Mucosal Protective Mechanisms

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Summary

Cytoprotection is the ability of agents to inhibit injury to the gastro-duodenal mucosa and promote healing of ulcerations without inhibiting acid secretion or neutralizing intra-lumenal acidity.

Cytoprotective agents: Prostaglandins (PGS), Essential fatty acids (EFA) and Sucralfate ——

—— Do not prevent initial disruption of the surface epithelium after exposure to necrotizing agents but

—— Prevent damage to the mucosal proliferative zone enabling prompt restitution of the mucosal surface.

Introduction

Mucosal protection by prostaglandin and prostaglandin-like substances is a new concept for the protection of mucosa from ulceration. The mechanism is free of the mucosal protective action from acid secretions.

The idea of this mechanism is called Cytoprotection. Cytoprotection is the ability to prevent mucosal necrosis produced by ulcerogenic and necrotizing agents to gastro-intestinal mucosa independent of gastric acid secretion.

The prostaglandin secreted by gastro-intestinal mucosa and its precursors in diet, called dietary essential fatty acids (EFA) including arachidonic acid (A.A.) and linoleic acid (L.A.) resulting in the formation of prostaglandin, are the substances which help in protection of the mucosa from damage.

The biochemical pathway of prostaglandin synthesis is given in Fig. 1.

Material and Methods

The idea of mucosal protection by prostaglandin has been studied in human volunteers and rats. Two groups of human volunteers (and of rats) were

*Dr. Daniel Hollandar delivered this lecture when he visited PGMI on 12th Nov. 1985. An abstract from his lecture has been documented by Dr. Mahmood Alam Kamil, PGMI.

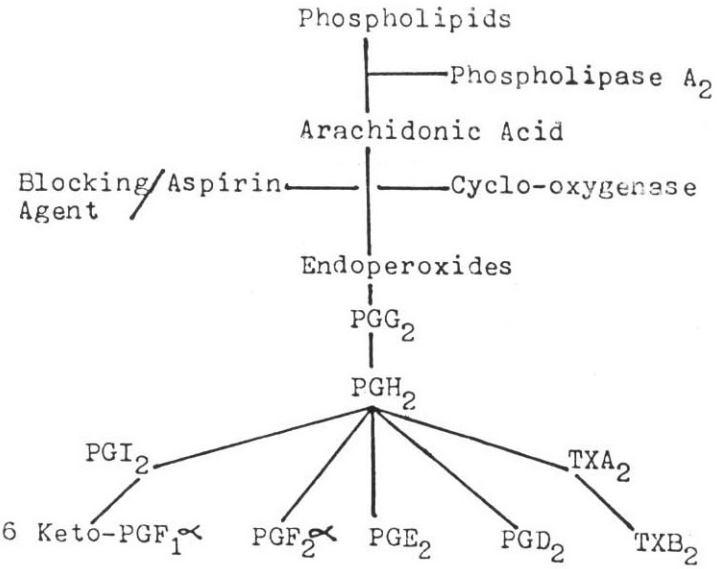

Fig. 1 – Mucosal protection by mucin production through accelerated cell proliferation.

studied, spraying the gastric mucosa with alcohol. In group I, no prostaglandin was given before the spray, and in group II, prostaglandin preceeded alcohol spray. The gastric mucosa was studied endoscopically in both the groups. The results were:–

Group	Method	Gastric Mucosa lookinga after 30 minutes of spray
Human Volunteers	a) Alcohol sprayed on gastric mucosa without prostaglandin administration.	Haemorrhagic patches.
	b) Alcohol sprayed after administration of prostaglandin.	Normal mucosa.
Rats	a) Alcohol sprayed without arachidonic acid administration.	Haemorrhagic patches.
	b) Alcohol sprayed after arachidonic acid administration.	Normal mucosa.

Gastric haemorrhagic lesions in the stomach were studied and damaged area, as percentage of the total mucosal area, was computerized. The lesions were studied after 3 hours of injury by ethyl alcohol (ETOH) spray and after 15 hours of ETOH :–

GASTRIC HAEMORRHAGIC LESIONS 3 HOURS AFTER ETOH

Pre-treatment	Haemorrhagic area (%)
PL + ETOH	33.8 ± 3.5
30 mM/A.A. + ETOH	15.4 ± 5.0 a
60 mM/A.A. + ETOH	3.0 ± 1.1 a b
120 mM/A.A. + ETOH	0.6 ± 0.4 a b c

a, b, c. $p < 0.025$
PL — Placebo
A.A. — Arachidonic acid
ETOH — Ethyl alcohol

GASTRIC HAEMORRHAGIC LESIONS 15 HOURS AFTER ETOH

Pre-treatment	Haemorrhagic area (%)
PL + ETOH	27.4 ± 5.3
120 mM/A.A. + ETOH	0.6 ± 0.4 *

* $P < 0.01$

The studies clearly indicated the mucosal protective action of A.A. against the injurious agents. The picture was studied by scanning/ electron – microscopy which showed deep necrosis of the surface cells after five minutes of injury and mucosal sloughing with infrastructure and connective tissue around the hollow cellular spaces after 6 hours of injury. The study was also done in cases receiving arachidonic acid before injury and the picture was as follows :–

A.A. + Injury — after 10 min. = Some Injury.
„ 1 hr. = New cells coming up.
„ 3 hrs. = Surface covered by new cells and lot of mucus.

The same study was done by transmission electron-microscopy and it was noticed that after 1 hour, the cells started migrating from the proliferative layer

having pseudopodia and by end of 3 hours, the surface was covered with migrated new cells alongwith mucus secreting cells.

This study gave an idea of cytoprotection which explains that prostaglandins and their precursors (EFA) do not protect the mucosal surface from initial injury but do accelerate the repair process by preventing injury to the proliferative zone of mucosa: thereby promoting accelerated repair and healing of the mucosa. If production of prostaglandin is blocked, the results of injury will be the same.

Indomethacin and like substances give injury to the mucosal cells by preventing production of prostaglandin :–

MUCOSAL DAMAGE 2 HOURS AFTER INJURY

Indomethacin Pre-treatment		% Haemorrhagic Area at 2 hours
PL + ETOH	—	29.0
120 mM/A.A. + ETOH	—	27.0

The idea of cytoprotection by prostaglandin is confirmed by estimating prostaglandin levels 30 minutes and 60 minutes after the administration of placebo and arachidonic acid :–

PROSTAGLANDIN E_2 CONCENTRATION IN GASTRIC CONTENTS AFTER INTRAGASTRIC INSTALLATION OF 1 ML PL OR A.A. (1 ML. 120 mM)

	PGE_2 CONCENTRATION LEVEL	
Group	30 Minutes	60 Minutes
PL	0.55 ± 0.14	0.88 ± 0.34
A.A.	7360.0 ± 1500	4100 ± 1000 *

* $p < 0.002$

PROTECTION OF THE GASTRIC MUCOSA BY NON-PROSTAGLANDIN AGENTS

Sucralfate has sucrose molecule attached with aluminium sulphate which is a substance which sticks to the gastric mucosa and stimulates the proliferative zone, thus repairing the damage to surface cells after injury.

The study was done by spraying alcohol to gastric mucosa and computerizing the damage as percentage of total area in controls and in subjects given sucralfate 1 hour before alcohol spray. The results were as follow :–

SURFACE NECROSIS AFTER ALCOHOL INJURY

Time (hr)	Control (%)	Sucralfate (%)
0.25	33 ± 4	5 ± 2
1	33 ± 2	4 ± 1
4	37 ± 4	3 ± 1
6	37 ± 2	4 ± 1
24	46 ± 5	3 ± 1

Gastric luminal prostaglandin E_2 concentration and out-put was estimated in both groups i.e. placebo and Sucralfate group for 30 minutes :–

Group	PGE_2 Concentration	PGE_2 Out-put
Placebo	0.56 ± 0.16 ng/ml	2.1 ± 0.6 ng/30 min.
Sucralfate	0.99 ± 0.2 *ng/ml	4.0 ± 0.7 ng/30 min.

* $P < 0.05$

Study Plans and Methods

Subjects = 28 healthy male volunteers, of age group 28 to 48 years with endoscopically normal gastric mucosa, received oral pretreatment with either :

Material = A. Placebo
B. Cimetidine (Tagamet) 300 mg
C. Sucralfate (Carafate) 1 G

One hour later, 100 ml 40% alcohol was sprayed through an endoscope directly onto the gastric mucosa (corpus) via an Olymous pw 5/6 spray type washing pipe.

ENDOSCOPIC CHANGES 15 AND 30 MIN AFTER ALCOHOL ADMINISTRATION (MEAN SCORE + SE)

Time	Placebo	Cimetidine	Sucralfate
Prior to alcohol	0	0	0
15 min. post alcohol	3.6 ± .3	3.8 ± .6	1.6 ± .5 *
30 min. post alcohol	3.9 ± .2	4.0 ± .5	1.8 ± .6 †

* $P < 0.025$ vs Placebo group.

† $P < 0.01$ vs Cimetidine group.

Mechanism of action of sucralfate was studied by estimation of prostaglandin in the mucosal cell and in the lumen of gut.

HUMAN GASTRIC MUCOSAL GENERATION OF PROSTAGLANDIN

	Mucosal Generation		Luminal	Release
	PGE_2 (ng/g)	TxB_2	PGE_2 (ng/30 min)	TxB_2
Placebo	583 ng ± 88	432 ng ± 82	426 ng ± 50	310 ng ± 52
Sucralfate	817 ng ± 133	408 ng ± 56	572 ng ± 70	184 ng ± 22

n = 12 (Konturk et al).

Conclusion

Protective action of sucralfate on the gastric mucosa is mediated (at least in part) by endogenous prostaglandins.

Sucralfate is a drug without any side effects and if used for 8 weeks, gives 100% recovery in terms of non-recurrence upto one year; while 80% recovery if used for 4 weeks. Pregnancy is the only contraindication for its use as is the case with prostaglandin E_2.

Review of peptic ulcer disease (PUD) in the 20th century gave a decreasing trend as cases of hospital admissions, surgical treatment and mortality rate from PUD. The data available for Duodenal ulcer (D.U.) mortality per million male subjects in different countries is given below :–

DEATHS PER MILLION MALE SUBJECTS

D.U. Scotland		D.U. England		D.U. U.S.	
1930	154	1930	109	1921	40
1976	24	1976	16	1976	7

This drop in mortality rate was correlated with the increased use of fat from vegetable source (EFA) as compared to animal sources. Following table gives year-wise picture of the use of fat from different sources in U.S.A. food supplies :–

Years	G of Fat from Vegetable Sources	G of Fat from Animal Sources
1909–33	22 gm	103 gm
1935–39	35 gm	98 gm
1957–59	42 gm	100 gm
1975	63 gm	89 gm
1982	68 gm	95 gm

The relationship of the use of saturated fatty acids to unsaturated fatty acids (linoleic acid + oleic acid) is given in the following graph :–

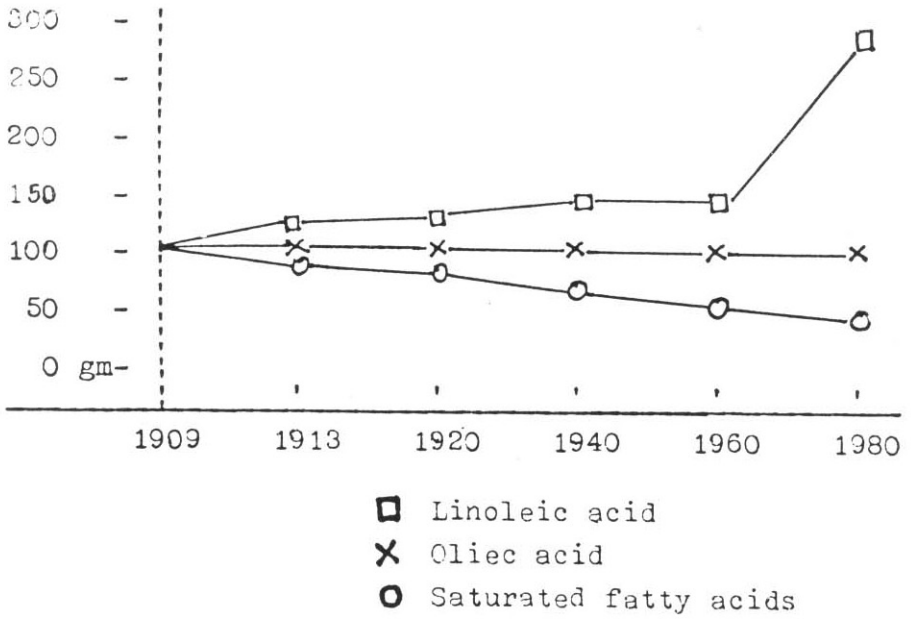

Fig. 2 – Use of saturated and unsaturated fatty acids in Gms from 1909 to 1980.

Increased use of free fatty acids and use of fat from vegetable sources has increased the use of prostaglandin precursers: thus increasing production of prostaglandin in the mucosal cells and lumen: resulting in cytoprotection of proliferative layer and thus accelerated repair of damage without inhibition of acid secretion.

Rich sources of essential fatty acids are vegetable oils like saf-flower oil, corn oil, palm oil and margarine which are the precursors of prostaglandin i.e. arachidonic acid and linoleic acid.