The Function of the Selective Inhibitors of Cycloxygenase 2

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Abstract: Cyclooxygenase plays a pivotal role in the transformation of the arachidonic acid to prostaglandins (PGs) and thromboxane. It is composed of two kinds of enzymes, namely cyclooxygenase 1 (COX-1) and cyclooxygenase 2 (COX-2). Cyclooxygenase 1 is the constructive enzyme whereas the cyclooxygenase 2 is the inducible enzyme. Inhibiting cyclooxygenase 1 is always associated with some undesirable side-effects, while inhibiting cyclooxygenase 2 can result in therapeutic effect. This has led the researchers to strive for searching the selective inhibitors inhibiting the COX-2 instead of COX-1. It is very well known that pain and inflammation are alleviated through the inhibition of COX-2 inhibitors such as Aspirin, which has resulted in the recent years, in the emergence of a range of COX-2 inhibitors. Moreover, while evaluating the functions of the COX-2 inhibitions, their significant role in treating glaucoma, preventing and suppressing cancer through their inhibitory activity was clearly revealed and many studies further demonstrated that COX-2 is not only related to the inflammation of peripheral tissues but also to the inflammation manifested in the central nervous system. In addition, the nervous disorders also found an effective treatment with the administration of COX-2 inhibitors. The above-mentioned findings delineate the role of the COX-2 inhibitors as promising agents to be exploited in the treatment of many illnesses. This review will elucidate the functions of the COX-2 inhibitors briefly and introduce some common selective inhibitors of COX-2.

1. INTRODUCTION

Cyclooxygenase, an important enzyme which is involved in the rate-limiting step of the conversion of the arachidonic acid to prostaglandins (PGs) and thromboxane, consists of two essential enzymes namely COX-1 and COX -2. Although COX-1 has a constructive influence whereas COX-2 is the inducible enzyme, the structures of the COX-1 and COX-2 are similar. They only exhibit subtle differences, which define their different functions.

COX-2 is expressed in normal brain and kidney, activated macrophages, synoviocytes during inflammation, and malignant epithelial cells. COX-2 is not expressed in ordinary condition, it is induced as an immediate early gene. COX-2 expression can be stimulated by a lot of inflammatory cytokines, growth factors, tumor promoters, peroxisomal proliferators, hypoxia, ionizing radiation, and carcinogens.

In the beginning, COX-2 was acknowledged as the target of the nonsteroidal anti-inflammatory drugs (NSAIDs) in suppressing inflammation and pain with less side effects. Pain and inflammation can be suppressed through inhibiting the activity of the COX-2 with the selective inhibitors owning particular structure features. In recent years, following the development of the study on the COX-2 and its inhibitors, COX-2 inhibitors have been found to have other functions which can treat many other diseases such as glaucoma and many kinds of cancers. COX-2 is also found to be constitutively expressed in the central nervous system and to be related with neurological diseases such as cognitive disturbance and depression, etc, so the selective inhibitors of COX-2 can also be used in all of these diseases. All of these broaden our view on the functions of the COX-2 inhibitors. Some of them will be discussed below.

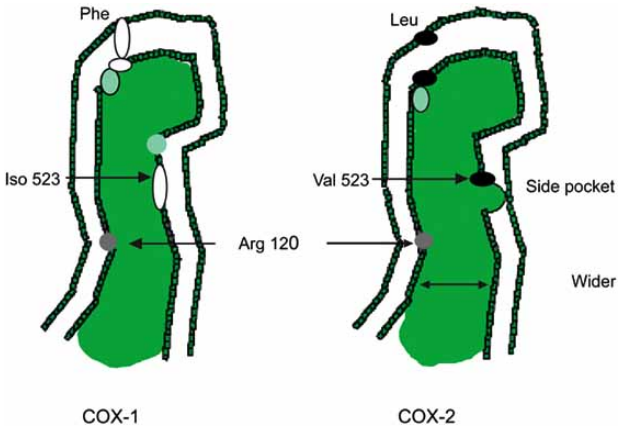

Fig. (1). The structure differences between the COX-1 and the COX-2.

2. FUNCTION

2.1. Anti-Inflammation

Both COX-1 and COX-2 have cyclooxygenase and peroxidase activities, they participate in the processes of the transformation of the arachidonic acid to prostaglandins (PGs) and thromboxane. The PGs contains the PGD2, PGE2, PGF2α, PGI2, just as the picture shown below.

PGs are important biological mediators that signal through a family of G-proteincoupled receptors. These signaling pathways result in widely divergent physiological

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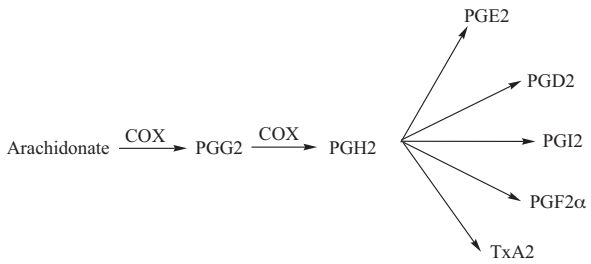


responses including transmission of pain and inflammation as well as maintenance of kidney function and intestinal homeostasis. As we all known that the occurrence of pain and inflammation is related to the secretion of the PGs. The PGs can combine with the pathway of G-protein-coupled cell-surface receptor. We can inhibit the synthesis of the PGs to control the pain and the inflammation, so we can resist the activity of the cyclooxygenase to fulfill our purpose.

NSAIDs can inhibit the synthesis of the PGs in the hypothalamus so as to resist pains and inflammations. But the traditional inhibitors such as aspirin, oxyphenbutazone, Indomethacin, Ibuprofen, etc, have certain side-effects such as serious gastrointestinal side effects. These side-effects are due to inhibiting COX-1. So people strive to discovery new agents which can selectively inhibit the COX-2 so as to decrease the side-effects. 3.

The structure of COX-1 and COX-2 is very similar. 61 percent amino acids of them are absolutely identical, and 84 percent amino acids are similar. The structural difference between the COX-1 and COX-2 is petty. The only and key difference of them is the 523 amino acid. In COX-1, the 523 amino acid is a isoleucine whereas in COX-2 is a valine just as the Fig. (**1**) shown above, the difference between them is just a methyl, but just a methyl can make a extra space which forms a side pocket in the structure of the COX-2, and the volume of the COX-2 is bigger than the COX-2. People can utilize these to design new NSAIDs to minimize the side-effects and get a better therapeutic effect.

Hitherto, people have designed many new NSAIDs which can make effect on the COX-2 exclusively. Some of them are shown below (Table **1**).

The selectivity of the inhibitors is attributed to the structure differences of the two isozymes and the structure features of the inhibitors themselves.

Firstly, we have discussed the structure differences of the isozyme above. Both COX-1 and COX-2 have polar amino

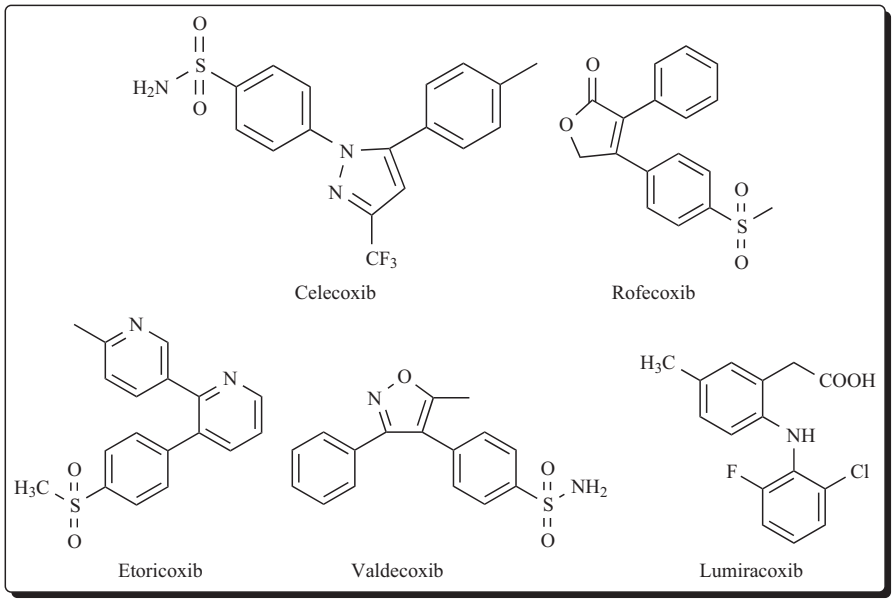


Table 1. [1]

	Celecoxib	Rofecoxib	Etoricoxib	Valdecoxib	Lumiracoxib
COX-1/COX-2 ratio	30	276	344	61	433
Oral bioavaibility	20-40	92-93	100	83	74
Tmax	2-4	2-3	1	2.3	2-3
Half-life	11	10-17	22	8-11	3-6
Bound to plasma %	97	87	98	92	>98

acid Arg 120 which interact (or bind) drugs *via* H-bond. Both COX-1 and COX-2 have an arginine with high polarity in the 120 which can combine with drugs *via* H-bond. In the 523, COX-2 has an extra side-pocket but COX-1 does not have. The selective agents can combine with the side-pocket *via* covalent bond. Besides that, the volume of the COX-2 is bigger than COX-1 and the flexibility of the COX-2 is better than the COX-1, both of these elevate the selectivity of the inhibitors.

Secondly, the structure feature of the selective inhibitor is very important for the combination too. Generally speaking, all of them have a rigid structure such as benzene ring, and there is a sulfamide group at the terminal of the side chain, which can combine with the side-pocket through covalent bond. The volume of the inhibitors is big, so they can insert into the COX-2 whose volume is bigger than the COX-1.

Celecoxib is the first selective inhibitor of the COX-2, and other selective inhibitors of COX-2 are designed followed by the principle of bioisostere. They all can inhibit the COX-2 while sparingly inhibiting the COX-1, so they are more effective and safer. The selective inhibitors of the COX-2 such as celecoxib (Celebrex) and rofecoxib (Vioxx), have been used to smooth the pain induce by osteoarthritis and rheumatoid arthritis extensively with less side-effects.

Recently, scientist have found some newly synthesized compounds with absolutely different structure compared with –coxib. New compounds are heterocyclic pyridone and pyridine derivatives fused with steroidal structure [2], some of which are shown below:

These compounds all have anti-inflammation potency. And [17, 16-c] cyanopyridone fused to ring D combined with some degree of unsaturation in the steroidal scaffold is essential for anti-inflammatory activities.

2.2. Anti-Glaucoma

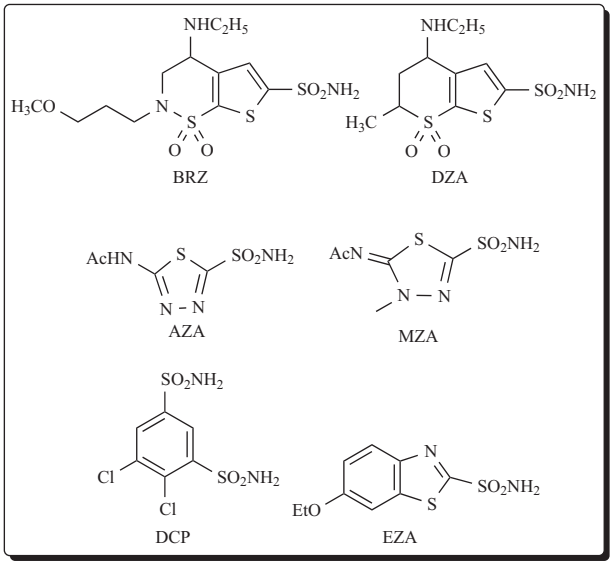
The glaucoma is a very common disease of eyes. The occurrence of glaucoma is attributed to the retarded circulation of hydatoid, which leads to the escalation of the intraocular pressure. The therapeutic means is to inhibit the carbonic anhydrase (CA).

2.2.1. Introduction of the CA

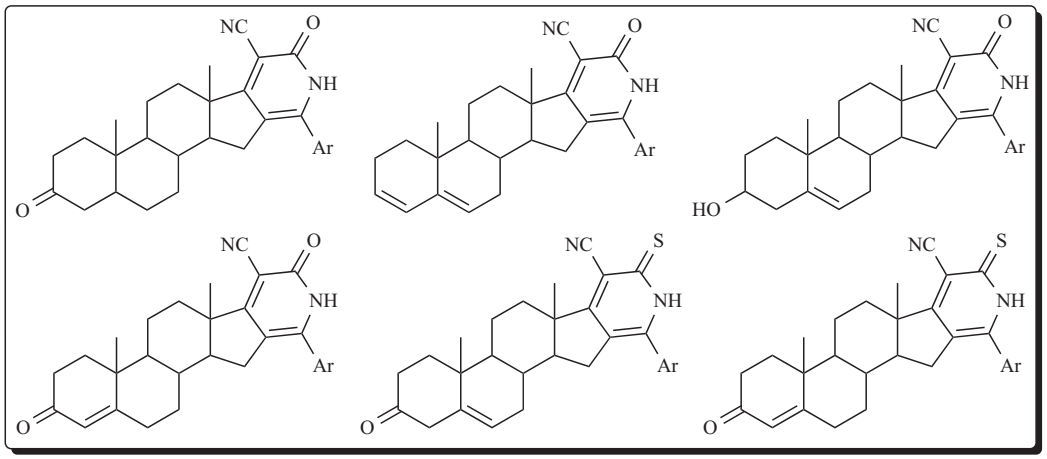
CA is a zinc-dependent metalloprotease. It is a family of 14 distinct enzymes, It is distributed in the ciliary epithelium cells where it can catalyze the transformation of CO_2 and H_2O to HCO_3^-. And then the HCO_3^- can be secreted into the hydatoid followed by the secretion of Na^+, Cl^- and H2O into the hydatoid which can keep the stability of the intraocular pressure. So if the activity of the CA is inhibited, the density of the HCO_3^- decreases, and the intraocular pressure can decrease. So we can utilize the inhibitors of the CA to treat the glaucoma.

2.2.2. Common CA Inhibitors in Clinic

Some common inhibitors of CA in clinic are shown below.



In the structure of these CA inhibitors, we can see that sulfamide is a necessary group which can be combined to the zinc ion of the CA through H-bond. So the sulfamide moiety can mediate high affinity interaction between the inhibitor and the CA.



2.2.3. Relationship Between Selective COX-2 Inhibitors with CA

We have shown some common CA inhibitors in clinic above, and we have demonstrated that the sulfamide is the necessary group for the inhibitors of the CA. But some selective inhibitors of COX-2 also contain the sulfamide group in their structure, so there may be cross-reactivity between the COX-2 and the CA [3]. So the selective inhibitor of the COX-2 may be used as CA inhibitor to treat the glaucoma. But it is clear that not all inhibitors of the COX-2 can be used as the inhibitor of CA, the requisite is that the inhibitor must contain the sulfamide moiety. So the celecoxib but not rofecoxib can be utilized to treat the glaucoma.

Here we show some selective inhibitors of COX-2 which also contain the sulfamide moiety.

SC-558 is the derivative of the celecoxib. We can see that in the structures of the three inhibitors above, there are all sulfamide moiety. The sulfamide moiety can combine to the zinc ion of the CA, and make a anti- glaucoma effect. We take celecoxib as an example to illustrate the combination mechanism of the celecoxib and CA (Fig. (**2**)).

In the structure of the complex one hydrogen of the sulfamide moiety of the celecoxib is derived forming a nitrogen negative ion. The nitrogen ion is combined to the zinc ion of the CA, besides that, the one of two oxygens is combined to the zinc ion too. Another oxygen and the hydrogen are combined to the hydroxyl and amino of the Thr-199 respectively which forms a strong affinity. Aryl of the celecoxib are combined to the hydrophilic residues of the CA.

So just as demonstrated above, the selective inhibitors of the COX-2 which contain the sulfamide group can be combined to the CA with high affinity, so they can be used as CA inhibitor like common used CA inhibitors in clinic to treat the glaucoma.

2.3. Anti-Cancer

Many evidences have tested that COX-2 is related with many kinds of cancers [4], it is overexpressed in tumor cells, playing important roles in tumorigenesis through stimulating epithelial cell proliferation, inhibiting apoptosis, stimulating angiogenesis, enhancing cell invasiveness, mediating immune suppression, and by increasing the production of mutagens. As we all known that the PGE2 is one of the major products derived from the COX-2, which has been reported to stimulate angiogenesis [5] which is very important for the survival of tumor. And many evidences have tested that both endothelial- and stromal- derived COX-2 play a critical role

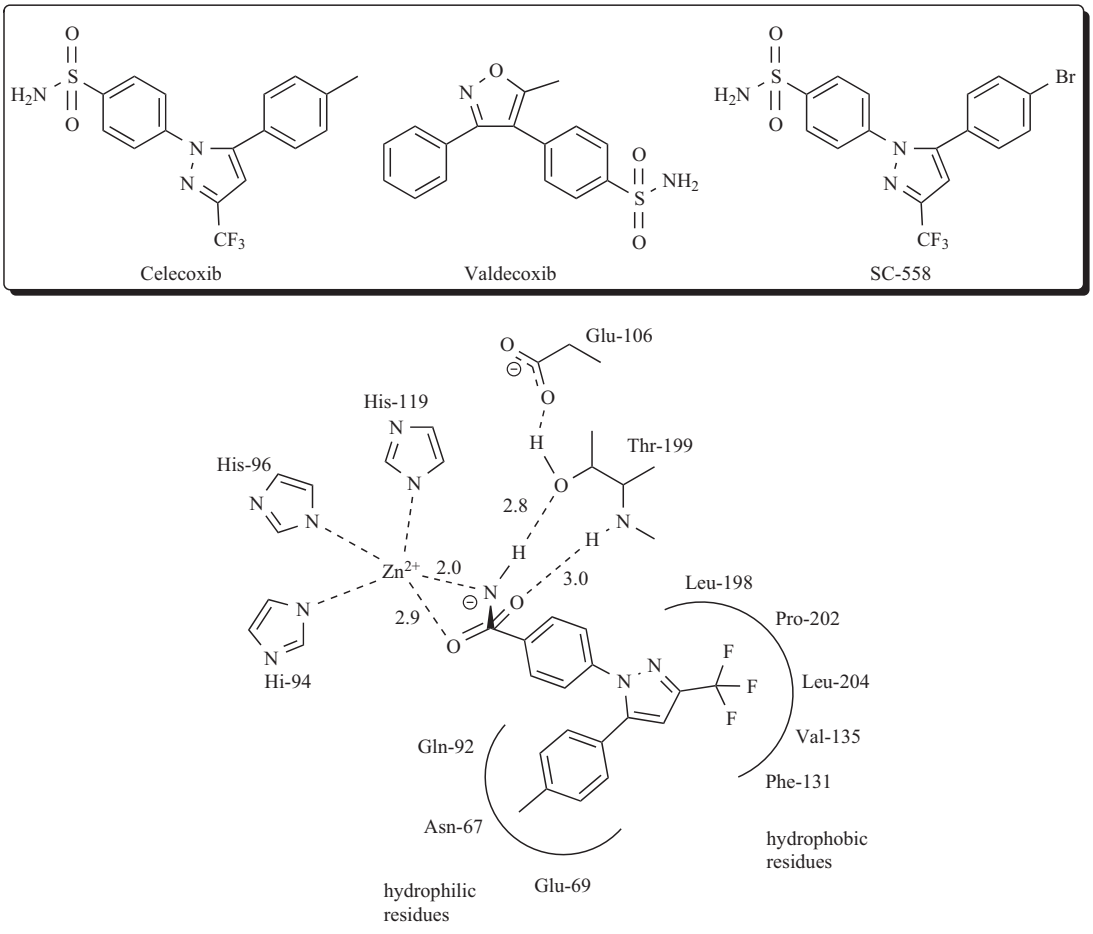


Fig. (2). The figure shows the mechanism of interaction between the CA and celecoxib [3].

in the regulation of tumor growth and angiogenesis. If the activity of the COX-2 is inhibited, the cancer we may be treated. So the selective inhibitors of COX-2 may be the new and promising chemopreventive [6] and chemotherapeutic agents of cancers.

The COX-2 is expressed in many kinds of cancer not only in premalignancy but also in malignancy. The cancers and their organs are shown in the table below.

We have discussed above that there are cross-reactivity between COX-2 and CA. The selective inhibitors of COX-2 can be used to treat the glaucoma because they can inhibit the CA Ⅱ. Except CA Ⅱ, the inhibitor of COX-2 also can inhibit the CAIX. CAIX is a tumor-associated CA isozyme, it is a transmembrane protein with a suggested function to either maintain acid base balance or to interact in intercellular communication. It consists of an N-terminal proteoglycan-like domain that is unique among the CAs, a highly active CA catalytic domain, a single transmembrane region, and a short intracytoplasmic tail. CAIX is related with many kinds of cancers such as cervix uteri, kidney, lung, esophagus, breast, and colon. CA IX protein appears to play a significant role in cancer adaptation to hypoxic environments and may be involved in tumor progression [8]. So the inhibitors of the COX-2 can be utilized to suppress the cancer. For example, celecoxib and valdecoxib are all potent inhibitors of CA IX.

2.3.1. Anti-prostate Cancer

Prostate cancer is the main cancer among males. Many males are deprived lives by prostate cancer every year. It has become one of the main killers of the males. The prostate cancer is related to the inflammation of the prostate gland. The human prostate gland is a common site of inflammation. Focal prostatic atrophy is associated with chronic inflammation, and it is proliferative. The lesions also have low apoptotic rate. All of these changes are due, at least in part, to the overexpression of the anti-death gene Bcl-2 and decreased expression of the cell-cycle regulatory gene p27. COX-2 is highly expressed in the prostate cancer [9]. It can be up-regulated by the inflammation in the prostate gland induced, and it can increase the expression of the anti-death gene Bcl-2 [10] and decreased expression of the cell-cycle regulatory protein p27. COX-2 has been shown to be positive targets for the treatment and chemoprevention of the prostate cancer.

As we all known that High-grade prostatic intraepithelial neoplasia (PIN) is the most likely precursor of prostatic cancer. Increased expression of COX-2 protein was demonstrated in most PIN cells and their surrounding basal cells. The mechanism is shown below.

$$\text{Prostate cells} \xrightarrow{\text{COX-2}} \text{High grade PIN} \xrightarrow{\text{COX-2}}$$

$$\text{Clinically significant prostate cancer} \xrightarrow{\text{COX-2}} \text{Metastatic prostate cancer}$$

As we all known that the prevention is the best way to control the cancers, and the inhibition of COX-2 has been tested to be promising approach to prevent cancers [11].

So all of these discussed above demonstrate that the COX-2 is related to the onset of the prostate cancer. In prostate cancer, the COX-2 mRNA is overexpressed leading to the overexpression of the COX-2, so if we inhibit the expression of the COX-2 using the selective inhibitors of it, we may decrease the incidence of the prostate cancer. Many experiments have tested that the selective inhibitor of COX-2 celecoxib and refocoxib can suppress the inflammation of prostate and can increase the cell apoptosis in the prostate. So the inhibitor of the COX-2 may be used to suppress the prostate cancer.

2.3.2. Anti-colon Cancer

Colon cancer is a very common malignant cancer. The highest mortality is between 40 and 50. Colon cancer is very common in northern American, western Europe, Australia, New Zealand, etc. In our country, the mortality trend to increase year by year. So people have strived for suppressing it.

COX-2 is believed to be one of the most important enzymes related to the colon cancer [12]. COX-2 mRNA and protein are up-regulated in the colorectal cancer tissue [12]. A large number of studies demonstrated that the mortality of

Table 2. [7]

Organ	Premalignancy	Malignancy
Colon	Adenoma	Adenocarcinama
Breast	Ductal carcinoma in situ	Adenocarcinama
Stomach	Metaplasia	Adenocarcinama
Liver	Chronic hepatitis	Hepatocellular carcinoma
Head and neck	Leukoplakia	Squamous cell carcinoma
Biliary system	Bile duct hyperplasia	Cholangiocarcinoma
Lung	Atypical adenomatous Hyperplasia	Adenocarcinoma
Bladder	Dysplasia	Transitional cell carcinoma
Skin	Actinic keratoses	Squamous cell carcinoma

the patients with colon cancer who had been taking Aspirin was significantly and dose-dependently reduced.

As we all known that chronic colon inflammation can lead to the formation of the polypus and then which can transform into colon cancer. The COX-2 is related to the inflammation, which may be involved in the occurrence of the colon cancer. And there are many evidences indicating that COX-2 and its product PGE2 are overexpressed in the colon cancer. So COX-2 may be related to the colon cancer. It can induce the colon cancer from five aspects.

1. Modify cells adhesion.
2. Inhibit natural NK cells.
3. Inhibit cell apoptosis [13].
4. Inducing angiogenesis
5. Increase metastatic potential.

Inducing angiogenesis may be very important because tumor depend on angiogenesis to supply nutrients and oxygen. The PGE2 and PGI2 which are two main products of COX-2 can induce the VGEF in the endothelial cells and accelerate the angiogenesis. So we may

PGE2 is one of the most important products of the COX-2, it can induce cell proliferation and inhibit cell apoptosis.

So if we inhibit the activity of the COX-2, we may suppress the colon cancer. Experiments tested that celecoxib, the selective inhibitor of COX-2, can induce cell apoptosis by inhibiting PDK-1 activity, modulating cell cycle-related proteins, enhancing binding activity of NF-KB and attenuating expression of anti-apoptosis protein survivin. Survivin is a 16.5KD cell intein, which can resist cell apoptosis, it expresses in all kinds of cancers.

So the selective inhibitor of COX-2 may be new potent agents to suppress the colon cancer, and can be used as the effective chemopreventive agents against colorectal neoplasia.

2.3.3. Anti-breast Cancer

Breast cancer is the most common cancer among females with high mortality. Just as other cancers discussed above, the breast cancer can also express high level COX-2 and its induced products including PGE2 [14]. COX-2 can induce breast cancer *via* stimulating cell proliferation, resisting apoptosis [15], inducing angiogenesis, enhancing cell metastasis and suppressing immune systerm. Besides that, recent studies have shown that the expression of the COX-2 can inducing IL-11 which is an osteoclastogenesis, it is involved in the breast cancer metastasis to bone. So the inhibitors of the COX-2 such as celecoxib can also be used to treat the breast cancer.

Beside the cancers discussed above, COX-2 also involves in the lung cancer [16], liver cancer [17], stomach cancer, skin cancer, cervical cancer [18] and many other cancers. So the selective inhibitors of COX-2 may be promising agents to prevent and treat various kinds of cancers.

2.4. Anti-neurological Diseases

In contrast to other tissues, COX-2 is constructively present in the central nerve system (CNS) [19] and regulated by different mediators [20], which distributes in many neuronal tissues such as forebrain, hippocampus, hypothalamus, and amygdale which are all involved in the psychiatric disorders. And it was found that the effects exerted on the CNS are mediated exclusively by COX-2 inhibitors but not the by the COX-1 inhibitors. The constitutive expression of COX-2 in the CNS may indicate that it may play important roles in the CNS.

Many studies have demonstrated that the activity of the COX-2 in brain is related to neuronal injury. The overexpression of the COX-2 in neurons may mediate the neurological diseases such as Parkinson's disease, amyotrophic lateral sclerosis, depression, and cognitive disturbance but the inhibitors of the COX-2 do not exhibit activity in treating the Alzheimer's Disease [21]. The high level of COX-2 and its product induced by it including PGD2, PGE2, PGI2, especially the PGE2 is related to the neuronal diseases. Some prostaglandins can promote the growth of the neurons and some can induce the apoptosis of the neurons, which indicates that the PGs may play crucial roles in certain neuronal disorders. So inhibition of the activity of the COX-2 which can catalyze the synthesis of the PGs with selective inhibitors may treat the neuronal disorders. Many selective inhibitors of COX-2 such as celecoxib and rofecoxib have been found to penetrate into the CNS and can be used to treat the neuronal diseases such as cognitive disorders and depression. So this may be a new and promising way to treat such kind of diseases.

In the CNS, COX-2 can interact with neurotransmitters such as acetylcholine, serotonin, and glutamate, but also participates in the regulation of immune system and in inflammation in the CNS through the effects of the PGs especially the PGE2. Many studies have demonstrated that many neuronal disorders are associated with immunological and inflammatory processes of the neuronal tissues.

Several studies have demonstrated the the neuro-inflammation may play a key role in the neuronal diseases such as amyotrophic lateral sclerosis (ALS). The inflammation in the CNS is different with the system inflammations. The inflammation in the CNS is mediated by the COX-2 dependent pathway. Inhibiting the activity of the COX-2 with its selectively inhibitors may suppress the neuronal diseases.

Immunological dysbalance is believed to be related to the neuronal disorders. Several studies have supported the hypothesis that the immunological dysbalance of immune response characterized with the decreased activation of the typy-1 and increased activation of the type-2 immune response. The type-2 response can induce the generation of the PGE2. The inhibition of the activity of the COX-2 can decrease the PGE2, inhibit the type-2 cytokines and decrease the type-1 cytokines which can balance the type-2 and type-1 response. So the inhibitors of the COX-2 can inhibit the dysbalance of the immune response *via* which can treat the neuronal disorders.

Take cognitive disturbance as an example, cognitive disturbance is a principal feature of the schizophrenia. In the CNS, the structures related to the cognitive disturbance are frontal cortex, amygdale, and hippocampus. All these structure constitutively express the COX-2. It has been discussed that COX-2 can interact with the neurotransmitter acetylcholine, and the cognitive functions are mediated by the cholinergic neurotransmitter system. In animal models the selective COX-2 inhibitor refecoxib showed activity of suppressing the inflammatory reaction in the CNS and decreasing the cholinergic neurons. So refecoxib may inhibit the cognitive disturbance.

Besides from the cognitive disturbance, the COX-2 is also involved in the depression which is also related with the neuro-inflammation. And it has been reported that the refecoxib but not celecoxib have an antidepressive effect.

CONCLUSION

COX-2 is one of the isozyme of the cycloxygenase, which has an extensive distribution in the peripheral tissues and nervous tissuses, which determines that it is a multifunctional enzyme. It has been well known that COX-2 is related to the occurrence of the inflammation and pain induced by the PGs which is the products of the COX-2. The selective inhibitors of the COX-2 have been used to suppress inflammation and pain for a long time. Following the development of the study on COX-2 inhibitors, it has been found that the selective inhibitors of the COX-2 have other functions such as treating glaucoma, preventing and treating many kinds of cancers, suppressing neuronal disorders. Some COX-2 inhibitors can treat glaucoma because of the cross-reaction between the COX-2 and the CA, and this may be a new therapeutic ways in treating glaucoma. COX-2 is overexpressed in many kinds of cancers, which is related to the angiogenesis, apoptosis, etc, so the inhibitors of the COX-2 also can be used to prevent and inhibit cancers. Because of the constitutive expression of the COX-2 in the CNS, it was found to be related with the nervous diseases, so the COX-2 inhibitors may be promising agents in treating the nervous diseases.

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