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BİLİMSEL TARAMALAR / SCIENTIFIC REVIEWS

Interaction Between Epidermal Growth Factor and Prostaglandins

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Summary : *Comparative analysis of the effect of epidermal growth factor , receptor functions, and signalling pathways in normal and neoplastic cells will aid in understanding the fundamental mechanisms that control cell proliferation.*

Epidermal growth factor(EGF) , a polypeptide comprising 53 amino-acids, has been isolated from extracts of the submandibular gland of male mice. The biological effects of EGF include stimulation of mitotic activity and cell differentiation, inhibition of gastric acid secretion, stimulation of the proliferation of gastric mucosal cells, protection of the mucosa against various noxious stimuli and promotion of healing of corneal and skin lesions . The probable mode of action of EGF, as well as other growth factors, may involve endocytosis of the occupied cell surface receptors and subsequent action within the cell . Epidermal growth factor stimulates phosphatidyl-inositol turnover in the cell, a source of diacylglycerol, fatty acids and arachidonate .

There are many in vivo and in vitro experiments indicating the relation between epidermal growth factor and prostaglandins . This report will summarize the literature data concerning the current knowledge of the effect of epidermal growth factor and its relation with the prostaglandins.

The results of in vivo and in vitro studies, including our own, shows that epidermal growth factor stimulates the production of prostaglandin E_2. Thus these results support the relation between prostaglandin E_2 levels and the mitotic activities of epidermal growth factor on different kinds of cell functions, especially in wound healing and cancer promotion .

Key words: *Epidermal Growth, Factor (EGF), Prostaglandins, Wound healing*

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Epidermal Büyüme Faktörü ve Prostaglandinler Arasındaki Etkileşme

Özet : *Büyüme faktörleri etkilerinin normal ve neoplastik hücrelerde reseptör fonksiyonları ve sinyal iletim yolları ile karşılaştırmalı analizleri, hücre proliferasyonunun kontrolündeki temel mekanizmaların anlaşılmasına yardımcı olacaktır.*

Epidermal büyüme faktörü(EGF) erkek fare çenealtı tükrük bezi ekstrelerinden izole edilmiş 53 amino asit taşıyan bir polipeptiddir. Epidermal büyüme faktörünün biyolojik etkileri içinde mitotik aktivitenin stimüle edilmesi ve hücre farklılaşması, gastrik asit sekresyonunun inhibisyonu, gastrik mukoza hücrelerinin proliferasyonunun stimülasyonu, çeşitli ülser yapıcı maddelere karşı mukozanın korunması, kornea ve deri yaralarının iyileşmesinde destek vermek yer alır. Epidermal büyüme faktörünün olası etki şekli,diğer büyüme faktörleri gibi hücre yüzeyindeki reseptöre bağlanarak hücre içine endositozla girip hücrede diğer etkilerini göstermek şeklinde olabilir. Epidermal büyüme faktörü hücrede diaçil gliserol,yağ asitleri ve arakidonatların kaynağı olan fosfatidil inozitol döngüsünü stimüle eder.

Epidermal büyüme faktörü ve prostaglandinler arasındaki bağlantıyı gösteren birçok in vivo ve in vitro deney vardır. Bu derleme bu konudaki bizim çalışma sonuçlarımız ve diğer çalışma sonuçlarına ait yeni bilgileri özetlemek üzere hazırlanmıştır.

Bizim yaptığımız çalışmaları da içeren in vivo ve in vitro araştırmaların sonuçları epidermal büyüme faktörünün prostaglandin $E_2(PGE_2)$ yapımını stimüle ettiğini göstermektedir. Bu sonuçlar özellikle değişik hücrelerde yara iyileşmesi ve kanser promosyonunda EGF'nin mitotik etkisine PGE_2 nin katkısını desteklemektedir.

Anahtar kelimeler: *Epidermal Büyüme Faktörü(EGF), Prostaglandinler, Yara iyileşmesi*

Introduction

Neoplasia and normal proliferation are related by virtue of the common utilization of certain molecular events. Normal proliferation involves autocrine and paracrine stimulatory phenomena. Normal control of growth probably involves the differential response of cell types exposed to tonic concentrations of several growth-regulating hormones simultaneously. Changes in the relative doses of these regulators might induce dramatic changes in cell morphology, physiology and growth. This is im-

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portant from the aspect of tumor induction. The relative importance of various growth factors in the homeostasis of growth of cells in vivo is not clear. Specific cell types, however, can be induced to neoplastic transformation by activation of an endogenous oncogene or addition of an exogenous oncogene. The largest class of these oncogenes, the tyrosine kinases, is structurally and functionally related to growth factor receptors such as the EGF family . Another oncogene encodes a growth factor-like protein. In addition, neoplastic cells sometimes secrete large amounts of growth factors and may have high numbers of growth factor receptors on the surface. However, it is unclear whether these phenomena represent effectors of autocrine growth stimulation or are merely artifactual. It seems reasonable, though, that comparative analysis of growth factor effects, receptor functions,and signaling pathways in normal and neoplastic cells will aid in understanding the fundamental mechanisms that control cell proliferation[1].

EGF (epidermal growth factor) is a polypeptide comprising 53 aminoacids which has been isolated from extracts of the submandibular gland of male mice[2] . It is found in various biological fluids such as plasma, saliva, urine, amniotic fluid, milk and tears but is produced mainly by salivary glands in mice[3]. In man, EGF was found to be identical with urogastrone found in human urine. The biological effects of EGF include stimulation of mitotic activity and cell differentiation, inhibition of gastric acid secretion, stimulation of the proliferation of gastric mucosal cells, protection of mucosa against various ulcerogens[2,4] and promotion of healing of corneal and skin lesions[5-8]. The probable mode of action of EGF, as with other growth factors, may involve endocytosis of the occupied cell surface receptors and subsequent action within the cell[8]. EGF stimulates phosphatidyl-inositol turnover, a source of diacylglycerol, fatty acids and arachidonate[9]. Phospholipids, diacylglycerol and arachidonic acid (AA) are implicated in the EGF mechanism of action. Since prostaglandins protect the gastric mucosa, it is important to examine protective and damaging agents on gastric eicosanoid formation. This is particularly interesting, since the relationship between the AA pathway (particularly the lipid peroxides) and cancer is a topic of active research. The metabolism of AA depends on the activity of a cyclooxygenase and lipoxygenases. Various products result from the cyclooxygenase activity including endoperoxides and prostaglandins, and hydroperoxy fatty acids, hydroxy fatty acids, and leukotrienes are derived from the activity of the lipoxygenases. Figure 1 summarizes the synthesis of prostaglandins.

Membrane phospholipids

⇓ Phospholipase A_2

Arachidonic acid
⇓ Cyclooxygenase
Endoperoxides
⇓
Prostaglandins → (PGE_2, $PGF_{2\alpha}$, PGD_2)
Prostacyclin
Thromboxanes

Figure 1. Prostaglandins produced from arachidonic acid by cyclooxygenase.

In brief, this report will summarize our results and the current knowledge of epidermal growth factor effects and their relationship with the prostaglandins. There are many in vivo and in vitro experiments indicating the relation between EGF and PGs . These experiments are presented under two subtitles in historical order.

In vitro Studies on Epidermal Growth Factor and Prostaglandins

EGF at concentrations of 10^{-9} to 10^{-10} M stimulated the biosynthesis of prostaglandins by canine kidney (MDCK) cells but not that by human fibroblasts (D-550), mouse fibroblasts (3T3), transformed mouse fibroblast (MC-5), and rabbit aorta endothelial cells (CLO). EGF also stimulated the release of radioactivity from MDCK cells radioactively labelled with [^{3}H] arachidonic acid[10].

Murine EGF stimulated the production of PGE_2 and bone resorption in neonatal mouse calvaria in organ culture. All concentrations of EGF which stimulated resorption also stimulated the production of PGE_2 in bone[11].

A number of serum constituents were unable to replace the activity of serum, including serum lipoproteins(HDL,LDL and VLDL) isolated serum lipids, alpha tocopherol, insulin, estrogen, platelet derived growth factor, fibroblast growth factor and endothelial cell growth factor. However, EGF at concentrations of 10 and 20 ng/ml progressively stimulated the recovery of PGI_2 synthesis following inactivation by aspirin and completely reconstituted the activity of the serum-free medium. Similar observations were made in cells inactivated by prior exposure to arachidonic acid. Addition of EGF in the range of 0.1 to 10 ng/ml progressively restored PGI_2 synthesis. Furthermore, EGF-dependent recovery was also completely prevented by the protein synthesis inhibitor cycloheximide. The measured doubling time for vascular smooth-muscle cells in these experiments was 24 to 30 h. The recovery of cyclooxygenase in self-inactivated or aspirin treated cells within 2 h following addition of EGF thus represents selective activation of cyclooxygenase synthesis, because recovery was blocked by cycloheximide but not by actinomycin D. This indicates that cells probably contain considerable amounts of mRNA for the cyclooxygenase in an inactive state. Addition of EGF stimulates translation of preexisting cyclooxygenase mRNA, thus allowing replacement of inactivated cyclooxgenase to occur[12].

EGF at physiologic concentrations (0.001-0.1 µg/ml) stimulated the release of [^{14}C] arachidonic acid [^{14}C-AA] from pig epidermis (skin slices). These results suggest that EGF stimulates phospholipase A_2 activity and increases release of arachidonic acid[13].

The arachidonic acid pathway can influence the effect of EGF on human choriogonadotropin secretion by cultured human choriocarcinoma cells and suggests an intermediary role for the lipoxygenase system[9].

Indomethacin (cyclooxgenase inhibitor) completely blocked the resorptive response to EGF of bones cultured with EGF alone . However, indomethacin totally blocked the resorptive response to EGF of bones cultured with hydroxyurea(HU). The effects of indomethacin on EGF-mediated resorption in HU-treated cultures appeared to be related to an inhibition of prostaglandin synthesis. This suggests that EGF-mediated resorption in these cultures is dependent on sustained DNA synthesis[14].

EGF stimulated arachidonate release and PGE_2 production in the presence of the Ca^{+2} ionophore A 23187 in cultured rat renal glomerular mesangial cells. This effect is synergistic with but not dependent on activation of protein kinase C[15] .

The calcium ionophore A 23187 stimulates release of free [^{3}H] arachidonic acid from radiolabelled cultures of mouse embryopalate mesenchyme(MEPM) cells which are growing, but not from those which are confluent. However, when confluent MEPM cells are pretreated with EGF release of [^{3}H] arachidonic acid does develop in response to A 23187, since EGF itself stimulates release of [^{3}H] arachidonic acid from these cells, but protein kinase C modulates the activities of phospholipid hydrolases in MEPM cells[16].

Rosengurt(1989) summarized the integration of early signalling events and synergistic effects elicited by EGF in the following figure17 ;

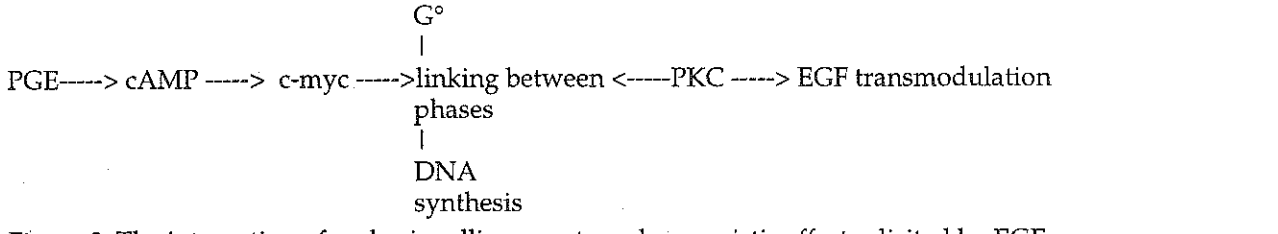

Figure 2. The integration of early signalling events and synergistic effects elicited by EGF

The effects of EGF and linoleic acid and arachidonic acid metabolites on DNA synthesis in BALB/c 3T3 fibroblasts were assessed by measuring incorporation of radioactive thymidine into trichloroacetic acid-insoluble material after 24 hours. When the linoate metabolites and PGs were added alone to quiescent BALB/c 3T3 cells, they stimulated [^{3}H] thymidine incorporation to a very small extent only. However, when added in the presence of EGF, these compounds greatly potentiated the growth factor-induced cellular response[18].

Kelner and Ulnik suggested in 1995 that there is a link between cellular oxygen radical homeostasis and three different classes of messenger molecules: growth factors, nitric oxide and prostaglandins[19].

Eling and coworkers have studied the regulation of arachidonic acid and linoleic acid metabolism by EGF in Syrian hamster embryo cells and the way by which these lipid metabolites modulate the EGF signalling pathway that leads to cell proliferation. The results indicate that arachidonic and linoleic acid metabolites can alter the EGF signalling pathway which influences mitogenic and apoptotic responses[20].

We can summarize the in vitro experiments on EGF and prostaglandin relation by stating that EGF stimulates PG synthesis in many cells.

In vivo Studies on Epidermal Growth Factor and Prostaglandins

EGF promotes the growth of gastric mucosa and protects it against various ulcerogens, including stress, but little is known about its role in the pathogenesis of stress-induced ulcer. Thus in the last decade most of the studies concerning EGF concentrate on this topic[21,22].

Gysin and coworkers designed a study to ascertain whether rats with gastric lesions induced by cold-water stress, ethanol or indomethacin have altered EGF levels in their gastrointestinal tract compared with controls. They showed that immunoreactive EGF content was increased in the duodenum and colon but did not change in the stomach and jejunum. When the formation of lesions was prevented by omeprazole(stress ulcer) or PGE_2 (ethanol and indomethacin- induced ulcer), the increase of immunoreactive EGF in submandibular glands and duodenum was abolished[22].

EGF accelerates the healing of chronic gastroduodenal ulceration and may contribute to the healing effects of sucralfate. These effects of trophic substances are related to their stimulation of cell proliferation and DNA, RNA and protein synthesis and can be reversed by the suppression of mucosal growth.

Prostaglandins, especially their stable methylated analogs, display trophic effects on the gastric mucosa but neither gastroprotective nor ulcer healing actions of PGs can be attributed to their trophic effect[23].

Exogenous EGF and PGE_2 significantly reduced the ulcerations in the stressed rats with intact salivary glands, but this reduction was significantly less pronounced after sialoadenectomy. This study indicates that the presence of salivary glands attenuates the stress ulcerogenesis probably by releasing EGF, which acts in part by enhancing ornithine decarboxylase activity, mucosal growth, PG and glutathione formation[23].

Both exogenous EGF(17 nmol/kg/h) and dimethyl prostaglandin E_2 (143 nmol/kg) prevented in part the formation of gastric lesions in rats exposed to water immersion and restraint stress, while inhibiting gastric acid secretion in rats with intact or resected salivary glands[24,25].

Solcoseryl , a deproteinized extract of calf blood, is used in the protection of gastric mucosa against various topical irritants. It was shown that solcoseryl, when given subcutaneously, prevented the formation of stress-induced gastric lesions and this was accompanied by an increased generation of PGE_2 in the gastric mucosa. Similar effects were obtained

with EGF and, using both radioimmunoassay and radioreceptor assay, EGF-like material was detected in the solcoseryl preparation. These results indicate that :

1. Solcoseryl contains EGF-like material,

2. Solcoseryl displays protective and ulcer healing effects similar to those of EGF and involving both PG and polyamines,

3. Solcoseryl acts via a similar mechanism to EGF[26].

Another study has been designed by Brozowski and coworkers to compare the gastroprotective effects of spermine and EGF against gastric damage induced by absolute ethanol, acidified aspirin and stress in order to determine the role of endogenous polyamines in EGF-induced gastroprotection. Spermine and EGF significantly reduced the lesions induced by all three ulcerogens. Since indomethacin failed to affect the gastroprotective effects of spermine and EGF and neither of these agents influenced the mucosal generation of PGE_2 in intact of injured gastric mucosa, Brozowski and coworkers concluded that prostaglandins are not major factors in spermine and EGF induced gastroprotection[27].

The results of a study carried out to determine whether repeated exposures to stress lead to the adaptation of the gastric mucosa to stress ulcerogenesis showed that the stomach has the ability to adapt to repeated exposures to stress and that this adaptation is mediated, at least in part, by endogenous PG and EGF[28].

Another study examined whether EGF, PG and polyamines(PA) affect the healing of acute gastric lesions induced by water immersion and restraint. Results indicated that EGF, PG and PA are implicated in healing of stress lesions and that EGF acts, at least in part, by the stimulation of PA formation in the gastric mucosa[29].

We examined the effect of EGF on serum zinc and plasma PGE_2 levels of mice with pressure sores because of the known relations between EGF, zinc and PGE_2 and wound healing . Our results indicate that EGF can be effective on wound healing by elevating the serum zinc and plasma PGE_2 concentrations, together with other physiological roles in the cellular events[30].

Expression of several growth factors and their receptors in the periimplantation embryo and uterus suggests that growth factors play important roles in the implantation process in an autocrine/paracrine manner. Recent findings particularly raise the possibility of ligand-receptor signalling with the epidermal growth factor family of growth factors, EGF itself and others. On the other hand, it is well known that prostaglandins play important roles in the process of implantation. Uterine concentrations of PGs are elevated after artificial stimulus to the uterus. Higher concentrations of uterine PGs are thought to favor induction of implantation by test agents in delayed implanting rats. Tamada and coworkers designed a study to determine whether estradiol(E_2) - induced implantation is influenced by PGs. Progesterone(P4)- treated delayed implanting rats were injected subcutaneously with indomethacin (INDO) an inhibitor of PG synthesis, 30 min before an intravenous injection of PGE_2 and intraluminal injections of phosphate buffered saline(PBS) medium on day 8 of pregnancy. To determine whether PGs influence EGF effects on implantation, P4-treated delayed implanting rats were subcutaneously injected with INDO 30 min before intraluminal injections of EGF on day 8 of pregnancy. On day 9 animals were checked for implantation sites. The results of the study showed that EGF could induce implantation in the P4-primed delayed implanting rats and also facilitate decidual response. However, since EGF increases PG synthesis in the uterus, part of the action of this compound may be mediated by PGs[31].

Another research on the gastroprotective effect of EGF suggests that EGF protects the gastric mucosal surface by way of increased tissue PG levels, and decreased both tissue malondialdehyde, which in-

dicates lipid peroxidation, and serum gastrin levels[32].

Our data showed that the increase in the plasma PGE_2 level caused by diethylnitrosamine (DENA) treatment was enhanced by EGF but opposed by dexamethasone. The blood PGE_2 levels increased significantly following DENA and EGF administrations alone or together[33].

Recently Konturek reported that adaptive cytoprotection of the stomach seemed to be mediated by activation of local mucosal biosynthesis of protective prostaglandins and NO, sensory nerves and mucosal expression and release of growth factors, including EGF, TGF-alpha and spasmolytic peptide (SP). The fact that exogenous PG, NO, EGF, TGF-alpha, SP and capsaicin, and stimulating sensory nerves protect the mucosa against strong necrotizing agents (direct cytoprotection) supports the hypothesis that these factors and sensory nerves are involved in the mechanism of adaptive cytoprotection[34].

Conclusion

In conclusion; concerning the in vivo and in vitro studies on EGF and prostaglandin relation, EGF stimulates PG synthesis in many cells and there are several mechanisms regulated via this EGF and PG relation especially wound healing, cancer promotion, and even embryonal implantation.

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