-1F. BMP-2 expression of the groups was demonstrated in Figure. 1G-1I.

No pathological changes were observed in the parotid glands of group 1 (Figure 2A). In group 2, slight histopathological findings such as slight degeneration in some acinus and degranulation in some acinar cells were observed. The first sign of degeneration was the appearance of nuclear psychosis in some cells, especially in the parenchyma. The cell imaging showed shrinkage of nucleus more than the cells of group 1. Sialadenitis characterized by inflammatory reaction was observed in group 2 (Figure 2B). In group 3, the parotid gland recovered an essentially normal appearance. The contour of the nuclei became rounded and the vesicular appearance was returned (Figure 2C). Degenerative changes were decreased but no statistically significant difference was observed among the group 2 and 3 in terms of inflammatory index ($p=1.000$, Table 2).

The caspase-3 and caspase-8 reaction of the parotid gland in group 1 was low. The immunopositive cells in group 2 were significantly higher than the number of positive cells of group 3 (Table 2). Caspase-3 and caspase-8 immunoreaction of the parotid glands in the groups was also demonstrated in Figure 2D-2F and 2G-2I, respectively.

Discussion

It is well documented that HFCS induces metabolic disturbances in rats (2). One of the organs affected by OS, which is an important parameter in these metabolic disorders, is the parotid gland. Mata et al. (11) mentioned the effect of ROS on rat parotid gland and reported that ROS could stimulate the activity of caspase in parotid gland tissue leading to apoptosis. It was reported that in the presence of high glucose concentrations, ROS levels and apoptosis rates were significantly increased in a dose-dependent manner (18). Increased caspase reaction demonstrating apoptotic activity in this study was confirmed the information mentioned above. The number of caspase-3 + cells of the gingiva and caspase-3 + and caspase-8 + cells of the parotid gland observed in group 2 was significantly greater than the number of caspase - positive cells in group 3. These results also confirm that ALA treatment attenuates the increase in apoptotic activity associated with HCFS ingestion.

The effect of sucrose and correspondingly OS is partly systemic and dose-dependent (19). Therefore, these effects don't remain limited with parotid glands. Several studies in rats have also confirmed the effects of a diet rich in sucrose on dentin apposition (19,20). However, it has also been noted that high glucose levels could restrict macrophage function (chemotaxis and bacterial death), resulting in an inflammatory state that damages host cellular proliferation (10). The microscopic and histopathological analysis verified the efficacy of the experimental protocol used in this study for inducing inflammation. Notably, this inflammatory state was observed in group 2 of the present study. The sign of the inflammatory reaction by increased PMN infiltrations was seen in both the gingiva and parotid glands of group 2. High concentrations of glucose may be responsible for reduced cell growth, which may have contributed to this outcome. And this result may also be attributed to a rise in apoptosis and/or cell-cycle arrest.

Neovascularization and advanced cellular differentiation of dental pulp are crucial in terms of pulp healing. The pulp's healing potential is related to the dental pulp cells ability of secreting growth factors (21). One of these growth factors is BMPs. BMPs are signaling proteins and play an important

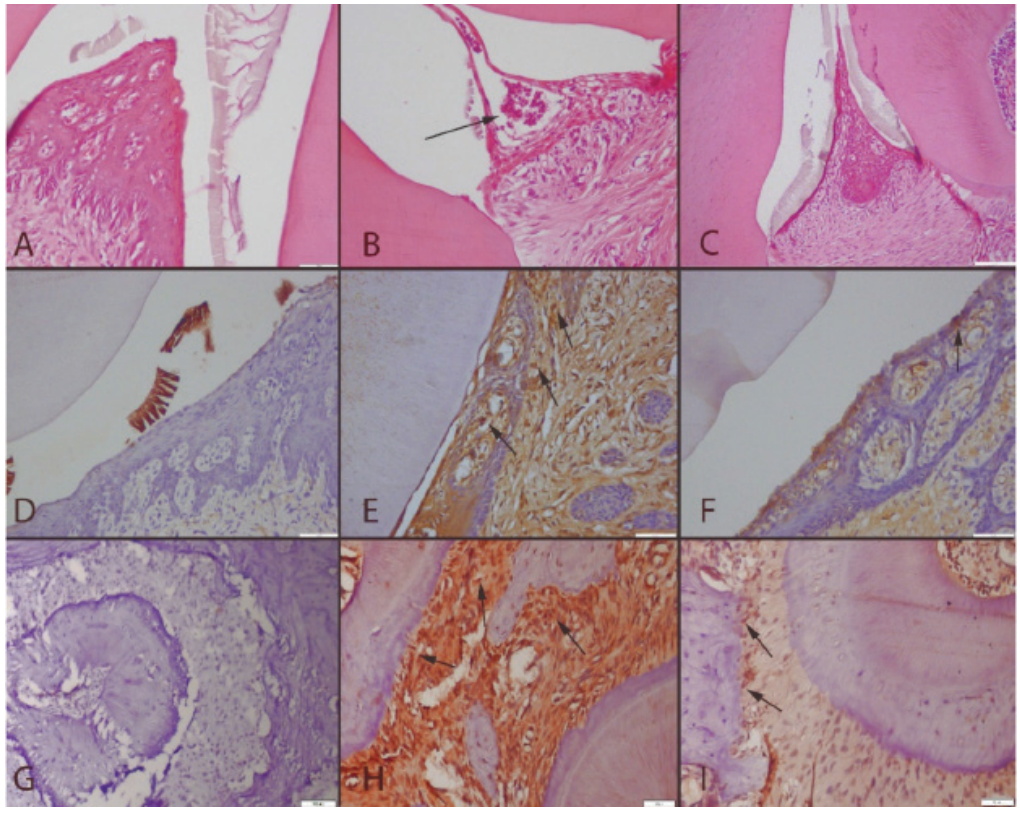

Figure 1. Representative histopathology of the oral mucosa in the groups (upper row).
(A) Normal appearance of the tooth, normal thickness with intact gingival mucosa in group 1, **(B)** Marked PMN infiltrations in gingival epithelium and sub adjacent connective tissue (arrows), marked decrease of thickness of the epithelial layer in group 2, **(C)** Ameliorated gingival lesions in group 3
Caspase-3 immunoreaction of the gingival tissue in the groups (medial row). **(D)** Negative immunoreaction both epithelial and connective tissue cells in group 1, **(E)** Marked increase in caspase-3 expression in gingival epithelium and connective tissue cells (arrows) in the group 2, **(F)** Decreased immunoreaction of caspase-3 (arrow) in group 3
BMP-2 expression between the groups (below row). **(G)** Negative immunoreaction in group 1. **(H)** Marked expression in cells (arrows) in group 2. **(I)** Decreased expression in cells (arrows) in group 3. Bars =50 μm.

Table 1. Histopathological and immunohistochemical results (mean ± SD) of gingiva and pulp

	Group 1	Group 2	Group 3	p-value
Inflammation scores of pulp	0.42±0.29	3.12±-1.15	1.37±0.32	1-2 (0.007)* 1-3 (1.000) 2-3 (0.044)*
PMN number at junctional epithelium of gingiva	1.28±0.35	6.75-0.36	3.50-0.56	1-2 (0.000)* 1-3 (0.008)* 2-3 (0.000)*
PMN number at connective tissue of gingiva	2.00±0.43	8.25-0.31	3.75-0.45	1-2 (0.000)* 1-3 (0.020)* 2-3 (0.000)*
Cas-3 positive cell (%)	0.28±0.18	11.25±2.21	2.75±0.70	1-2(0.000)* 1-3 (0.006)* 2-3 (0.000)*
BMP-2 positive cells (%)	1.14±0.45	29.75±2.54	7.75±1.28	1-2 (0.000)* 1-3 (0.000)* 2-3 (0.000)*

PMN: Polymorphonuclear leukocyte, BMP: Bone morphogenetic protein, SD: Standard deviation, *Statistically significant ($p<0.05$)

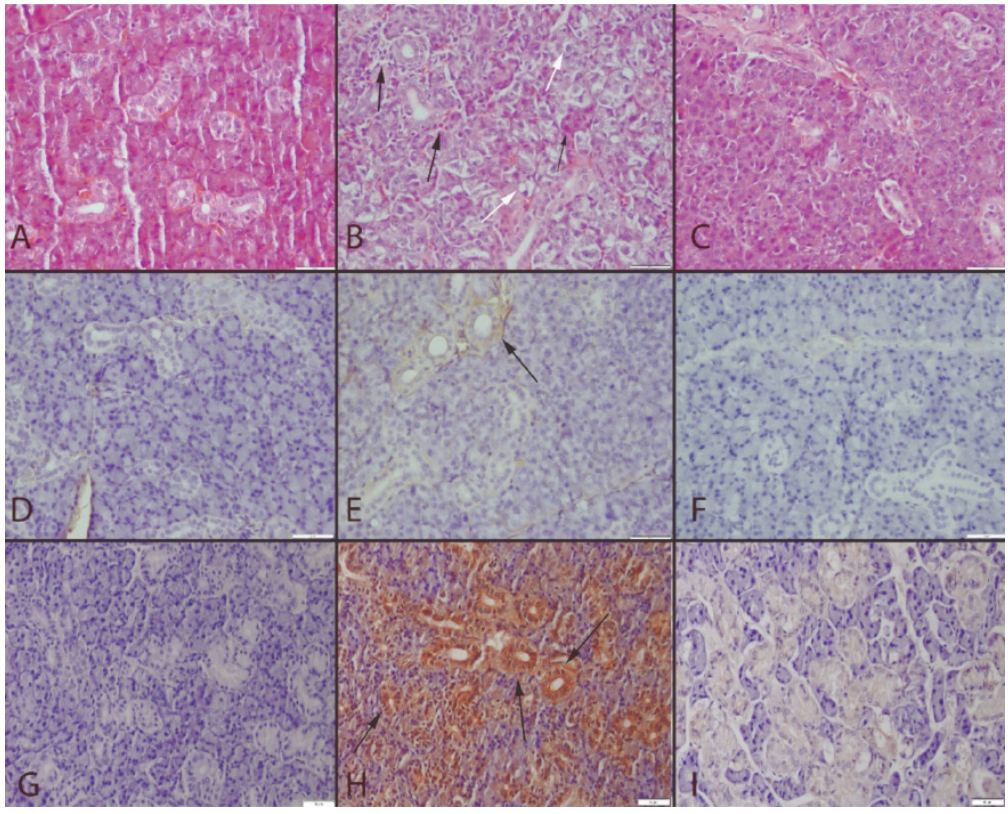

Figure 2. Representative histopathology of the parotid glands in the groups (upper row). **(A)** Normal histology of the parotid gland in group 1, **(B)** PMN infiltrations (black arrows), vacuolization at the cytoplasm (white arrows) and psychosis (thin arrow) at the nucleus of parotid gland cells in group 2, **(C)** Amelioration of the pathological findings of the group 3.
Caspase-3 immunoreaction of the parotid glands in the groups (medial row). **(D)** Negative caspase-3 reaction of the parotid gland in group 1, **(E)** Increased caspase-3 immunopositivity at the duct of parotid gland (arrow) in group 2, **(F)** Negative caspase-3 reaction of the parotid gland in group 3
Caspase-8 immunoreaction of the parotid glands in the groups (below row). **(G)** Negative caspase-3 reaction of the parotid gland in group 1, **(H)** Increased caspase-3 immunopositivity at the duct of parotid gland (arrows) in group 2, **(I)** Negative caspase-3 reaction of the parotid gland in group 3. Bars =50 μm.

Table 2. Histopathological and immunohistochemical results (mean ± SD) of parotid gland

	Group 1	Group 2	Group 3	p-value
Inflammation scores	0.00±0.00	2.12±0.22	1.87±0.29	1-2 (0.000)* 1-3 (0.000)* 2-3 (1.000)
Cas-3 positive cells (%)	0.85±0.35	22.75±2.54	7.75±1.28	1-2 (0.000)* 1-3 (0.000)* 2-3 (0.000)*
Cas-8 positive cell (%)	1.85±0.67	29.75±1.83	9.00±1.06.	1-2 (0.000)* 1-3 (0.000)* 2-3 (0.000)*

*Statistically significant ($p<0.05$), SD: Standard deviation

role in functions such as matrix synthesis, cell proliferation, embryogenesis, bone formation, and mesenchymal stem cell differentiation (22). In recent studies, it has been reported that BMPs play an important function in glucose homeostasis as a bridge between glucose metabolism and bone metabolism (23,24). A previous study noted that endothelial cells readily respond to high glucose therapy through upregulation of BMPs and their inhibitors and receptors (23). In present study, the BMP-2 reaction was significantly increased as a result of inflammation induced by taking fructose syrup for 10 weeks as aforementioned studies.

ALA is a component that is produced in very small amounts in the body and acts as a coenzyme in various reactions, is involved in glycolysis, and is responsible for converting blood sugar into energy (25). Nevertheless, the protective effects of ALA in different tissues have long been studied (3,12,13,18,25). The results of this study have supported the potential of therapeutic approaches of ALA. The group treated with ALA presented a lower inflammatory index and lower number of caspase-3+, caspase-8+ cells, and BMP2 than the group 2. ALA prevents microvascular damage and has a protective effect on neurons (3). This effect of ALA may provide the return of a modified appearance of cells and glands in group 2 to normal appearance in group 3 essentially in present study. As a result of all these results, the null hypothesis was rejected. To the best of our knowledge, in the literature, there are no previous studies evaluating the anti-inflammatory effects of the ALA in rat dental tissues and parotid glands, so it is not possible to make a comparison with other study models. The limitation of this study is that there were no markers of OS induced ROS. The inclusion of OS markers in this study may diversify the results of this study.

Conclusion

It was concluded that intercellular ROS formation and OS in oral mucosa, pulp and salivary gland cells enhanced by high glucose was attenuated by treatment with ALA due to the results of decreased degenerative changes and the reduced number of caspase + cells. Further studies are necessary to investigate the possible effects of corn syrup and ALA with a larger number of samples using longer treatment duration to evaluate not only the reduction in symptoms, but also the toleration.

Ethics

Ethics Committee Approval: The animal experiments were approved by the Experimental Animal Committee on Animal Research of the Süleyman Demirel University, Isparta (decision no: 3, date: 22.08.2013).

Informed Consent: Informed consent is not required.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ö.K.H., F.N.Ç., Concept: Ö.K.H., U.B.T., F.N.Ç., Design: Ö.K.H., U.B.T., F.N.Ç., Data Collection or Processing: Ö.K.H., F.N.Ç., Ö.Ö., Analysis or Interpretation: Ö.K.H., Ö.Ö., Literature Search: Ö.K.H., U.B.T., Writing: Ö.K.H.

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References

1. Ma R, Sun M, Wang S, Kang Q, Huang L, Li T, et al. Effect of high-fructose corn syrup on the acidogenicity, adherence and biofilm formation of Streptococcus mutans. Aust Dent J 2013; 58: 213-8.
2. Akar F, Uludağ O, Aydın A, Aytekin YA, Elbeg S, Tuzcu M, et al. High-fructose corn syrup causes vascular dysfunction associated with metabolic disturbance in rats: protective effect of resveratrol. Food Chem Toxicol 2012; 50: 2135-41.
3. Nebbioso M, Pranno F, Pescosolido N. Lipoic acid in animal models and clinical use in diabetic retinopathy. Expert Opin Pharmacother 2013; 14: 1829-38.
4. Kołodziej U, Maciejczyk M, Miąsko A, Matczuk J, Knaś M, Żukowski P, et al. Oxidative Modification in the Salivary Glands of High Fat-Diet Induced Insulin Resistant Rats. Front Physiol 2017; 8: 20.
5. Ahmadi-Motamayel F, Goodarzi MT, Hendi SS, Kasraei S, Moghimbeigi A. Total antioxidant capacity of saliva and dental caries. Med Oral Patol Oral Cir Bucal 2013; 18: e553-6.
6. Rahmani M, Ghorchi V, Rezaei F, Vaisi-Raygani A. Evaluation of Total Antioxidant Capacity of Saliva in High School Students. Glob J Health Sci 2015; 8: 89-94.
7. Kołodziej U, Maciejczyk M, Niklińska W, Waszkiel D, Żendzian-Piotrowska M, Żukowski P, et al. Chronic high-protein diet induces oxidative stress and alters the salivary gland function in rats. Arch Oral Biol 2017; 84: 6-12.
8. Yumoto H, Hirao K, Hosokawa Y, Kuramoto H, Takegawa D, Nakanishi T, et al. The roles of odontoblasts in dental pulp innate immunity. Jpn Dent Sci Rev 2018; 54: 105-17.
9. Lima SM, Grisi DC, Kogawa EM, Franco OL, Peixoto VC, Gonçalves-Júnior JF, et al. Diabetes mellitus and inflammatory pulpal and periapical disease: a review. Int Endod J 2013; 46: 700-9.
10. Takanche JS, Lee YH, Kim JS, Kim JE, Han SH, Lee SW, et al. Anti-inflammatory and antioxidant properties of Schisandrin C promote mitochondrial biogenesis in human dental pulp cells. Int Endod J 2018; 51: 438-47.
11. Mata A, Marques D, Martínez-Burgos MA, Silveira J, Marques J, Mesquita MF, et al. Effect of hydrogen peroxide on secretory response, calcium mobilisation and caspase-3 activity in the isolated rat parotid gland. Mol Cell Biochem 2008; 319: 23-31.
12. López-Jornet P, Camacho-Alonso F, Leon-Espinosa S. Efficacy of alpha lipoic acid in burning mouth syndrome: a randomized, placebo-treatment study. J Oral Rehabil 2009; 36: 52-7.
13. Sehirli AO, Aksoy U, Kermeoglu F, Kalender A, Savtekin G, Ozkayalar H, et al. Protective effect of alpha-lipoic acid against apical periodontitis-induced cardiac injury in rats. Eur J Oral Sci 2019; 127: 333-9.

14. Ventura EE, Davis JN, Goran MI. Sugar content of popular sweetened beverages based on objective laboratory analysis: focus on fructose content. Obesity (Silver Spring) 2011; 19: 868-74.

15. Aşcı H, Saygın M, Yeşilot Ş, Topsakal Ş, Cankara FN, Özmen Ö, et al. Protective effects of aspirin and vitamin C against corn syrup consumption-induced cardiac damage through sirtuin-1 and HIF-1α pathway. Anatol J Cardiol 2016; 16: 648-54.

16. Ekuni D, Yamamoto T, Yamanaka R, Tachibana K, Watanabe T. Proteases augment the effects of lipopolysaccharide in rat gingiva. J Periodontal Res 2003; 38: 591-6.

17. McClanahan SB, Turner DW, Kaminski EJ, Osetek EM, Heuer MA. Natural modifiers of the inflammatory process in the human dental pulp. J Endod 1991; 17: 589-93.

18. Zhen D, Chen Y, Tang X. Metformin reverses the deleterious effects of high glucose on osteoblast function. J Diabetes Complications 2010; 24: 334-44.

19. Pekkala E, Välikangas L, Puukka M, Tjäderhane L, Larmas M. The effect of a high-sucrose diet on dentin formation and dental caries in hyperinsulinemic rats. J Dent Res 2002; 81: 536-40.

20. Leonora J, Tjäderhane L, Tieche JM. Parotid gland function and dentin apposition in rat molars. J Dent Res 2002; 81: 259-64.

21. Boyle M, Chun C, Strojny C, Narayanan R, Bartholomew A, Sundivakkam P, et al. Chronic inflammation and angiogenic signaling axis impairs differentiation of dental-pulp stem cells. PLoS One 2014; 9: e113419.

22. Beederman M, Lamplot JD, Nan G, Wang J, Liu X, Yin L, et al. BMP signaling in mesenchymal stem cell differentiation and bone formation. J Biomed Sci Eng 2013; 6: 32-52.

23. Elmasry K, Habib S, Moustafa M, Al-Shabrawey M. Bone Morphogenetic Proteins and Diabetic Retinopathy. Biomolecules 2021; 11: 593.

24. Chen Y, Ma B, Wang X, Zha X, Sheng C, Yang P, et al. Potential Functions of the BMP Family in Bone, Obesity, and Glucose Metabolism. J Diabetes Res 2021; 2021: 6707464.

25. López-D'alessandro E, Escovich L. Combination of alpha lipoic acid and gabapentin, its efficacy in the treatment of Burning Mouth Syndrome: a randomized, double-blind, placebo controlled trial. Med Oral Patol Oral Cir Bucal 2011; 16: e635-40.