ORIGINAL ARTICLE

CONTENTS

Effects of (EGFR-Her1) with continuous illumination on the immunohistochemical and histomorphometric changes of sublingual glands in male mice

Noor Kadhiam Jawad[1], Umalbaneen Hilal Hadi[2], Zahra Ismail Abdel-Hussein[3], Haider Abdulrasool Jaafar[1]

[1]DEPARTMENT OF HUMAN ANATOMY, COLLEGE OF MEDICINE, AL-NAHRAIN UNIVERSITY, BAGHDAD, IRAQ

[2]UMALBANEEN HILAL HADI,NATIONAL CENTER OF HEMATOLOGY, MUSTANSIRIYAH UNIVERSITY, BAGHDAD, IRAQ

[3]DEPARTMENT OF APPLIED PATHOLOGICAL ANALYSIS, COLLEGE OF SCIENCE , AL-NAHRAIN UNIVERSITY, BAGHDAD, IRAQ

ABSTRACT

Aim: To evaluate the effects of constant light on the histological, histomorphometric and expression of EGFR of sublingual.

Materials and Methods: 20 male mice were applied and classified in to group A was kept in continuous light and control group B was kept in the normal daily variance for 45 days.

Results: Group A changes in behavior they become irritable, aggressive, loss of appetite, lethargic& lose weight. Histological examination with H&E showed degeneration of the sublingual tissue, loss architecture and necrosis (acini and ducts), the distraction of cell membrane and vacuolization, loss of nuclei in the necrotic tissue about 60%. Histomorphometric revealed significant differences in acini diameter between groups ($p \leq 0.001$). The mean of group A was 116.5960 ± 3.41668 compared with B group was 340.2720 ± 6.95821. Immunohistochemistry technique by used EGFR antibody in group A revealed expression evaluated as 0.8362 ± 0.00822 increase in values in comparison with group B 0.6988 ± 0.02489.

Conclusions: Light has an indirect oxidative stress effects that causes oxidative damage to glands, which affects mucin secretion. Therefore, there was a decrease in diameter of acini sublingual glands of light group than control group, however, there was increase in the expression EGFR of sublingual glands in light group compare with control group as compensatory mechanism for oxidative stress in glands by light.

KEY WORDS: salivary gland, circadian rhythms, EGFR

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INTRODUCTION

The smallest of the three salivary glands is a sublingual gland, which involves the sublingual, mandibular, and parotid glands. Salivary glands are fundamental organs that secrete and produce viscous saliva composed mainly of sulfated-glycoproteins and neuronal and epidermal growth factors, encouraging lubrication and protection of the oral mucous [1-3]. The sublingual glands receive their parasympathetic input from the chorda tympani nerve, which is a branch of the facial nerve, by the submandibular ganglion. The nerve functions in a secretomotor capacity [4]. Life on our planet is adapted to the 24-hour solar day. The prestable light/dark cycle has been internalized in the form of circadian rhythms. Circadian rhythms allow the concurrence of behavioral and biological processes with the external environment. Thus, the optimal timing of physiological events is harmonic by these internal timekeepers. Endogenous circadian rhythms have a time of ~24 hours and are reset daily to explicitly 24 hours via exposure to a dark-light cycle [5]. Despite that, the outline between night and day has been confused via the spread adoption of electric light at night. As a result, psychiatric consequences and behavioral health of circadian disruption by night light are becoming increasingly apparent [6, 7] furthermore, there is a relationship between mood disorders and the light/dark cycle. Mood disorders are often related to disrupted circadian clock-controlled responses, such as cortisol secretion and sleep, whereas disruption of circadian rhythms by jet lag or exposure to artificial light at night or night-shift work can precipitate or exacerbate affective signs in susceptible individuals. Evidence shows a strong link between mental health and circadian rhythms [8]. Often, all physiological processes show circadian rhythms, which are controlled via the circadian clock, permitting organisms to be familiar with the changes. In recent years, there has been increasing evidence that the circadian rhythm

system is involved in physiological processes in the maxillofacial region, as well as pathological processes, such as tooth and jaw development, oral carcinoma, salivary gland function, craniofacial malformations, and other diseases. Dialectically analyzes the importance of the circadian rhythm and circadian clock system to the activities of maxillofacial and oral tissues [9]. The epidermal growth factor receptor (EGFR; ErbB-1; HER1 in humans) is a protein transmembrane; it is a receptor for many proteins of the epidermal growth factor family (EGF family) ligands of extracellular protein. EGFR has been embroiled in the function of circadian and is expressed in the SCN suprachiasmatic nuclei. The response to EGFR activation is expected to count on circadian rhythms [10]. This research revealed the indirect effect of change in the light-dark cycle on sublingual glands. This is consistent with other research that have found effects of changing in the circadian rhythm on different organs, like the effect on the thyroid gland [11], ovary [12], and mammary gland [13].

AIM

The current study aims to evaluate the effects of constant light on the histological, histomorphometric and expression of EGFR of sublingual.

MATERIALS AND METHODS

Experimental Animals: twenty adult healthy male mice (albino mice) were obtained from College of pharmacy Al-Nahrain University at about 12-14 weeks of age and weighing 20-30 g, and were kept and fed under specified conditions. The animals were placed in a plastic cage, easy to clean with free access to water (fresh tap water) and food (standard pellet diet), and 10 animals for each cage. These were kept at room temperature (20±2 °C) in a clean and well-ventilated room. Collections of samples from the animals were divided into two groups and were kept in the special illuminating-conditioned room according to daily illumination times (dark/light cycle). There were 20 male mice applied in the study and were assigned to groups A and B in accordance to the periods in which the animals were kept. The Group A include 10 animals that were kept with full-time light in 24 hrs. Light for forty-five days; the Group B - control group, include 10 animals, which were kept with a normal dark/light cycle (10 hrs. darkness/14 hrs. light) for forty-five days. Animals were sacrificed and a midline inverted T-shaped incision was made on the ventral side from the chin to the thoracic region of the animal to expose the salivary glands and obtain samples using a dissecting microscope. After dissection of the salivary glands from the cervical region, samples were chemically fixed by immersion in 10% neutral buffered formalin, then 70% ethanol. Then further histological procedures were done to obtain a paraffin block of specimens for histological and immunohistochemical assessment. Then we prepare the paraffin section. Glandular specimens were prepared for paraffin sectioning as follows: initial fixation, dehydration, clearing, impregnation and embedding in tissue blocks, sectioning on glass slides, then dewaxing, hydration, staining and finally embedding according to Kim SS et al [14]. Staining was used for histological examination for tissue preparation with Harris hematoxylin (Fisher) and eosin yellow (Fluke) (ready to use).

IMMUNOHISTOCHEMICAL STAINING

Dako company supplied the EGFR protein, the immunohistochemical staining of the EGFR-H11 antibody (Epidermal growth factor receptors) was used is Code M3563. Mouse monoclonal anti-epidermal Growth Factor Receptor (anti-EGFR) for use in laboratories for qualitative identification by light microscopy as epidermal growth factor receptor-positive in both experimental and normal tissues using immunohistochemical (IHC) test method. Epidermal growth factor receptor, EGFR is a 170 kD transmembrane glycoprotein bind thin activated by various ligands such as EGF, TGFα and some virally encoded growth factors. The histological tissue slides prepared from the tissue samples, stained with hematoxylin and eosin stain and IHC for EGFR-H11 were subjected to histological evaluation and estimation under the light microscope. Image J software was used for histomorphometric to measure the diameter of acini (a Java-based image processing program developed at the National Institutes of Health, USA).

STATISTICAL ANALYSIS OF DATA

For statistical analysis of the data we used the Statistical Package for Social Sciences (SPSS). software, version 23. The data are expressed as mean and standard error of the mean (SEM). The variance between the mean percentages of EGFR expression in sublingual glands was examined for statistical significance using an independent T-test to show the difference in the mean positively ± standard error between groups according to circadian rhythms [15].

IMMUNOHISTOCHEMICAL ASSESSMENT

The Aperio image inspection software with 12 scoring algorithms was used to measure the amount of a par-

Table 1. Diameter of the acini of the sublingual salivary glands

Group	Diameter	P-value
Control	340.2720 ± 6.95821	0.001
Light	116.5960± 3.41668	

ticular color in tissue sections, which depend on color quantification parameters in three intensity ranges (strong positive (brown), positive (orange), and weak positive (yellow) and negative (blue).

RESULTS

This study shows many morphometric and histological changes in sublingual salivary glands in the experimental animal when exposure male mice (albino mice) to the light period for 45 days were internalized in the form of circadian rhythms; these differences varied compared with the control group.

EXTERNAL FEATURES OF THE ANIMALS

During the present study, several changes in the animals' behavior were observed: they became irritable, quarrelsome and aggressive, lost their appetite, became lethargic, apathetic, became fearful, lost weight, lost hair, and became weaker compared to the control groups.

HISTOLOGICAL CHANGES OF GLANDS

The statistical analysis results showed that there were significant differences between groups exposed to the light and control groups ($p \leq 0.001$). The mean diameter of the acini of the sublingual salivary glands of animals exposed to light after 45 days was 116.5960±3.41668 compared to the control group, which was 340.2720±6.95821 (Table 1, Fig.1).

In the animals in the light group (Group A), the histological features appearance of necrosis and degeneration of the salivary gland tissue loss architecture and small acini (116.5960± 3.41668), distraction of cell membrane and vacuolization, loss of nuclei in the necrotic tissue compromised about 60%, degenerative acini show vacuolization of cell with enlarged hyperchromatic nuclei, ducts necrotic (Table 1, Fig.2).

In the present study, the results obtained by using H&E stains showed the histological appearance that the normal section of sublingual salivary glands of the control group (Group B) of albino mice showed the mucous glands with tubular an arrangement of poorly stained mucous cells with small interlobular duct are seen in connective tissue and normal size of acini (Table 1, Fig.2).

EFFECTS OF CIRCADIAN RHYTHMS ON THE MARKER EXPRESSION OF THE EGFR OF SALIVARY GLANDS

The samples were prepared for two groups to perform immunohistochemical method using epidermal growth factor receptor antibody in the mild group; they showed a pronounced expression, which was estimated as an increase in the acinar cell values in the salivary glands by 0.8362±0.00822 compared with the control group, was recorded as 0.6988±0.02489 (Table 2, Fig.3, Fig.4).

DISCUSSION

In this study the effect of options of illumination on animal behavior we revealed that as a result of exposing experimental animals to continuous lighting for 45 days, many changes occurred in the animals, including behavioral changes, as it was observed that the animals suffer from symptoms of stress and anxiety represented by loss of appetite, lack of movement and laziness. This agrees with the author's finding that excessive exposure to light wreaks havoc on circadian rhythms in different ways. It decreases the production of melatonin, the hormone that promotes sleep., another agent regulated by circadian rhythms, disrupting not just sleep but other biological operations, as well as finding a clear correlation between nighttime light, including shift work, and psychiatric disorders such as depression, insomnia, and anxiety that were most influenced by minim influential factors in light exposure. Excessive exposure to night light in particular contributed to a 20% increase in mental health symptoms [16-19]. Moreover, those who work shifts at night expose their bodies to constant light, they are forced to become depressed more often compared to those who sleep at night; this brings back the attention of teenagers who spend most of their time at night on their gadgets, such as computer, smartphone, etc., which has been shown to interfere with the synthesis of melatonin, which affects their sleep patterns, sleep and mood, especially anxiety. [20]. Furthermore, researches revealed that through several retina-brain pathways light influences our mood. They proved that mice subjected to acute bright light exposure exhibited anxiety-related phenotype in chronic condition. Since mice are active during the night, confrontation with light activity of some threat, for example, fire and the loss of a shelter [21, 22]. We have revealed that exposure of a group of exper-

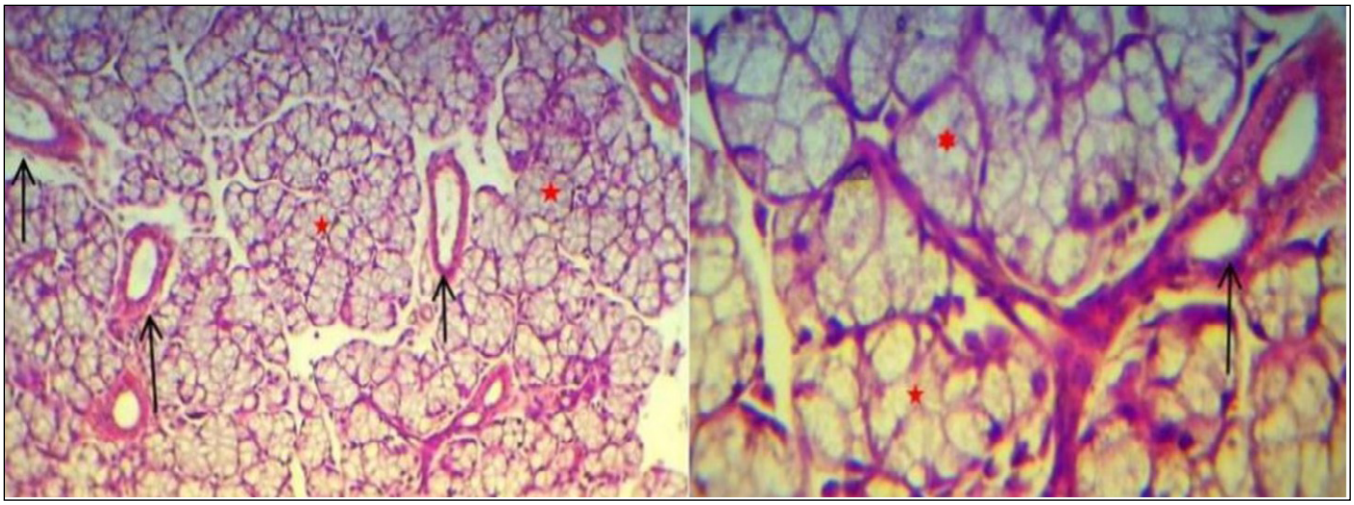

Fig. 1. Cross-section of the sublingual salivary glands in the control groups showed the presence of predominantly mucous glands with interlobular ducts (arrows) with normal sizes and shapes of acini. (Asterisk) (H&E) X10, X40.

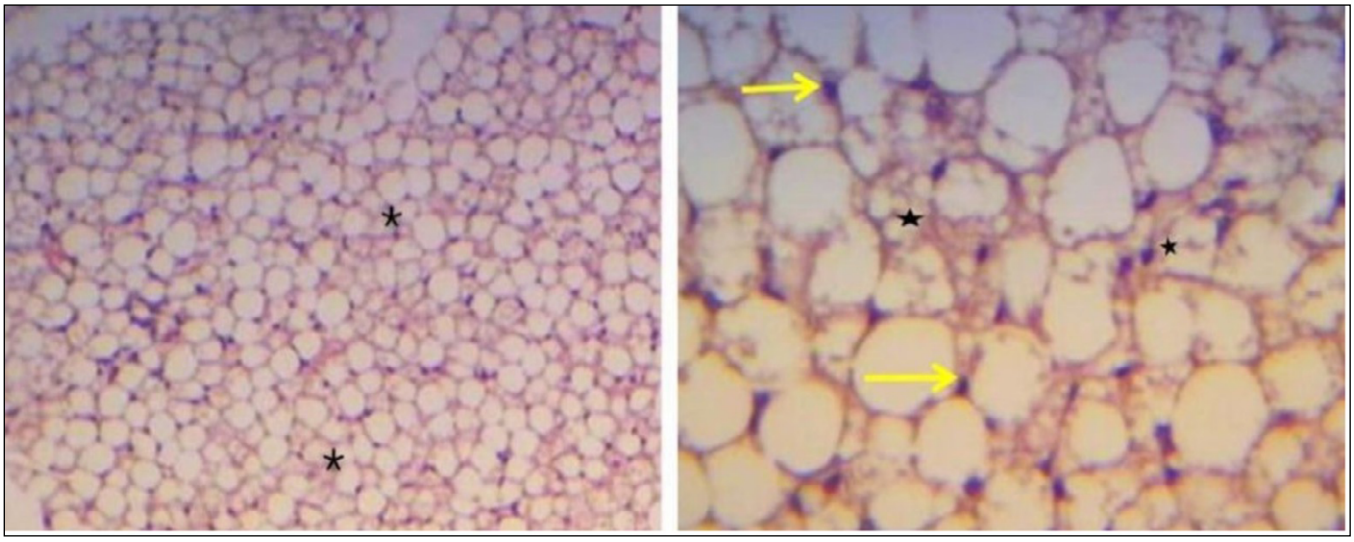

Fig. 2. Cross-section of sublingual salivary glands in light groups showed loss of architecture, necrotic ducts, necrosis of acini (asterisk), enlarged hyperchromatic nuclei (arrows) (H&E) X10, X40.

imental animals to continuous lighting led to behavioral changes in the animals, including anxiety and stress. Thus, lighting directly affects the nervous ssystem, and it is consistent with studies, which appears that exposure to night light can disrupt circadian clock mechanisms in the peripheral and CNS tissues [23]. The primary role of the salivary glands are to liberate saliva, which is essential for coated tongue, immunity, and oral digestion, as well homeostasis in the body. Sympathetic and parasympathetic division of the autonomic nervous therefore controls salivary secretion [24, 25]; moreover, the light in humans activates the sympathetic nervous system, as explained by a transient increase in sympathetic nerve activity [26]. The role of illumination on histological changes of sublingual glands: as a result of continuous illumination for 45 days in routine stain (H&E), histological examination with the usual dye showed that there was necrosis and degeneration of the sublingual gland tissue, loss of architecture and acini, distraction of cell membrane and vacuolization, loss of nuclei in the necrotic tissue compromised about 60% t as shown in Figure 2, and the size of the acini decreased to 116.5960±3.41668 compared to the control group 340.2720 ± 6.95821, as shown in Table 1. Since the necrosis in our cells occurs as a result of a lack of access to blood to the tissue, this is in accord with the generally held opinion that the nerve fibers supplying the salivary gland secretory elements are parasympathetic (cholinergic). At the same time sympathetic action stimulates secretion of a large amount of saliva in the mouth. However, stimulation of the sympathetic nervous system results in either little or no protein-rich blood flow [26, 27]. Furthermore, salivary production is controlled by sympathetic permanently oversees the production of saliva of through the superior cervical ganglion. These changes lead to; (a) decrease in saliva secretion by the acinar cells; (b) increase in protein

Table 2. Expression of EGFR in the sublingual salivary glands

Group	Mean ±Std Error	P-value
Control	0.6988 ± 0.02489	0.001
Light	0.8362±0.00822	

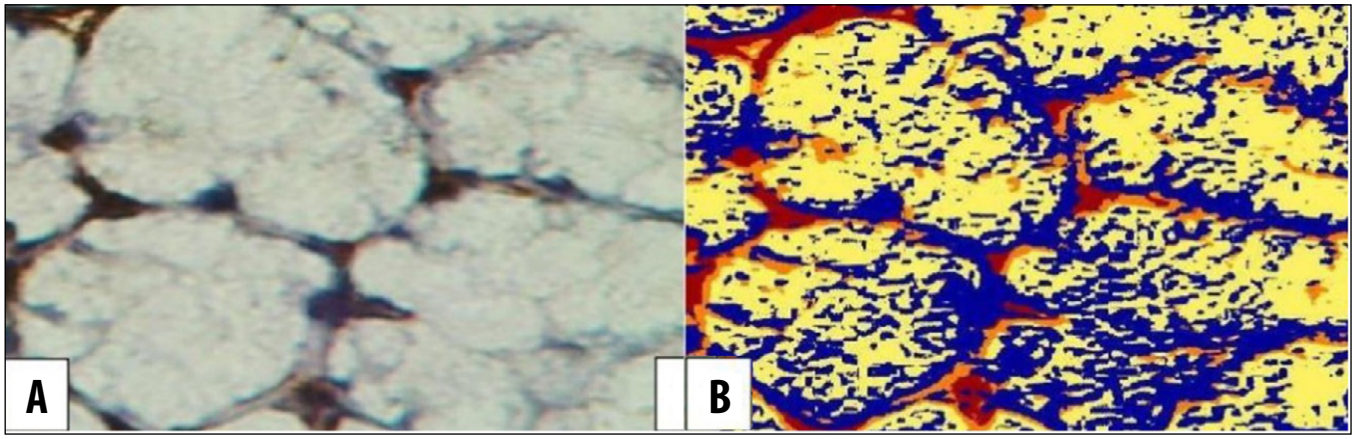

Fig. 3. A - EGFR expression in the sublingual salivary gland of the control group, B - EGFR expression in the sublingual salivary gland of the control group in analytical representation.

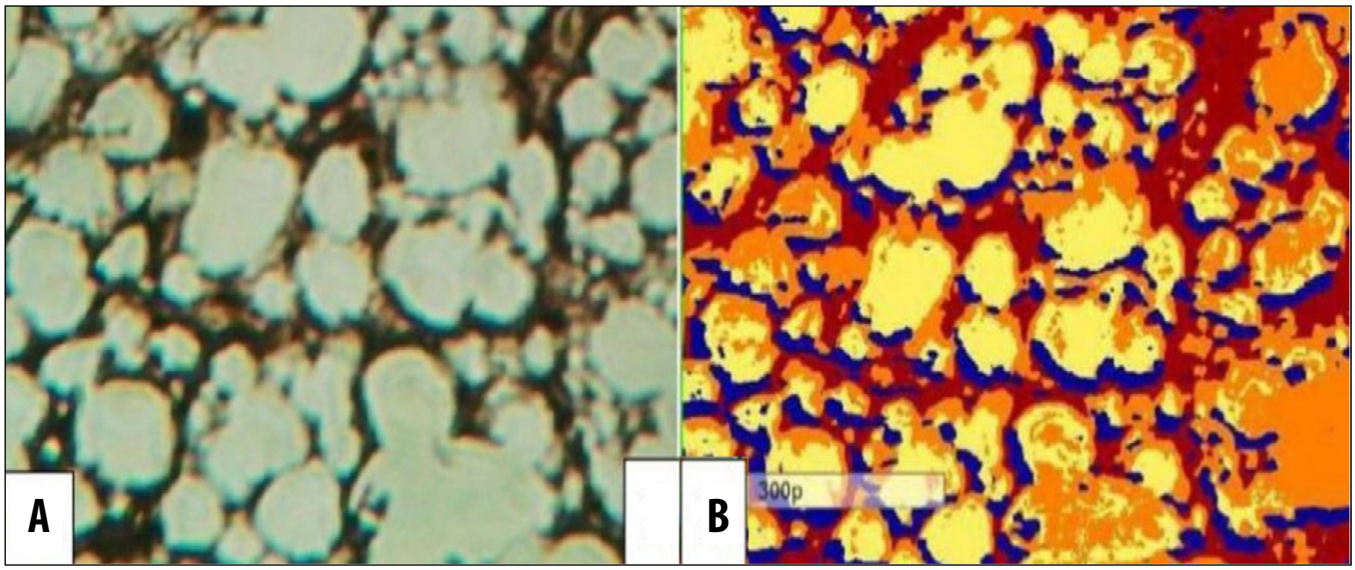

Fig. 4. A- EGFR expression of the sublingual salivary gland of the light group, B- EGFR expression of the sublingual salivary gland of the light group in analytical representation.

secretion; and (c) decrease in blood flow to the glands [28]. Moreover, sympathetic flow outcomes cause the release of acetylcholine to M3 muscarinic receptors. This leads to (a) stimulated acinar cells secretion of saliva; (b) HCO3 secretion rise by duct cells; (c) an increased blood flow to the submandibular gland via co-transmitters; and (d) an increased rate of saliva evacuation as a result of myoepithelium contraction [29-31]. Oxidative stress effect of circadian rhythm on EGFR expression of sublingual salivary gland present in this study reveals an increase in the expression of EGFR in light group (0.8362±.00822) mice than in control groups (0.6988±.02489) (Table 2, Fig.3&4). So that the present study concluded that stress effects of light on stimulation of the supraoptic nucleus in the hypothalamus will activate its sympathetic nucleus which affects the blood supply of the salivary glands consequently leading to hypoxic oxidative stress, therefore it will interfere with mucin protein production in the salivary gland acini and its excretion via their ducts, this agrees with researchers found the light plays an important role in oxidative stress. As a grant to study mechanisms of stress related to cellular signaling passage, light permits temporal and spatial control of ROS output in the heterogeneous environment of living cells [32]. In this study, it has been spotted that the antioxidant and oxidant systems of the salivary gland were affected by

any foreign oral application. These showed that the salivary glands were affected by alteration in the mouth so quickly and gave them suitable biochemical and physiological responses [33]. Moreover, other researchers have used the same pointing out that the epidermal growth factor (EGF) detected in the salivary glands promotes tissue damage, gastric wounds and healing there by increasing saliva EGF synthesis [34, 35]. In addition, the researchers reported that changes were recorded in the presence of the EGF receptor and oxidative events in the submandibular salivary glands, which localize the source of EGF [36, 37]. In another research, Garcia-Ojalvo et al., found the EGF effective in antioxidant markers and oxidative stress and synthesis of a significant oxidative. Also, they showed that locally penetrated EGF had a systemic influence on the recuperation of a pro-physiological redox balance and was effective in the level of stress [38]. Discovered that the use of diagnostic salivary biomarkers of oxidized condition in saliva gland of children is due to elevated oxidative degradations of saliva proteins and lipids linked with chronic kidney disease that affect the enzymes of antioxidant and non-antioxidant systems. They also found out that the salivary parameters of redox homeostasis can be potential diagnostic biomarker of the patients suffering from chronic kidney disease in children. Which is responsible for alterations in salivary antioxidant systems and for oxidative changes in salivary proteins secretion [39, 40].

CONCLUSIONS

Light has strenuous effects on various body organs, like salivary glands. These animals of the light group reveal irritability, quarreling aggressive behavior, loss of appetite, and lethargy. The acini in the sublingual salivary glands of the animal's light group reveal a marked decrease in the mean diameter and low mucin protein excretion than that of the control groups. There was an increase in the expression of EGFR of acini cells in the salivary glands of the light group mice than the control group, probably due to a compensatory mechanism to the oxidative stress in salivary glands.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR
Noor Kadhiam Jawad
AL-Nahrain University
Al Jadriyah Bridge, Baghdad, Iraq
e-mail: noor.kadhiam@nahrainuniv.edu.iq

ORCID AND CONTRIBUTIONSHIP
Noor Kadhiam Jawad: 0009-0009-2518-0339 A F
Umalbaneen Hilal Hadi: 0009-0002-5517-6268 B C
Zahra Ismail Abdel-Hussein: 0009-0009-4225-3608 C D
Haider Abdulrasool Jaafar: 0000-0003-1571-4316 D E

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

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