The Effect of EGF on VEGF Expression on Submandibular Salivary Gland of Albino Rats Receiving Doxorubicin

Original Article

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ABSTRACT

Background: Vascular endothelial growth factor (VEGF) has two prominent biological effects of inducing mitogenesis and migration of vascular endothelial cells and to produce permeability on the microvasculature. Epidermal growth factor (EGF), known by its mitogenic activity on different types of cells, could induce the proliferation and differentiation of the epithelial cells and stimulate its regeneration. Doxorubicin (DXR) is a widely used anticancer drug and is one of most commonly used chemotherapeutic drugs, however it may cause some serious complications such as toxicity in various tissues in the body.
Aims: The present study aims to investigate the effect of EGF on the VEGF immunoexpression in submandibular salivary gland tissue of rats receiving Doxorubicin (DXR).
Methods and Material: 30 male Albino rats, two months old and weighing 200-250 gm body weight, were divided equally into three groups as follows: Group I (control group). Group II: rats received 20 mg/kg body weight DXR as a single intra peritoneal injection. Whereas, group III: rats received the same dose of DXR and on the next day they were injected intraperitoneally with EGF in a daily dose of 10µg/kg body weight for 7 consecutive days.
Submandibular salivary glands were dissected out and processed for histological investigation and immunohistochemical localization of VEGF in the glandular tissue.
Statistical analysis used: ANOVA was used to compare the mean area percentage of VEGF immunostaining among the specimens of different groups followed by Tukey's Multiple Comparison Test.
Results: VEGF expression in submandibular salivary glands of rats significantly decreased after DXR injection. However, daily intraperitoneal injections of EGF restored normal levels of VEGF expression in the glandular tissue.
Conclusions: EGF preserved glandular architecture after DXR injection and consequently the immunohistochemical expression of VEGF in the glands to approximately the normal level.

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Key Words: EGF, DXR, salivary glands, VEGF.

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INTRODUCTION

Growth factors are protein molecules synthesized by the body that regulate many aspects of cellular functions. Vascular endothelial growth factor (VEGF) are a family of secreted growth factors and are considered to be a powerful angiogenic factor that acts specifically on vascular endothelial cells. Two important biological properties of VEGF are its ability to induce mitogenesis and migration of vascular endothelial cells and to produce permeability on the microvasculature more potently than histamine and its expression and production were found influenced by numerous and diverse factors[1-4].

Growth factors have a vital role during wound healing by contributing to different patterns of cell activation and of the prominent growth factors is the Epidermal growth factor (EGF). EGF is known by its mitogenic activity on different types of cells like epidermal cells, fibroblasts, muscle cells and mammary epithelial cells. It is synthesized in several organs as the salivary glands, kidneys, lactating mammary glands, small intestine, liver and pancreas[5-7].

The interaction of the EGF with its receptor on the fibroblasts and epidermal cells results in the stimulation of cell proliferation across wounds. This biological activity has encouraged the development of recombinant growth factors which enhanced the healing capacity of acute and chronic wound healing[8-10].

Doxorubicin (DXR) is a widely used anticancer drug and is one of most commonly used chemotherapeutic drugs. However, it shows some serious adverse effects such as the significant toxicity that can occur not only during, but also years after treatment[11,12].

Jensen, *et al*., 2003[13] studied the effect of chemotherapy on the salivary gland of patients with different types of cancers. Apart from xerostomia, the salivary glands of almost

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half of the patients showed many pathological changes such as degeneration of the cells of the acini and ducts as well as inflammatory cells infiltration. Also, degenerated salivary glands were markedly detected less than 2 weeks after chemotherapy.

The protective role of EGF against the destructive effect of anticancer drug Doxorubicin on the salivary gland tissues has not been investigated before and the thus the present study was designed to investigate the effect of EGF injection on the VEGF immunoexpression in submandibular S.G. of rats receiving DXR.

SUBJECTS AND METHODS

This study was approved by the Ethics committee, Faculty of Dentistry, Cairo University. Thirty male adult albino rats, two months old, pathogen free of average weight 200 gm were used. The animals were housed in controlled environment (temperature 25o ± 2 0C, humidity 70 -80 % and 12hr dark/light cycle). The rats were equally divided into three groups. These groups were categorized as follows:

Control Group

The rats were kept on the normal control diet and subjected to intraperitoneal injection of 9% saline and did not receive DXR or EGF.

Doxorubicin Group (DXR gp)

The rats received 20 mg/kg body weight Doxorubicin (DXR) as a single intra-peritoneal injection[14].

Epidermal growth factor Group (DXR + EGF)

The rats received the same intraperitoneal dose of DXR (20 mg/kg body weight) and on the next day they were injected intra-peritoneally by 10µg/kg body weight of EGF provided by Sigma-Aldrich, Inc. for 7 consecutive days[5].

At the end of the experimental procedures , animals were sacrificed by euthanization and their submandibular salivary glands were dissected out. The glands were then processed for histological examination by hematoxylin and eosin (H&E) staining and immunohistochemical localization of VEGF using staining reaction incubated by anti-VEGF.

Measurement of area percentage of positive cells was done in the form of an area and area percent inside a standard measuring frame of an area 114342.9 mm2 per 10 fields from different slides using a magnification of 400X by the light microscope transferred to the monitor. Areas containing the most uniformly stained tissues were chosen for evaluation. These areas were masked by red color and analyzed using Image J (1.46 a, NIH, USA) computer system (Figure 1). Values were presented as mean and standard deviation values and statistically analyzed.

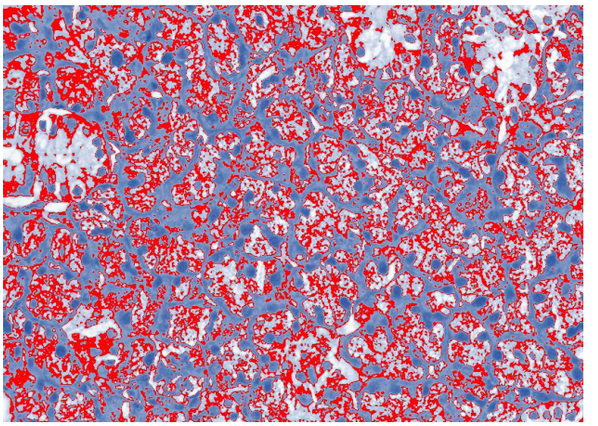

Fig. 1: Showing an example of calculation of VEGF area percentage expression

Image analysis data representing experimental values of VEGF immunostain were given as mean and standard deviation. ANOVA (ONEWAY ANOVA test, n=10, $P < 0.05$) was used to compare the mean area percentage of VEGF immunostaining among the specimens of different groups. This has been followed by Tukey's Multiple Comparison Test (Post Hoc Tukey HSD), using SPSS 25.0 for Windows (SPSS Inc., Chicago, IL, USA) to perform a pair-wise comparison between each group versus the other[15].

RESULTS

Histological examination of submandibular salivary gland of rat of control group revealed its main structural components composed of parenchymal tissue supported by connective tissue stroma containing the blood vessels and nerves. The secretory acini were numerous, rounded in shape, small in size and exhibited narrow lumen. They appeared lined by pyramidal cells having deep basophilic cytoplasm. Their nuclei were rounded. The striated ducts were clearly recognized and appeared lined with a single layer of columnar cells having centrally placed vesicular nuclei and intense eosinophilic cytoplasm. The granular convoluted tubules appeared folded and lined by columnar cells having basally situated nuclei. They were packed apically with acidophilic granules (Figure 2A).

Glandular histological sections of rats treated with DXR showed several pathological changes. The secretory acini appeared with massive cytoplasmic vacuolization. Deformation in the acini and loss of normal cellular orientation were frequently encountered. Moreover, some acini displayed complete degeneration of their secretory cells. Increase inflammatory response in the form of increased inflammatory cells was evident. A clear space separated the parenchymal elements which might be an index of interstitial edema and extravasated RBCs in between acini and ducts (Figure 2B).

As compared to the histological findings of DXR group, the glandular tissues of rats of the DXR+EGF group showed great improvement in the architectural features of the glands. No evidence of an increased inflammatory condition was noticed. On the other hand, multiple blood vessels engorged with RBCs were detected in association with the striated ducts. Moreover, a rich vascular network was found in close vicinity to the excretory ducts and circumscribed them (Figure 2C).

The submandibular salivary glands of rats of the control group showed +ve cytoplasmic immunoreactivity to VEGF in the secretory acini, duct system and blood vessels (Figures 3A,4A). On the other hand, the immunohistochemical findings of DXR group corroborated with the histological results where VEGF protein expression in the DXR group was evidently different from that of the control group.

The VEGF immunoreactivity in the submandibular salivary glands of rats of DXR group obviously decreased in the parenchymal elements of the glands and -ve immunoexpression of VEGF in the blood vessels (Figures 3B,4B). A statistically significant decrease in the mean area percent of VEGF expression was recorded when comparing control and DXR groups with p=0.003 (Table 1).

The glandular sections of rats of (DXR+EGF) group revealed a surge in the anti-VEGF antibody expression in the parenchymal tissue of the glands to an extent similar or slightly exceeding that of the control group (Figure 3C). Moreover, the blood vessels showed positive reaction to VEGF that was negative in the previous group of DXR (Figure 4C).

On the other hand, Post Hoc Tukey HSD test, comparing each two group revealed no significant difference between the control group and (DXR+EGF) group (p=0.253). However, a significant decrease was recorded between the control and DXR gp (p=0.008) and a significant increase was recorded between DXR and (DXR+EGF) group (p=0.0001) (Table 2, Chart 1).

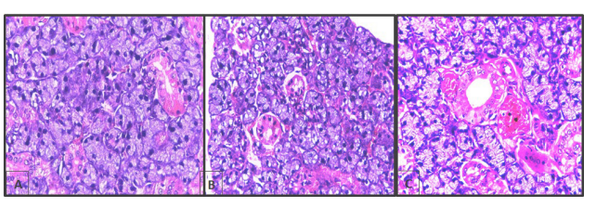

Fig. 2: A. Photomicrograph of submandibular salivary gland of rat of control group showing regular gland architecture (H&E, orig. mag. X400).

B. Photomicrograph of submandibular salivary gland of rat of DXR group showing degenerated acini with multiple vacuoles extravasated RBCs in between acini and ducts (H&E orig. mag. X400).

C. Photomicrograph of submandibular salivary gland of rat of DXR+EGF group showing well aligned acini together with blood vessels engorged with RBCs in association with the striated ducts exhibiting good cell alignment and minute areas of small vesicles (H&E orig. mag. X400).

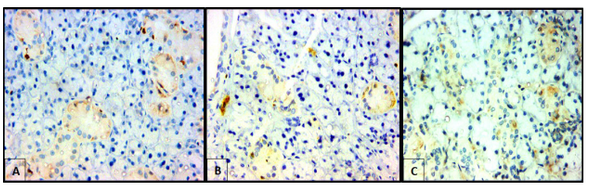

Fig. 3: A. Photomicrograph of submandibular salivary gland of rat of control group showing +ve VEGF expression in the striated ducts, granular convoluted segments and few nuclei of the secretory acini (DAB, orig. mag. X400).

B. Photomicrograph of submandibular salivary gland of rat of DXR group showing a noticeable decrease in VEGF immuno-expression in the glandular tissue (DAB, orig. mag. X400).

C. Photomicrograph of submandibular salivary gland of rat of DXR+EGF group showing a generalized increase in the expression of VEGF in the parenchymal tissue of the glands (DAB, orig. mag. X400).

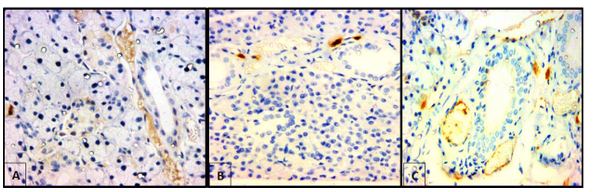

Fig. 4: A. Photomicrograph of submandibular salivary gland of rat of control group showing +ve VEGF immunoreactivity in the blood vessels (DAB, orig. mag. X400).

B. Photomicrograph of submandibular salivary gland of rat of DXR group showing -ve immunoexpression of VEGF in the blood vessels (DAB, orig. mag. X400).

C. Photomicrograph of submandibular salivary gland of rat of DXR+EGF group showing positive immuno-expression of VEGF in the blood vessels (DAB, orig. mag. X400).

Table 1: Area Percentage of VEGF immuno-expression in different groups

Groups	Control	DXR	DXR + EGF	*P- value*
Minimum	3.80	2.88	5.49	0.003
Median	6.12	3.33	7.68	
Maximum	7.73	4.02	8.73	
Mean	6.05	3.40	7.40	
Standard Deviation	1.49	0.42	1.25	
Standard Error	0.67	0.19	0.56	

Table 2: Tukey's Post Hoc Test for VEGF immuno-expression in different groups

Tukey's Multiple comparison	*P-value*
Control vs DXR	0.008*
Control vs DXR+EGF	0.253
DXR vs DXR+EGF	0.0001*

* Significant at p<0.05

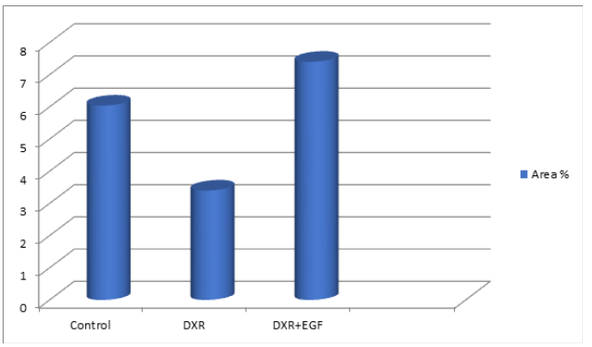

Chart 1: Bar chart showing the area percent of VEGF immune-expression in submandibular gland of all groups

DISCUSSION

Doxorubicin (DXR) is a highly effective chemotherapeutic agent, interfering with the growth of cancer cells by blocking topoisomerase-2 enzyme needed for division of these cells. The DXR chemical structure cause the formation of free radicals intracellularly which in turn induces the generation of oxidative stress. These formed oxidative stress is directly correlated to cellular destruction[16]. Moreover, DXR also causes an imbalance between free oxygen radicals and antioxidants. The main function of the antioxidants is to combat the free oxygen radicals to prevent cellular injury, so any decrease in the antioxidants or increase in the amount of free radicals will shift the body from a state of health to a state of pathology. This disturbed oxidant–antioxidant system results in tissue damage that is evident with lipid peroxidation and protein oxidation in tissue[17].

The results of the present study indicated that the systemic injection of DXR in rats resulted in pathological structural alterations within the submandibular S.G. tissue. Atrophied and degenerated acini with multiple cytoplasmic vacuolization were detected.

The frequently observed intracytoplasmic vacuolizations in both the acinar and ductal cells might be caused mainly by mitochondria. This is explained by the fact that sodium ions enters the cells profusely due to failure of cellular metabolism. This profusion causes an osmotic effect which induces breakdown of the macromolecules found in the injured cell and subsequently presence of the vacuoles. Moreover, the intracytoplasmic vacuolations had also been explained by deterioration of other cell organelles specially the Golgi apparatus, that if acquiring fatty nature they appeared as vacuoles[18].

The submandibular S.G. of rats treated with DXR and EGF showed great improvement in the gland architecture. Resolution of vacuolar degeneration was noted apart from minute areas of microvesicles found in the parenchymal tissue. Cells of both the acini and ducts appeared to be histologically similar to those of the control group.

The anti-inflammatory response of EGF was evident in the current work and confirmed previously conducted studies. Berlanga, *et al*., 2002[19] recorded a protective effect of EGF on intestine from ischemia/reperfusion injury. They noticed the marked decrease of inflammatory infiltrates (mainly neutrophils) in the intestine of the EGF treated animals. They also registered decreased level of TNF-α (a major pro-inflammatory cytokine) which may contribute to the cytoprotective effect.

The healing potential of EGF was documented in several studies. It was prevalent in epithelial cell proliferation, migration, re-epithelialization and regeneration of gastric glands during renal epithelium regeneration[20], gastric ulcer healing[21] and corneal epithelium[22].

Administration of exogenous EGF in a neonatal rat necrotizing enterocolitis (NEC) model reduced the expression of pro-inflammatory mediators and at the same time upregulated production of anti-inflammatory cytokine in the ileum[23]. Moreover, EGF was found to be of clinical importance in the prevention as well as treatment of NEC. It helped to increase healing after inflammation, to decrease bacterial translocation and restore function[24].

The results of the current study can be explained by the EGF binding to its receptor EGFR which subsequently leads to activation of pathways that are involved in regulating cellular activities such as proliferation and differentiation. This also explains the role of EGF in facilitating epidermal cell regeneration and in the process of dermal wound healing through stimulating the proliferation and migration of keratinocytes[25].

The VEGF immunoreactivity in the glandular tissues of rats of DXR group obviously decreased in the parenchymal elements of the glands. These results were statistically confirmed where a significant reduction in the mean area percent of VEGF expression was found when comparing control and DXR groups with $p<0.01$.The decrease of this angiogenic factor in the submandibular salivary glands of DXR group was found consistent with the histopathological finding of the generalized decrease of vasculature in the glandular tissue. Duyndam, *et al*., 2007[26] concluded that DXR can repress VEGF expression by inhibiting hypoxia inducible factor 1 (HIF-1) through different mechanisms.

Merighi, *et al*., 2009[27] explained such mechanisms by indicating that treatment with DNA damaging drug like DXR resulted in increase in the proangiogenic cytokine interleukin-8 (IL-8) and downregulation in the production of hypoxia inducible factor 1α (HIF-1α) which sequentially decrease the expression of VEGF. Furthermore, they registered that DXR could affect the adenosynergic signaling through blockage of different receptors such as A3 receptors which could be the cause of more decrease of VEGF expression. Moreover, Kawagishi, *et al*., 2001[28] approved that DXR significantly decreased the VEGF expression into human melanoma cells after 24 hour of injection and they insisted about future treatment schedules including agents that target the HIF-1α signaling pathway.

The immunoexpression of VEGF in the DXR and EGF group was nearly at the same level as in the control group

and a statistically non-significant difference was found comparing both groups. Thus furtherly indicating the role of EGF in counteracting the oxidative stresses caused by DXR in the submandibular salivary glands.

Similar results were found in other studies which showed that EGF restored normal levels of cytokeratin expression in the submandibular glands of diabetic rats[29] as well as myosin levels in submandibular glands of rats receiving Botulinum toxin[30]. Cytokeratin and myosin levels are indications of the healing capacity of the epithelial cells to proliferate and regenerate. Both proteins showed an immunohistochemical expression similar to their controls after EGF injection. These studies showed that EGF has the ability to counteract the deleterious effect of the production of oxidative stresses caused by diabetes and Botulinum toxin. The previous studies comes in agreement with the results of the current study.

Moreover, Yamawaki, *et al*., 2010[31] stated that the addition of EGF and nerve growth factor to culture media containing epithelial rests of Malassez collected from porcine periodontal ligament increased the expression of VEGF. Also, EGF and transforming growth factor-β (TGFβ) have been shown to induce VEGF expression in cell culture models[32].

We concluded that EGF has a cytoprotective and reparative effect against DXR induced changes on the S.G. tissue. DXR injection significantly decreased to VEGF immunoexpression in the glandular tissue. However, exogenous EGF preserved the immunohistochemical expression of VEGF in the glands or restored it to approximately the normal level.

KEY MESSAGES

Systemic injection of DXR in rats resulted in pathological structural alterations within the submandibular S.G. tissue. Submandibular salivary gland of rats treated with DXR and followed by EGF showed great improvement in the gland architecture. Resolution of vacuolar degeneration was noted apart from minute areas of microvesicles detected in the parenchymal tissue.

CONFLICT OF INTERESTS

There are no conflicts of Interest.

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الملخص العربى

تأثير عامل نمو البشرة على تعبير عامل النمو البطاني الوعائي على الغدة اللعابية تحت الفك السفلي للجرذان البيضاء التي تتلقى الدوكسوروبيسين

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المقدمه: عامل النمو البطاني الوعائي له تأثيران بيولوجيان بارزان للحث على الانقسام وهجرة الخلايا البطانية الوعائية وإنتاج نفاذية على الأوعية الدموية الدقيقة. يمكن لعامل نمو البشرة ، المعروف بنشاطه الانقسامي على أنواع مختلفة من الخلايا ، أن يحفز تكاثر الخلايا الظهارية وتمايزها ويحفز تجديدها .دوكسوروبيسين هو دواء مضاد للسرطان يستخدم على نطاق واسع وهو أحد أكثر أدوية العلاج الكيميائي شيوعًا ، إلا أنه قد يسبب بعض المضاعفات الخطيرة مثل التسمم في أنسجة مختلفة في الجسم.

الهدف من الدراسة: تهدف الدراسة الحالية إلى التحقق من تأثير عامل نمو البشرة على التعبير المناعي لعامل النمو البطاني الوعائي في أنسجة الغدد اللعابية تحت الفك السفلي للفئران التي تتلقى دوكسوروبيسين .

طرق و مواد البحث: ٣٠ ذكور جرذ ألبينو عمر شهرين ووزن ٢٠٠-٢٥٠ جم قسمت بالتساوي إلى ثلاث مجموعات على النحو التالي: المجموعة الأولى (المجموعة الضابطة). المجموعة الثانية: تلقت الفئران ٢٠ مجم / كجم من وزن الجسم دوكسوروبيسين كحقنة واحدة داخل الصفاق. في حين أن المجموعة الثالثة: تلقت الجرذان نفس الجرعة من دوكسوروبيسين وفي اليوم التالي تم حقنها داخل الصفاق مع عامل نمو البشرة بجرعة يومية ١٠ ميكروجرام / كجم من وزن الجسم لمدة ٧ أيام متتالية.

في نهاية التجربة تم التضحية بالفئران واستخراج الغدة اللعابية تحت الفكية لفحصها مجهرياً و للفحص المناعي.

النتائج: انخفض تعبير عامل النمو البطاني الوعائي في الغدد اللعابية تحت الفك السفلي بشكل ملحوظ بعد حقن دوكسوروبيسين. ومع ذلك ، فإن الحقن اليومية داخل الصفاق من عامل نمو البشرة أعادت المستويات الطبيعية لتعبير عامل النمو البطاني الوعائي في الأنسجة الغدية.

الاستنتاجات: حافظ عامل نمو البشرة على البنية الغدية بعد حقن دوكسوروبيسين وبالتالي التعبير الكيميائي المناعي لـ عامل النمو البطاني الوعائي في الغدد إلى المستوى الطبيعي تقريبًا.