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REVIEW ARTICLE

A Potential Mechanism of Cytoprotection - A Review

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ABSTRACT

Cytotoxicity means a substance or process which results in cell death. Upon cell death induction cells undergo different cell fates and morphological alterations including apoptosis, autophagic and necrosis. There are many mechanisms of Cytotoxicity and beneficial effects of Cytotoxicity. Cytoprotection i.e. protecting the cells from harmful agents, physiological stress and pathological stimuli has always been a topic of interest amongst researchers. This review deals with the mechanism of Cytoprotection and its clinical importance.

KEYWORDS

Cytotoxicity, Cytoprotection, Mechanism, Cell Death

INTRODUCTION

The term "cytotoxicity" is a combination of two Greek words: Kytos," which refers to the cell, and "Toxikon," which pertains to poison. Cytotoxicity is the quality of being toxic to cells. Cytotoxicity refers to a substance or process which results in cell damage or cell death. Substance that can be described as cytotoxic can include some chemicals or even other types of cells. Examples of toxic agent are chemical substance, an immune cell or some types of venom e.g. from the puff adder or brown recluse spider[1].

Types of Cell Death

There are three types of cell death have been distinguished in mammalian cells by morphological criteria.

Apoptosis, also known as type 1 cell death

Apoptotic cells reveal characteristic changes in nuclear morphology, including chromatin condensation and fragmentation, overall cell shrinkage, blebbing of plasma membrane and formation of apoptotic bodies that contain nuclear or cytoplasmic material.

Autophagic, type 2 cell death

Autophagy is characterized by a massive accumulation of double – membrane containing vacuoles, called autophagosomes, which originate from phagophores or isolation membranes and encapsulate cytoplasmic material. The autophagosomes subsequently fuse with Iysosomes to from autolysosomes, which causes the degradation of the autophagosomal contents. Under physiological conditions, autophagy is a survival mechanism that enables adaptation to starving conditions, whereas excessive autophagy can lead to cell death.

Necrosis, also known as type III cell death

Necrosis is morphologically defined by cytoplasmic swelling, dilation of organelles which causes cellular vacuolation and rupture of the plasma membrane, resulting in the proinflammatory leakage of the intracellular content[2].

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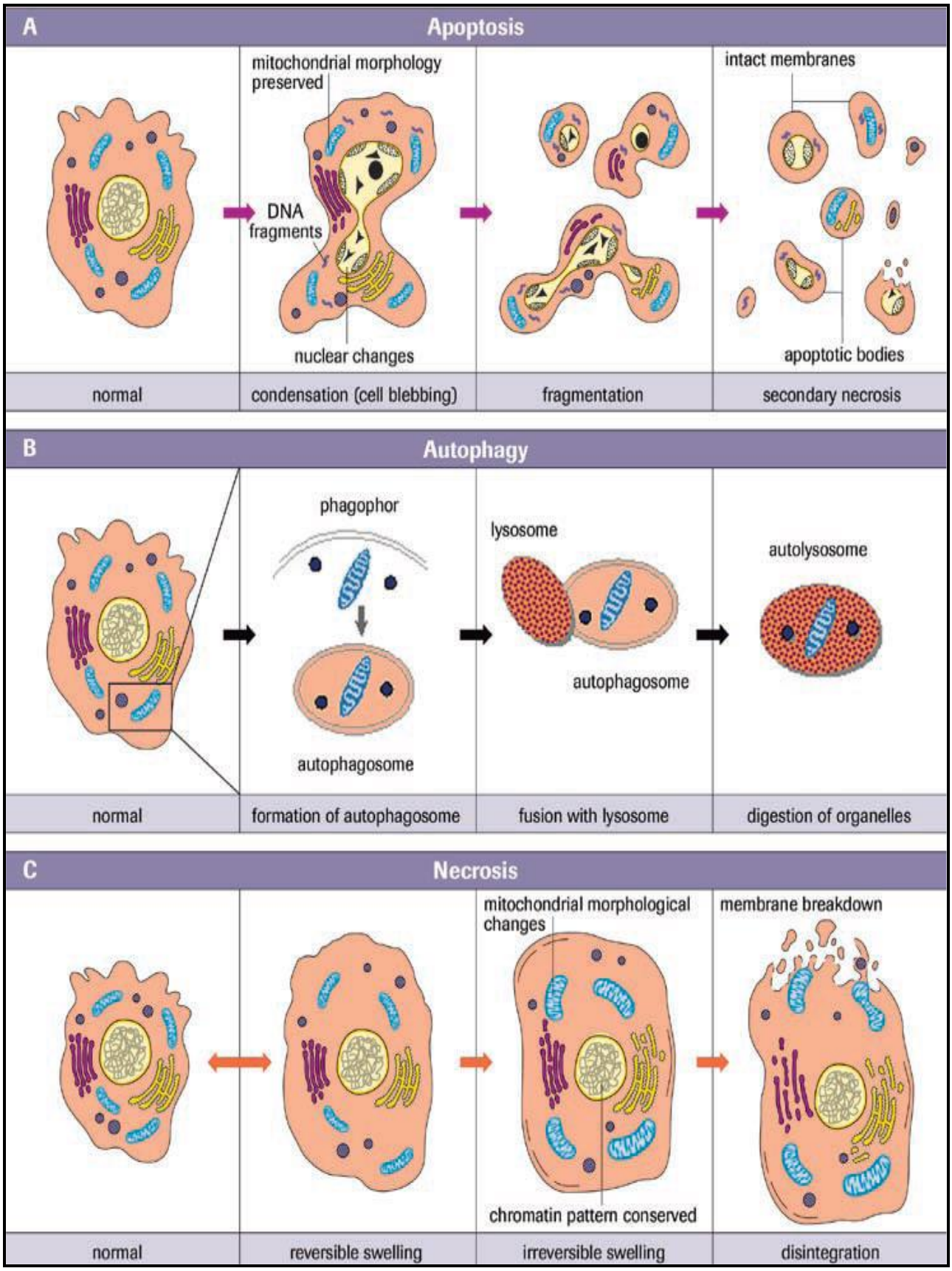

Figure 1: Three Forms of Cell Death

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Mechanism of Cytotoxicity

The cell mediated responses of the immune system achieve two types of results. The first and most important is the lysis (killing) of cells recognized as foreign. This can be achieved by one of three different mechanisms: killing by cytotoxic lymphocytes (CTL), killing by natural killer (NK) cells, and killing by antibody – dependent, cell – mediated cytotoxicity (ADCC).

The second is the generation of a local tissue reaction known as delayed – type hypersensitivity (DTH).

Cell Killing By Cytotoxic Lymphocytes (CTL)

The physiological role of cytotoxic T lymphocytes (Tc) is the elimination of altered self – cells, typically as a result of viral infection. Resting Tc (also referred as CTL-P) are incapable of cytotoxic activity. They acquire cytotoxic activity as a result of MHC – restricted antigen recognition on altered cells.

The mechanism of cell killing by Tc is well understood. It occurs through direct contact between the Tc and target cell via TCR and class I MHC molecules respectively. It subsequently involves several adhesion molecules and triggers release by the Tc of monomeric perforin, a pore forming protein, a set of serine proteinases (granzymes A-G) that can activate caspases in the target cells and TNF which kills target cells by apoptosis as a result of recruiting the adaptor FADD and caspase 8 to the TNF receptor 1 complex.

Contact between perforinmonomers and the plasma membrane of target cells triggers membrane insertion, polymerization and the formation of a perforin pore that is largely responsible for the death of the target cell.

Antibody – Dependent Cell – Mediated Cytotoxicity

The antibody – dependent cell – mediated cytotoxicity (ADCC) is a mechanism of cell – mediated immune defense whereby an effector cell of the immune system actively lyses a target cell, whose membrane – surface antigens have been bound by specific antibodies. It is one of the mechanisms through which antibodies, as part of the humoral immune response, can act to limit and contain infection.

Classical ADCC is mediated by natural killer (NK) cells; macrophages, neutrophils and eosinophils can also mediate ADCC.

For example, eosinophils can kill certain parasitic worms known as helminthes through ADCC.

ADCC is part of the adaptive immune response due to its dependence on a prior antibody response.

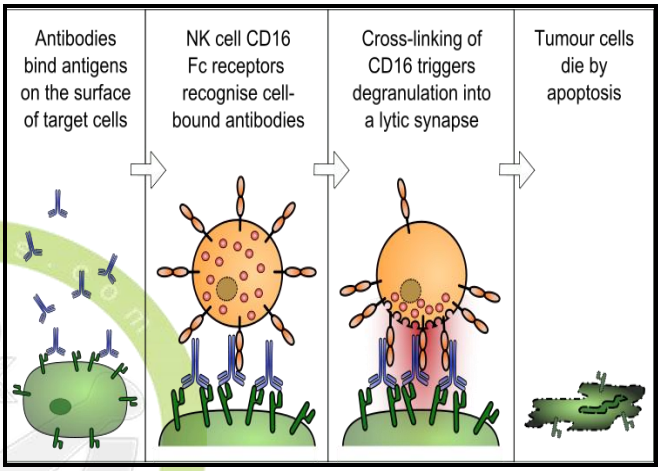

Figure 2: Antibody Dependent Cellular Cytotoxicity.

ADCC by NK cells

The typical ADCC involves activation of NK cells by antibodies. An NK cell expresses CD 16 which is an Fc receptor. This receptor recognizes, and binds to, the Fc portion of an antibody, such as IgG, which has bound to the surface of a pathogen – infected target cell. The most common Fc receptor on the surface of an NK cell is called CD16 or FcγRIII. Once the Fc receptor binds to the Fc region of IgG, the Natural Killer cell releases cytokines such as IFN - γ

ADCC by Eosinophils

Large parasites like helminthes are too big to be engulfed and killed by phagocytosis. They also have an external structure or integument that is resistant to attack by substances released by neutrophils and macrophages. After IgE coat these parasites, the Fc receptor (FceRI) of an eosinophil will then recognize IgE. Subsequently, interaction between FceRI and the Fc portion of

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helminth – bound IgE signals the eosinophils to degranulate[3].

Therapeutic Usefulness of Cytotoxicity

Ricin as Anti Cancer Agent

Ricin is a heterodimeric protein produced in the seeds of the castor oil plant (Ricinuscommunis). It is exquisitely potent to mammalian cells, being able to fatally disrupt protein synthesis by attacking the Achilles to reach its substrate, it must not only negotiate the endomembrance system but it must also cross an internal membrane and avoid complete degradation without compromising its activity in any way. Cell entry by ricin involves a series of steps:

I. Binding, via the ricin B chain (RTB), to a range of cell surface glycolipids or glycoprotein's having β-1, 4 – linked galactose residues;

II. Uptake into the cell by endocytosis;

III. Entry of the toxin into early embosoms;

IV. Transfer, by vesicular transport, of ricin from early endosome to the trans-Golgi network;

V. Retrograde vesicular transport through the Golgi complex to reach the endoplasmic reticulum.

VI. Reduction of the disulphide bond connecting the ricin A chain (RTA) and the RTB;

VII. Partial unfolding of the RTA to render it translocation ally – competent to cross the endoplasmic reticulum (ER) membrane via the Sec61p translocon in a manner similar to that followed by misfolded ER proteins that, once recognized, are targeted to the ER – associated protein degradation (ERAD) machinery;

VIII. Avoiding, at least in part, ubiquitination that would lead to rapid degradation by cytosolic proteasomes immediately after membrane translocation when it is still partially unfolded;

IX. Refolding into its protease – resistant, biologically active conformation; and

X. Interaction with the ribosome to catalyse the depurination reaction.

It is clear that ricin can take advantage of many target cell molecules, pathways and processes. It has been reported that a single molecule of ricin reaching the cytosol can kill that cell as a consequence of protein synthesis inhibition[4].

The Use of Immunosuppressive and Cytotoxic Drugs in Non – Malignant Disease

Cytotoxic drugs prevent cell division or causes cell death. They act predominantly on rapidly dividing cells such as T lymphocytes, and are therefore immunosuppressive and anti – inflammatory. When cytotoxic drugs were initially used in the treatment of cancer, it became apparent that they had profound effects on the immune system. This "unwanted" side effect has subsequently been exploited for the treatment of non – malignant disease where autoimmune mechanisms are considered important in the pathogenesis. More recently drugs such as cyclosporine, which act more specifically on the immune system via the inhibition of T lymphocyte function, are being used for the treatment of disease with immunologically mediated mechanisms. Generally speaking cytotoxic drugs (CDs) have anticancer activity as well as immunosuppressive properties, whereas immunosuppressive drugs (ISDs) show a more specific immunosuppressive effect, although this distinction is partly arbitrary. The classification described in the British National Formulary defining cyclosporine as an ISD; cyclophosphamide, vincristine, chlorambucil, and methotrexate as CDs; and azathioprine (and its active metabolite 6 - mercaptopurine) and mycophenolatemofetil as "cytotoxic immunosuppressant's"[5].

Cytoprotection

Cytoprotection is a process by which chemical compounds provide protection to cells against harmful agents.

For example, a gastric cytoprotectant is any medication that combats ulcers not by reducing

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gastric acid but by increasing mucosal protection. Examples of gastric cytoprotective agents include prostaglandins which protect the stomach mucosa against injury by increasing gastric mucous secretion. Non – steroidal anti – inflammatory drugs (NSAIDs) inhibit the synthesis of prostaglandins and thereby make the stomach more susceptible to injury. Gastric cytoprotective drugs include carbenoxolone, deglycyrrhizinised liquorice, sucralfate (aluminium hydroxide and sulphated sucrose), misoprostol (a prostaglandin analogue) and bismuth chelate (tri – potassium di – citrate bismuthate).

Clinical Importance of Cytoprotection

The Role of Cytoprotection in Treating Therapy- Related Toxicity

Amisfostine, an inorganic thiophosphate is a selective broad spectrum cytoprotector of normal tissue that provides Cytoprotection against ionizing radiation and chemotherapeutic agents, thus preventing the efficacy of radiotherapy and chemotherapy. Amisfostine, is an inactive prodrug, is transformed to an active thiol after dephosphorylation by alkaline phosphatase found in normal endothelium. The absence of alkaline phosphatase in the tumoral endothelium and stromal components, and the hypervascularity and acidity of the tumor environment, may explain its cytoprotective selectivity. The cytoprotective mechanism of Amisfostine is complicated, involving free radical scavenging, DNA protection and repair acceleration, and induction of cellular hypoxia. The US Food and Drug Administration has approved the use of Amisfostine as cytoprotector for cisplatin chemotherapy and for radiation induced xerostomia[6].

Fumarates Promote Cytoprotection of Central Nervous System Cells against Oxidative Stress

Oxidative stress is central to the pathology of several neurodegenerative diseases, including multiple sclerosis, and therapeutics designed to enhance antioxidant potential could have clinical value. The objective of this study was to characterize the potential direct neuroprotective effects of dimethyl fumarate (DMF) and its primary metabolite monomethylfumarate (MMF) on cellular resistance to oxidative damage in primary cultures of central nervous system (CNS) cells and further explore the dependence and function of the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway in this process. Treatment of animals or primary cultures of CNS cells with DMF or MMF resulted in increased nuclear levels of active Nrf2, with subsequent up-regulation of canonical antioxidant target genes. DMF-dependent up-regulation of antioxidant genes in vivo was lost in mice lacking Nrf2.DMF or MMF treatment increased cellular redox potential, glutathione, ATP levels, and mitochondrial membrane potential in a concentration-dependent manner. Treating astrocytes or neurons with DMF or MMF also significantly improved cell viability after toxic oxidative challenge in a concentration-dependent manner. This effect on viability was lost in cells that had eliminated or reduced Nrf2. These data suggest that DMF and MMF are cytoprotective for neurons and astrocytes against oxidative stress-induced cellular injury and loss, potentially via up-regulation of an Nrf2-dependent antioxidant response. These data also suggest DMF and MMF may function through improving mitochondrial function. The clinical utility of DMF in multiple sclerosis is being explored through phase III trials with BG-12, which is an oral therapeutic containing DMF as the active ingredient[7].

Mechanism of Cytoprotection

Redox Mechanisms of Cytoprotection by Bc1-2

Bcl-2 is a multifunctional protein that protects against cell death induced by a wide variety of stimuli. The best characterized antiapoptotic Bcl-2 mechanism of action involves direct binding to proapoptotic proteins, e.g., Bax, inhibiting their ability to oligomerize and form pores in the mitochondrial outer membrane, through which soluble mitochondrialproapoptotic proteins, e.g., cytochrome c, are released into the cytosol. Bcl-2 also exerts antiapoptotic and antinecrotic effects that are mediated by its influence on cellular redox state and apparently independent of its interaction with proapoptotic proteins. Bcl-2

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expression increases cell resistance to oxidants, augments the expression -of-intracellular defenses against reactive oxygen species, and may affect mitochondrial generation of superoxide radicals and hydrogen peroxide[8].

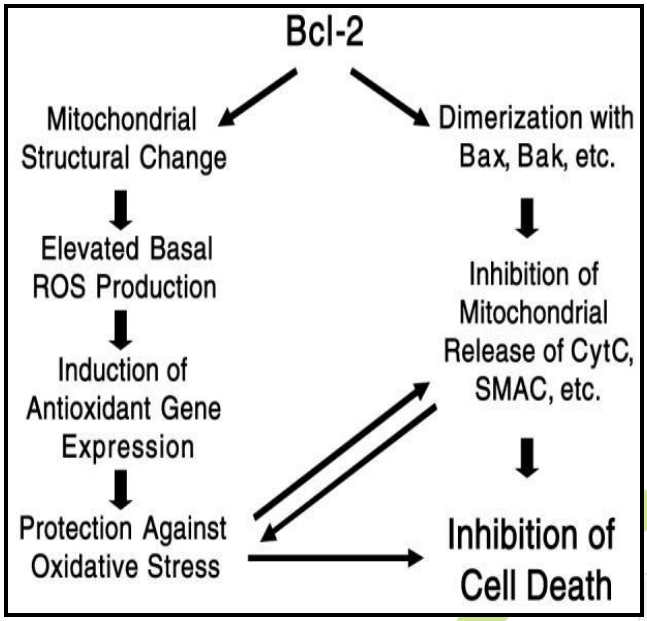

Figure 3: Protection by Bcl-2 against Cell Death

Implication of Cyclooxygenase (COX)-1 and COX-2 products in the Mechanism of Gastroprotection

Recent advances on the enzymatic pathways of arachidonate metabolism revealed that PG synthesis depends upon the activity of cyclooxygenase (COX), a rate-limiting enzyme in the synthesis of eicosanoids. Two isoforms of COX were identified in many cells; a constitutive enzyme designated as COX-1 and inducible isoform known as COX-2. COX-1 appears to be responsible for the production of PG that is physiologically important for homeostatic functions, such as maintenance of the mucosal integrity and mucosal blood flow. Under physiological conditions prostanoid synthesis depends upon the availability of arachidonic acid and the COX-1 activity that is a major target for Nonsteroidal anti-inflammatory drugs (NSAID) causing mucosal damage in the stomach. PG derived from the activity of the COX isoforms, especially COX-1, play an important role in mechanism of gastric integrity, gastroprotection and ulcer healing. Recently, prostaglandins derived from COX-2 were implicated in the protective and ulcer healing activities of growth factors by the demonstration that COX-2 is upregulated on the edge of the gastric ulcer and this is significantly enhanced by the treatment with growth factor. Moreover, endogenous prostaglandins derived from COX-1 and COX-2 are involved in the mechanism of mucosal recovery from ischemia/reperfusion-induced acute gastric erosions that subsequently progressed into deeper ulcerations and that healing of these ulcers is associated with an over expression of COX-2 mRNA.

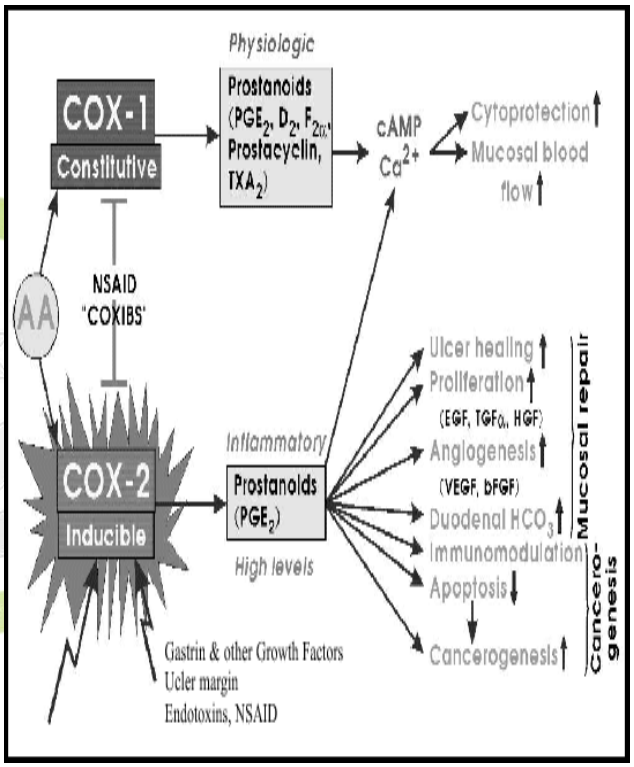

Figure 4: Schematic Characteristics of COX-1 and COX-2

Cyclooxygenase (COX)-1 and COX-2 that convert arachidonic acid to unstable endoperoxidase PGG2 and then to PG. COX-1 is expressed constitutively and releases PGE2 and PGI2 (prostacyclin) involved in Cytoprotection and accompanying increase in the gastric blood flow (GBF). Another product of COX-1, thromboxane (TXA2) exhibits vasoconstrictor and anti-platelet activity. COX-2 produces PG and enhances activity of proteases and growth factors increasing cell proliferation and contributing to ulcer healing and mucosal

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repair *via* enhancement in the bicarbonate secretion and angiogenesis mediated by proangiogenic growth factors such as VEGF and bFGF[9].

CONCLUSION

Cytotoxic refers to the cells which pertain to poison. Cytotoxic substance includes chemicals which are harmful to cells. Protection to cells against cytotoxic agents is done by cytoprotectant and phenomenon is called as Cytoprotection. Cytoprotection is used in various diseases such as treating therapy related diseases and in central nervous system cells. There is various mechanisms by which Cytoprotection is observed. Mechanism of Cytoprotection by prostaglandins (PG) prevents necrosis and hemorrhages produced by noxious agents. Probable mechanism involving is preventing penetration of necrotizing agent. Inhibition was observed in dose depended manner. Yet another mechanism involving in cytoprotection is a multifunctional protein B cell lymphoma (Bcl-2). That protects the cell death by a wide variety of stimuli.

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