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THE HISTOPATHOLOGIC EFFECTS OF LITHIUM ON RAT SALIVARY GLANDS

RAT TÜKRÜK BEZLERİNDE LİTYUMUN HİSTOPATOLOJİK ETKİSİ

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This study was organised to evaluate histopathologic changes on salivary glands of rats fed with lithium carbonate. 20 male Wistar-albino rats weighting 280±50 gr were taken as experimental group and control group consisted of 20 rats. On 35th day all rats were anaesthetized and salivary glands were removed. In histological slides of the experimental group; vacuolar and hydrophic degeneration, cell ruptures, a prominent cellular damage were seen. Dysfunctional effects of Lithium on salivary glands has been reported in various studies as a change in electrolyte and protein content of saliva composition. Present study shows that dysfunctional effects of Lithium on salivary glands may occur as a result of direct toxic effect of Lithium on salivary glands.

Bu çalışmada lityum karbonatın deney hayvanlarının tükürük bezleri üzerindeki histopatolojik etkisi araştırılmıştır 280+-50 gr ağırlığındaki 20 adet Wistar-albino rat deney grubu, 20 adet rat ise kontrol grubu olarak incelenmiştir. 35. günde anestezi altında deney hayvanlarının tükürük bezleri çıkartılarak histopatolojik olarak incelenmiştir. Deney grubunda tükürük bezlerinde vakuolar ve hidrofik dejenerasyon ve belirgin hücresel hasar bulunmuştur. Lityumun tükürük bezleri üzerindeki disfonksiyonel etkisi, tükürük yapısındaki elektrolit ve protein değişiklikleri olarak değişik çalışmalarda bildirilmiştir Bu çalışmada lityumun tükürük bezleri üzerindeki etkisi lityumun tükürük bezlerine doğrudan toksik etkisi ile de oluşabileceği gösterilmiştir.

Keywords: *Rat salivary glands, histology, lithium, toxic effect.*

Anahtar kelimeler: *Rat tükrük bezleri, histoloji, lityum, toksik etki.*

Introduction

Lithium was discovered to be an elemental constituent of nature more than 150 years ago. Although knowledge of its physical and chemical properties has accumulated rapidly over the past four decades, our understanding of the biochemistry and pharmacology of lithium has grown more slowly.

It is used in a wide range of diseases such as aggression control drug and for alcohol dependency, premenstruel syndrome, Parkinson's disease, trigeminal neuralgia, Addison's disease (1).

Lithium is given orally as a salt in the form of tablet or capsule. Some investigators have tried to get quicker action by using an injectable solution of the drug, lithium iodide, but there is no evidence that this is an advantageous route of administration.

Standard preparations take 1-2 hours to reach the maximum plasma concentrations. The absorbed lithium is distributed to whole body tissues. The biological half life of the drug is 12-41 hours. The cure range of lithium is 0.5-

1.2 mmol/L. Doses higher than 1.4 mmol/L are toxic (2).

Most patients receiving lithium experience some side effects. Some effects are relatively pronounced at the beginning of treatment, but generally diminish or disappear rapidly. The most frequently reported subjective side effects of lithium are excessive thirst, dry mouth, polyuria, memory problems, tremor, weight gain, diarrhea and tiredness (3).

Dry mouth and hyposalivation are very important findings in the dentistry. Saliva has many functions. The glycoproteins in saliva provide both mechanical protection (4), also, because of its large volume and continuous flow, saliva flushes away large numbers of bacteria and accumulating toxins. The properties of saliva which make it a good lubricant also help to protect the soft tissue surfaces from physical damage which might otherwise be caused by hard textured foods or excessive temperatures. Similarly, buffers present in saliva help to protect both hard and soft tissues from chemical damage resulting from bacterial acid production (5). If the flow of saliva is suppressed ,pathological changes may supervene and excessive dryness leads to stomatitis, inflamation of the mouth and an increase in dental caries.

1000-1500 ml of saliva is secreted daily in adults. Saliva without the pharyngeal, tracheal and bronchial secretions is a mixture of the secretions that are obtained from the salivary glands that secretes into the oral cavity. Salivary glands are divided into two main groups, major and minor salivary glands. Major salivary glands are parotid gland, sublingual gland and submandibular gland.

Parotid gland has serous secretions, submandibular and sublingual gland has mixed secretions. Salivary secretion may alter with age,dehydration, infectious disorders, emotional factors, nervous system diseases and with various drugs.

Saliva plays an important role in the maintenance of oral health. The oral health status of an individual is influenced by both the composition of saliva and histopathologic changes of the salivary glands.

It is also pointed out that the quantity of saliva and histologic changes of salivary glands are important in caries risk and other oral problems.

With respect to the above-mentioned data, this study was designed to examine effect of lithium therapy on rat salivary gland histology.

Materials and Methods

The experimental group was carried out on 40 Wistar-albino rats weighting 280±50 gr. The whole rats were male. The control group consisted of 20 male rats. All of them fed with standard breed and tap water in private rat cages. Lithium Carbonate (1 mg/Per kg body mass) prepared in serum physiologic were given by gavage at the same hours for 35 days. The control group was given only serum physiologic by gavage. On the 35^{th}. day of Lithium Carbonate administration the rats were anaesthetisized intraperitoneally by pentothal-sodium of 35 $mg.kg^{-1}$. Following anaesthesia, submandibular sites of 40 (control and experimental group) rats were shaved and cleaned with povidon-iodine. Caring for the rat anatomy, after skin incisions, submandibular and parotid glands were reached in turn by blunt dissection. Salivary glands were removed totally. Tissue samples were embedded in 10% buffered formalin solution and bovine solution. Then samples were processed, embedded in paraffin wax. Sections were stained hematoxylane- eosin and PAS (Periodic acid schiff) and examined in light microscopy.

Results

Parotid Gland

In control group, parotid glands were normal with pure serous acini and excretory canals. The nucleus in serous acinar cells was located centrally. Their cytoplasm contained many secret granules (Figure 1).

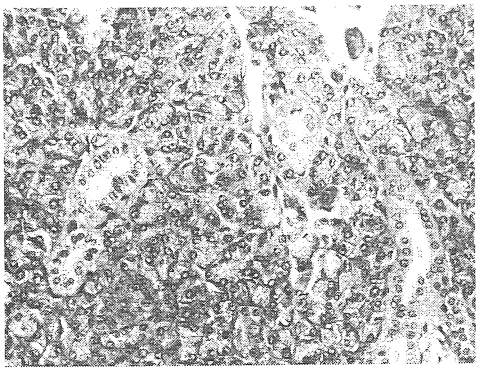

Fig. 1.

In experimental groups the epithelial cells of parotid glands showed prominent cellular damage. Vacuolar and hydrophic degeneration were seen in most of the acinar cells. Some of these cells were ruptured and cytoplasm were scattered into the lumen. Ducts in the degeneration areas were filled with secretion. Some of the secretion canals showed mild degenerative findings (Figure2). It was observed that acinar cells were replaced by fat cells at the lobules (Figure3).

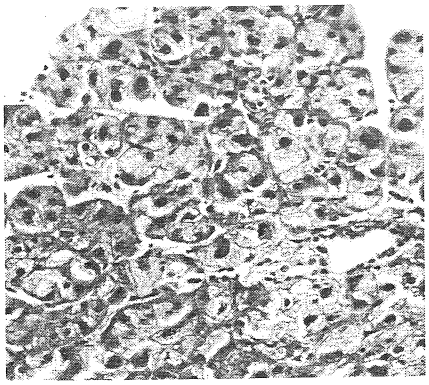

Fig. 2.

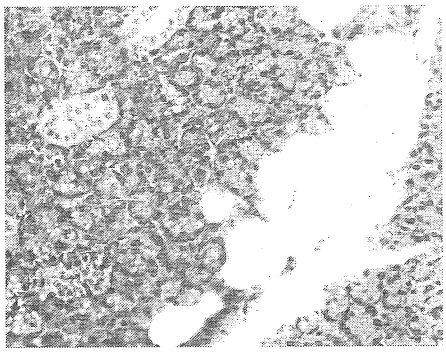

Fig. 3.

Submandibular Gland

In the control group; the submandibular glands were formed by mucous-acinas and secretory canals formed lobules (Figure 4).

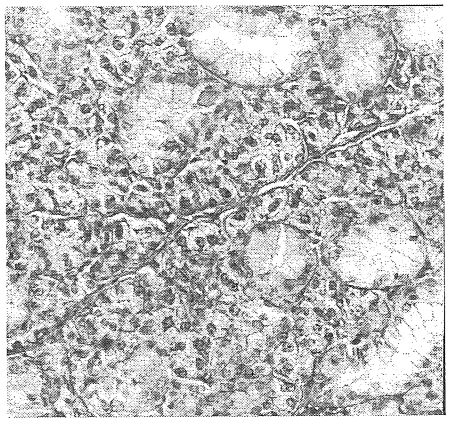

Fig. 4.

The serous acinar cells had central and round nucleuses and apical secretory granules. The mucous acinar cells had oval or flat basal nuclei. In the experimental group; the parenchyma of the submandibular gland showed mild degeneration (Figure 5). The acinar cells were effected in some areas as observed in the parotid gland. There were vacuolar degeneration and cell ruptures in the serous and mucous cells. The ductal cells were mostly normal.

Sublingual Gland:

In control group (Figure 6), the sublingual gland had normal formations

in the slides but the experimental group showed minimal degeneration in some areas (Figure 7). The other areas had the similar appearance to the control group.

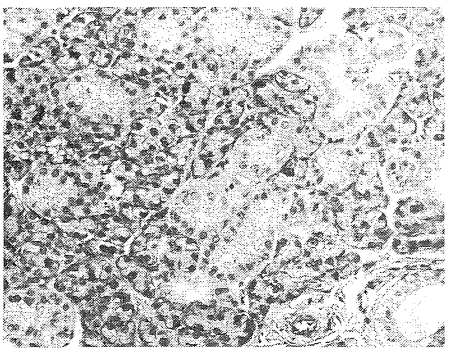

Fig. 5.

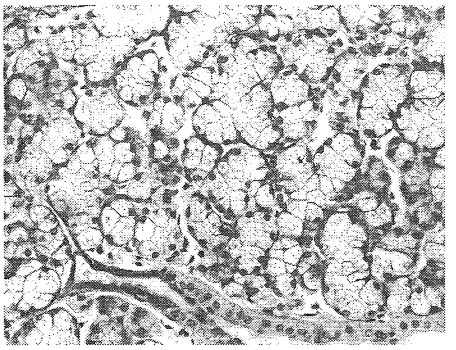

Fig. 6.

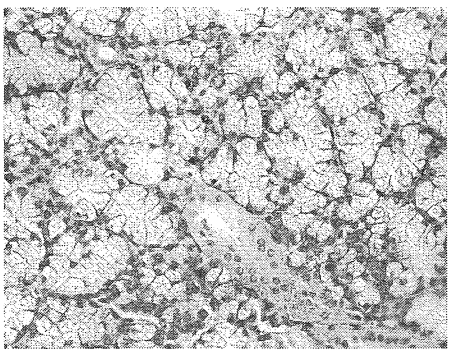

Fig. 7.

Discussion

There are various clinical and experimental studies about the effect of Lithium therapy on many organ systems (6). Most patients receiving Lithium experience some side effects. Some effects are relatively pronounced at the beginning of treatment but generally diminish or disappear rapidly or more gradually. The most frequently reported subjective side effects of Lithium are excessive thirst, polyuria, memory problems, tremor, weight gain, tiredness, diarrhea, skin problems, loss of libido and altered taste sensation. From the dentistry point of view, dry mouth, altered taste sensation and dental caries are observed in patients treated with lithium.

When the literature is reviewed, there were studies about the effect of Lithium on salivary composition but no study was found about the effect of Lithium on histopathology of salivary glands (4,5,7). Histopathologic changes on the salivary glands were investigated in our study.

Dehpour et all. (4) found that Lithium caused a significant decrease in protein, calcium, potasium and sodium concentrations of parotid saliva and also found a significant decrease in protein, potassium and calcium concentrations of submandibular saliva. The results of Dehpour's study suggest that lithium used in the treatment of affective disorders can influence the secretory mechanisms of both submandibular and parotid glands. Markitziu (7) evaluated the salivary gland functions in 14 manic-depressive patients treated with lithium carbonate and found hyposalivation in 71% of the patients.

In our study, the histopathological changes of the salivary glands supported hyposalivation. Prominent cell damage, vacuolar and hydrophic degenerations and ruptures were seen in acinar cells. These histopathological findings in the salivary glands cause hyposalivation and changes in salivary composition. Ben Aryeh (5) examined salivary and lacrimal secretion rates and salivary composition in 22 manic-depressive

patients on Lithium therapy. Ben Aryeh reported that significantly lowered tear secretions was detected in his patients, while their salivary secretion rates were normal. This finding shows that hyposalivation may not occur in some patients under Lithium therapy. However, changes in saliva composition was found also in his study. He also showed significant correlation between serum and salivary concentrations. His results indicate that Lithium is excreted in good amounts in saliva and causes changes in saliva composition. These findings when combined with our findings provide evidence that Lithium cause direct toxic effect on salivary glands.

The reduced protein content of saliva can be related to inhibitory effects of Lithium on cAMP and DAG signaling pathways that are the final modulators of protein excretion in saliva (4). Our study adds that other than neurohumoral and enzymatic pathways, direct toxic effect of Lithium on salivary glands is responsible from hyposalivation and changes in saliva composition.

The present study is important in the aspect that histopathologic effect of lithum on salivary glands has not been investigated by now. This study shows for the first time that hyposalivation in lithium treated patients is caused by direct toxic effect of the drug on salivary glands.This study should induce future studies in understanding the mechanism of hyposalivation in patients treated with lithium, because both histopathologic changes in the salivary glands and changes in quality and quantity of saliva play an important role in the well being of hard and soft tissue in the oral cavity.

References

1. Kingsbury, SJ., Garver, DL: Prog-Neuropsychopharmacol-Biol-Psychiatry. 22,2 (1988).
2. Kilts CD.: J.Clin Psychiatry. 59,6 (1988).
3. Das Gupta, K., Jefferson, J.W.: Gen. Hosp. Psychiatry. 12, 83 (1990)
4. Dehpour, AR., Abdollahi, M., Alghasi, H.: Gen Pharmacol. 26,4 (1995)
5. Ben Aryeh, H., Naon, H., Horovitz, G, Szargel R, Gutman D: Salivary and lacrimal secretions in patients on lithium therapy. J. Psychiatry Res 18, 3 (1984)
6. Doshi, BS., Rout, SJ., Kulkarni, RD.: Indian J Med Res. 78, 12 (1983)
7. Markitziu, A., Shani, J, Auni, J.: Oral Surg. Oral Med. Oral Pathol 66,5 (1988)

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