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Review

Nonsteroidal anti-inflammatory drugs– What do we (not) know about them

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Abstract

Nonsteroidal anti-inflammatory drugs (NSAIDs) reversibly inhibit the functioning of cyclooxygenase (COX) – the rate-limiting enzyme in prostaglandin synthesis, and express anti-inflammatory, antipyretic and analgesic effects. NSAIDs are among the most widely used medications in the world and are prescribed for the treatment of various forms of chronic and acute pain, arthritic conditions, rheumatism, fever/pyrexia, gout, etc. Some of them (aspirin) are used also for prevention of secondary cardiovascular disease due to their ability to suppress platelet aggregation. The mini-review summarizes data about mechanism(s) of action, clinical application and side effects/toxicity of these drugs as well as their potential antitumor activity.

Keywords: Anticancer, Cyclooxygenase, Non-steroidal anti-inflammatory drugs, Prostanoids, Side effets, Toxicity

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (usually abbreviated to NSAIDs) are a group of medications that relieve pain and fever and reduce inflammation. It is estimated that there are more than 1 billion NSAIDs prescriptions in the world every year, and about 30 million people take NSAIDs every day (Ascherio and Schwarzschild, 2016).

The first representative of NSAIDs was introduced into clinical practice in 1899. This is the well-known aspirin (acetylsalicylic acid), put into commercial form by the

Table 1. Biological characteristics of COX-1 and COX-2

Parameter	COX-1	COX-2
Gene size	25 kb	8.6 kb
Exons	15	10
Chromosome	9q33.2	1q31.1
mRNA	2,8 kb	4.1 kb
Gene expression	Constitutive (ubiquitous)	Constitutive (brain, thymus, gut, and kidney) and inducible (sites of inflammation, infection, cancer)
Factors promoting expression	-	cytokines, lipopolysaccharide, phorbolesther, etc
Amino acid composition	599	604
Molecular weight	68.5 kDa	70 kDa
Cell localization	Nuclear envelope, endoplasmic reticulum	Nuclear envelope, endoplasmic reticulum
Cofactors	1 molecule heme	1 molecule heme
Acetylated regions	Ser 530	Ser 516
Substrates	arachidonic acid, aminoacids, γ-linoleic acid	arachidonic acid, aminoacids, γ-linoleic acid, α- linoleic, eicosapentaenoic acid

Yokoyama and Tanabe, 1989; O'Banion, 1991; Hla and Neilson, 1992; Dannhards and Laufer,2000; Lemke and Williams, 2007,Kirkby et al., 2016;Ornelaset. al., 2017

German chemist Felix Hoffmann (1868-1946) in 1897. Hoffman's father suffered from severe debilitating arthritis and this stimulated the work of the scientist in this field. Aspirin™ has made the Bayer company name world-famous like no other drug product. Today aspirin continues to be one of the most commonly used drugs in the world, with more than 40,000 tonnes of "consumption" each year (Dannhardt and Laufer, 2000; Rigas and Tsioulias, 2015).

Mechanism of action

Biological activity of NSAIDs is based on their ability to reversibly suppress the functioning of cyclooxygenase (COX) – the rate-limiting enzyme in prostaglandin synthesis. COX is a homodimeric enzyme responsible for the conversion of arachidonic acid (AA) to prostaglandine H2 (PGH2), a crucial first step for further downstream biosynthesis of prostanoids of significant physiological importance – prostaglandins (PGs – D_2, E_2, $F_{2\alpha}$), prostacyclins (PCs – prostaglandin I_2) and thromboxanes (TXs – thromboxane A_2), that are important mediators of inflammation (process involved in many pathological conditions, including cancer and neurodegeneration), fever and pain. There are two isoforms of this protein in humans – COX-1 and COX-2 (Table 1). COX-1 is found to be constitutively expressed in all tissues and plays a vital role in homeostasis, COX-2 was first found to be an inducible isoform, expressed only at sites of inflammation, infection or cancer. COX-1 regulates platelet aggregation, thrombosis, gastric cytoprotection, kidney functions. In response to inflammatory signals (e.g. IL-1β, TNF-α, lipopolysaccharide), mitogenic or oncogenic stimuli (e.g. phybole esters, v-src) the concentration of COX-2 can be increased up to 10-50 times (Dannhardt and Laufer, 2000; Rigas and Tsioulias, 2015). However, since the initial promising introduction, subsequent scrutiny and re-evalution due to adverse cardiovascular and other side effects of COX-2-selective inhibitors (Katz, 2013), it has been widely established that COX-2 is constitutively present in specific discrete locations and maintains important non-inflamarory-related physiological functions (Kirkby et al., 2016).

A splice variant of COX-1 – referred to also as COX-1v, COX-1b and COX-3 (Hersh, 2005), was first isolated from canine cerebral cortex (Chandrasekharan et al., 2002). The mRNA of this form differs from that of COX-1 by retaining intron 1. In canines, intron 1 is composed of 90 nucleotides, resulting in insertion of 30 amino acids and a functional protein, albeit with different patterns of inhibition than COX-1 and COX-2. In humans this intron contains 94 nucleotides (Schwab et al., 2003), which would lead to a frame shift and completely different amino acid sequence. As a result, the product of translation of this mRNA in humans would be truncated and non-functional (Kis et al., 2005).

Classification

NSAIDs represent a group of more than 20 preparations

Table 2. Classification of nonsteroidal anti-inflammatory drugs

	Group	Subgroup	Example
1.	Acid derivatives	Salicylic acid	Acetylsalicilic acid (Aspirin)
		Phenylacetic acid	Diclofenac, Aceclofenac
		Indoleacetic acid	Indometacin
		Propionic acid	Ibuprofen, Ketoprofen, Dexketoprofen
		Enolic acid (Oxicams)	Meloxicam, Piroxicam, Tenoxicam
		Niftyloacetic acid	Nabumetone
2.	COX-2 selective NSAIDs (Coxibs)		Celecoxib, Rofecoxib*, Etoricoxib, Valdecoxib*, Lumiracoxib

*Cyclooxygenase 2 (COX-2) inhibitors rofecoxib and valdecoxib were withdrawn from the market in 2004 and 2005, respectively, because of their association with cardiovascular problems (Sun et al., 2007).

based on their structure divided into different classes (Table 2) (Rigas and Tsioulias, 2015).

According to their ability to influence the activity of the COX isoenzymes, NSAIDs are divided into two classes:

• Non-selective NSAIDs – significantly suppress both COX-1 and COX-2 isoenzymes (e.g piroxicam) and

• Selective COX-2 inhibitors (called also coxibs) – primarily inhibit the action of COX-2 (e.g. Celecoxib), introduced in clinical practice in 1998.

The ratio between the 50% inhibitory concentration (IC_{50}) values for COX-1 and COX-2 has been used to determine the rate of COX-2 selectivity of these agents. The classification of NSAIDs into these two classes is rather relative than absolute since all of these drugs can inhibit both COX-1 and COX-2 activity in vitro in a concentration dependent manner. Administered at high doses, even the most selective COX-2 inhibitors (e.g. etoricoxib, lumiracoxib) can also suppress COX-1 activity (Patrono, 2016).

And vice versa, aspirin is a traditional non-selective COX inhibitor. However, taken in low doses (75-300mg), aspirin reduces platelet aggregation by inhibiting predominantly more than 70% COX-1 and less than 5% of COX-2 (Blanco, 1999, Dovizio, 2013). Higher doses (>1200mg) lead to pronounced anti-inflammatory and analgesic effects due to inhibition of both COX forms (Ornelas et al., 2017).

Clinical application

The clinical use of NSAIDs is based on their main therapeutic effects and can be summarized in three main directions (Ho et al., 2018; Ghlichloo and Gerriets, 2019):

- For analgesia in acute and chronic pain conditions (eg headache, dysmenorrhea, toothache, postoperative pain). The ability of NSAIDs to induce peripheral analgesia by inhibiting cyclooxygenase activity and prostaglandin synthesis is well documented. In addition, there are data suggesting the central analgesic effects of NSAIDs based on various mechanisms including modulation of inhibitory fast synaptic currents in lamina I and II of the dorsal horn, glycine-dependent modulation of pain, effect on β-endorphin (Cashman, 1996; Luan et al., 2017; Vuilleumier et al., 2018).
- Antipyretic effect. Fever is induced by binding of prostaglandin G2 (PGE2) to EP3 receptors on neurons in the preoptic anterior hypothalamic area, which control thermoregulation. Through exposure to exogenous pyrogens (pathogen-associated molecular patterns), cells of the immune system produce and release endogenous pyrogens (interleukins, TNFα and others) to stimulate PGE2 synthesis in the above-mentioned hypothalamic area. NSAIDs's antipyretic activity is a result of their ability to inhibit prostaglandin synthesis. However, it should be emphasized that in the cases of abnormal elevation of temperature, independent of the COX-mediated pathway, like malignant hyperthermia and heat stroke, NSAIDs have no effect (Osafo et al., 2017).
- For anti-inflammatory (mainly anti-exudative) action in acute and chronic inflammatory conditions (rheumatoid arthritis, gout, etc.).

Low-dose aspirin regimens are widely administered for prevention of secondary cardiovascular disease due to their ability to suppress platelet aggregation– as a result of reduced production of the potent vasoconstrictor and platelet activator thromboxane A2 (Ansa et al., 2019). It has been suggested that selective COX-2 inhibitors do not affect platelet aggregation because the enzyme COX-2 is not expressed in these cells. However, the role of aspirin in primary cardiovascular disease remains controversial (Raber et al., 2019). Aspirin is used also in women undergoing assisted reproductive technology with the aim of optimising the chance of live birth (Siristatidis et al., 2016).

Neuroinflammation plays an important role in neurodegenerative processes and there are data that NSAIDs possess the potential to decrease the risk for Alzheimer's disease (AD) (McGeer et al., 1990; Benito-León et al., 2019) and Parkinson's disease (Etminan and Suissa, 2006). NSAIDs have been reported to inhibit the activity of the enzyme gamma-secretase that is responsible for cutting the transmembrane domain of the amyloid β-protein precursor to form the amyloid β-protein (Aβ), that accumulates in the brain in Alzheimer's disease – this protease has been recognized as a target for AD

treatment (Wolfe, 2012; Cudaback et al., 2014). In addition NSAIDs modulate the phagocytic activity of microglia, contributing to the removal of plaque and debris (Lim et al., 2000; Koenigsknecht-Talboo et al., 2005). The results obtained in a recent study indicate that NSAIDs intake was associated with 71% decreased risk of AD mortality in older adults (Benito-León et al., 2019).

There are data indicating that COX-2 inhibitors (e.g. celecoxib) and aspirin may be helpful in treating the symptoms of neuropsychiatric disorders including schizophrenia (Sethi et al., 2019; Müller, 2019). A meta-analysis of randomized, double-blind, placebo-controlled trials reveal that celecoxib appears to be an efficacious and safe treatment in improving psychotic symptoms, particularly in first-episode schizophrenia. (Zheng et al., 2017). It has been known since the 1970s that aspirin can reduce the risk of pre-eclampsia (Mirabito and Colafella et al., 2019).

Side effects/Toxicity

The main adverse reactons of NSAIDs affect gastrointestinal (GI) tract and kidneys, cardiovascular system (associated mainly with selective COX-2 inhibitors), central nervous system and platelet functions. Up until 1999, GI toxicity represented the main safety concern of NSAIDs therapy. The symptoms range from milder (dyspepsia, pain) to significantly more serious manifestations including bleeding and ulceration (Rigas and Tsioulias, 2015; Zavodovsky and Sivordova, 2018; Walker and Biasucci, 2018; Yang et al., 2017). For example, it has been reported that the prolonged use of aspirin increases the risk for GI bleeding (1.6-3.1 times increased relative risk compared to those who did not use aspirin) and elevates the risk for nausea and dyspepsia (Roderick et al., 1993). The toxicity of aspirin increases with increasing dose of the drug and with increasing age of the patient (Serebruany et al., 2004).

The prevalence of nephrotoxicity in patients treated with NSAIDs is relatively low, the side effects are sometimes transient and often reversible upon drug withdrawal. Their incidental rate and severity increase in patients with risk factors such as diabetes, heart failure, renal dysfunction and in the elderly (Harirforoosh and Jamali, 2009).

Prostaglandins regulate vascular tone and salt and water homeostasis in the mammalian kidney and play an important role in renal hemodynamics (Smith, 1992). The most common adverse reaction of NSAIDs is increased sodium reabsorption that causes peripheral edema through the inhibition of prostaglandins (PG2). Hyperkalemia is also observed. The side effects range from electrolyte retention and reduced glomerular filtration to nephritic syndrome and chronic renal failure (Whelton, 1999; Harirforoosh and Jamali, 2009; Mérida and Praga, 2019; Gunaydin and Bilge, 2018; Bakhriansyah et al., 2019).

NSAIDs and especiaaly selective COX-2 inhibitors (coxibs) have been associated with cardiovascular adverse effects such as increased blood pressure and elevated risk of atherothrombotic events (Coxib and traditional NSAID Trialists' (CNT) Collaboration et al., 2013; Patrono, Baigent, 2014). The mechanism of their cardiovascular toxicity is not fully understand but is not surprising since COX-2 enzyme produces biologically active moleculs (such as PGE2 and PGI2) that are involved in regulation of various life supporting processes including renal haemodynamics, blood pressure, endothelial thromboresistance as well as in pathophysiology of pain and inflammation (Smyth et al., 2011; Patrono and Baigent, 2014; Dovizio et al., 2015). The interaction between prostanoids and T cells has been recognized as a possible factor, mediating elevated cardiovascular disease risk with NSAID use (Khan et al., 2019). Cardiovascular side effects, confirmed in long-term placebo-controlled studies, led to the withdrawal of rofecoxib and valdecoxib from the market in the United States and Europe (Sun et al., 2007).

NSAIDs are the most common drugs involved in hypersensitivity reactions (Planca-Lopez et al., 2019).

Some prostaglandins exert important regulatory effects on respiratory epithelial cells. Decreased PG production can induce leukotriene pathway, causing bronchoconstriction. A special case about COX inhibition on the respiratory system is the so called aspirin-exacerbated respiratory disease (AERD, known also as NSAIDS exacerbated disease) consisting of asthma, aspirin sensitivity, and nasal polyps (known as Samter's triad). AERD affects approximately 0.3-0.9% of the general population in the USA and approximately 7% of asthmatic patients (Kim and Cho, 2018; Laidlaw, 2018; Li et al., 2019).

Prostaglandins (especially prostaglandins E2 and D2) have been found to be involved in bone remodeling by mediating the control of osteoblast and osteoclast functions. PGs have a mitogenic effect on osteoclasts and stimulate their biological activity (Paralkar et al., 2002; Hadjidakis and Androulakis, 2006). On the other hand, there are data demonstrating the capacity of PGs to stimulate the multiplication and differentiation of osteoblasts and to express anabolic effects of the bone (Machwate et al., 2001). Prostaglandins act as paracrine regulators of the bone remodeling cycle (Kenkre and Bassett, 2018). NSAIDs have been suggested as a risk factor for bone healing impairment, and their administration should be avoided in high-risk patients (Pountos et al., 2012). The influence of PGE2 and PGD2 on proliferation and osteogenic capacity of human mesenchymal stem cells has been innestigated (Ern et al., 2019)

Drug interactions

Drug interactions (pharmacokinetic and/or pharmaco-dynamic) with NSAIDs have been reported some of which may be clinically significant. NSAIDs can displace other drugs from their plasma protein binding sites, inhibit their metabolism or interfere with their renal excretion (Verbeeck, 1990). Concomitant use of NSAIDs with some commonly used medications – corticosteroids, aldosterone antagonists, selective serotonin reuptake inhibitors or other antiplatelet and anticoagulant medications, produces significant excess risk of upper gastrointestinal bleeding when used in combination (Chan, 1995; Delaney et al., 2007; Cheetham et al., 2009; Masclee et al., 2014; Tielleman et al., 2015). On the other hand, a number of treatments are known to affect the rate or extent of aspirin absorption. NSAIDs can adversely influence blood pressure control, particularly during the use of angiotensin-converting enzyme (ACE) inhibitors, diuretics, and beta blockers (Whelton A., 1999).

New/NonconvetionalNSAIDs

A number of research groups have focused their efforts on the design and development of new NSAIDs (in most cases using various chemical modifications) with a stronger therapeutic effect and a better safety profile, some of which are in preclinical and initial clinical trials (Rao et al., 2010; Rigas and Tsioulias, 2015):

- Nitric oxide releasing NSAIDs (e.g. nitro-aspirin) - Nitric oxide (NO) is known to play a protective role in the gastrointestinal tract by maintaining gastric mucosal integrity through increasing the mucose secretion and mucosal blood flow as well as inhibiting neutrophil aggregation. In preclinical studies NO has been found to repair NSAID-induced damage. In addition, epidemiologic studies have shown that the use of NO-donating agents with NSAIDs or aspirin result in reduced risk for gastrointestinal bleeding (Wallace et al., 2002; Lanas, 2008). NO exhibits also beneficial effect on the cardiovascular system by inhibiting platelet aggregation and adhesion (Mitchell and Warner, 2006; Ruschitzka et al., 2000).
- NSAIDs with phosphatidylcholine (PC) (e.g. PC aspirin). PC is the most abundant of the gastric phospholipids that form extracellular lining on the mucus gel layer protecting in this way the underlying epithelium from gastric acids;
- Esterified/Amidated NSAIDs (e.g. des-methyl (DM)-sulindac);
- Pegylatedphospho-NSAIDs (e.g. pegylated phosphor-ibuprofen) – polyethylene glycol protects ibuprofen from the hydrolytic action of esterases.

Leukotrienes and lipoxygenases (LOXs – enzymes that play a crucial role in leukotriene biosynthesis) have been recognized as potential targets for the treatment of a wide range of pathologies including asthma, cardiovascular diseases, cancer, neurodegenerative disorders (e.g. Alzheimer's disease) and various inflammatory conditions (Charlier and Michaux, 2003; Fourie, 2009; Poeckel and Funk, 2010; Colazzo et al., 2017; Haeggström, 2018). It has been hypothesized that blocking the arachidonic acid metabolism by NSAIDs could result in generation of proinflammatory leukotriens and lipoxins via the LOX signaling pathway. This reaction in turn is related to some of the side effects presented by NSAIDs. Several dual COX/LOX inhibitors have been prepared in order to overcome this problem.

It has been reported that Cu(II) complexes with NSAIDs exhibit increased anti-inflammatory activity and at the same time reduced gastrointestinal toxicity compared to parent drug products (Roy et al., 2006).

NSAIDs and cancer

Preclinical and clinical studies have shown a benefit of NSAIDs in reducing risk for at least some types of cancer (e.g. colorectal cancer as well as cancers of the breast, lung, etc.) (Smalley and DuBois, 1997; Harris et al., 2003; Arun and Goss, 2004, Cha et al., 2006; Arber et al., 2006; Rostom et al., 2007, Thun and Blakard, 2009; Bosetti et al., 2012, Chan et al., 2012). A large number of epidemiological studies indicate that continued use of NSAIDs leads to a significant reduction in adenomatous polyps, disease incidence, reccurence and death from colorectal cancer (Cruz-Correa et al., 2002; Rostom et al., 2007; Rayburn et al., 2009; Garcia-Albeniz and Chan, 2011).

It has been suggested that antitumor effect of NSAIDs is pleiotropic (Shiff and Rigas, 1999a, 1999b; Kashfi and Rigas, 2005; Schror, 2011; Stolfi et al., 2013) and includes at least three groups of mechanisms of action: i) related to suppression of COX activity; COX independent pathways; influencing cancer stem cells (CSC).

The infiltration of tumors with white blood cells was described for the first time by the German pathologist Rudolf C. Virchow in 1863 (Balkwill and Mantovani, 2001). Today it is widely accepted that (chronic) inflammation is important for tumorigenesis and is one of the cancer hallmarks (Hanahan and Weinberg, 2011). Inflammatory cells and mediators can be detected in most tumor tissues, where they modulate the functioning of both tumor and stromal cells and contribute to the establishment of a tumor-promoting microenvironment (Coussens et al., 2013).

The "relationship" between of prostaglandins and cancer was initially reported in 1986 (Botha et al., 1986) when it was found that PGE and PGF production influence the invasive and metastatic potential of human esophageal carcinoma cells in athymic nude mice. Increased levels of prostaglandins (PGE2, PGD2) have

been proved in a wide range of cancers and it has been suggested that these molecules are involved in signaling pathways important for cancer induction and progression (Wang and Dubois, 2010; Nakanishi and Rosenberg, 2013; Sha et al., 2012; Oshima and Oshima, 2012; Kalinski, 2012). Colorectal cancer is characterized by elevated levels of prostaglandin E2 - PGE2 (Rigas et al., 1993), which stimulates cancer cell proliferation (Qiao et al., 1995) and contributes to their resistance to radiation and chemotherapy (Bijnsdorp et al., 2007; Kuipers et al., 2007) - effects that are blocked by NSAIDs (Shiff et al., 1996). PGE2 has been reported as potent therapeutic target for treatment of colon cancer (Karpisheh et al., 2019). In addition, thromboxane A2 (TXA2) has been found to be involved in pathogenesis of colorectal cancer (Li et al., 2015; Dovizio et al., 2012) as well as in modulation of multiple myeloma (Liu et al., 2016) and lung cancer (Li et al., 2009) cell proliferation.

Cyclooxygenase is the best studied molecular target of NSAIDs. Of particular interest is the COX-2 enzyme (inducible cyclooxygenase) which is not surprising because the expression of this enzyme is associated with inflammatory conditions and cancer (Williams et al., 1999) and has been demonstrated to be overexpressed in many solid tumors, such as colorectal cancer, cancers of the prostate, mammary gland, pancreatic and lung cancer (Liu et al., 2015). COX-2 is released by cancer-associated fibroblasts, macrophage type 2 cells, and cancer cells to the tumor microenvironment (Hashemi and Goradel et al., 2019). The enzyme promotes tumor growth and suppresses antitumor immunity (Liu et al., 2015; Pang et al., 2019). Members of mitogen-activated protein kinase (MAPK) family, epidermal growth factor receptor (EGFR), and nuclear factor-κβ are main upstream modulators for COX-2 in cancer cells (Hashemi and Goradel et al., 2019).

COX-2 enzyme has been proposed as a promising target for cancer therapy (Yu et al., 2016).

Unlike COX-2, the role of COX-1 (constitutive cyclooxygenase) in cancer has generally received less attention. However, increased COX-1 expression has been occasionally detected in several cancers, including colorectal cancer, head and neck cancer, esophageal cancer, breast cancer, cervical cancer, haematological tumors, etc. (Rouzer and Marnett, 2009; Pannunzio and Coluccia, 2018).

Increasing number of evidence indicate that both isoforms - COX-1 and COX-2, play an important role in cancerogenesis (Chulada et al., 2000; Tiano et al., 2002; Pannunzio and Coluccia, 2018). Something more, there are data that at least in some cases (e.g. serous ovarian carcinoma) COX-1 enzyme may play a pivotal role (Kino et al., 2005; Lau et al., 2010; Pannunzio and Coluccia, 2018). COX-1 was first identified as ovarian cancer marker in 1995 (Lee and Ng, 1995) and later the overexpression of this enzyme has been proven in various human, mouse and avian (han) models of ovarian cancer (Gupta et al., 2003; Daikoku et al., 2005, 2006; Hales et al., 2008; Urick and Johnson, 2006; Eilati et al., 2012).

While the biological activity of selective COX-2 inhibitors has been extensively investigated, the number of the available COX-1 selective inhibitors is extremely limited and a very small part of them have been tested for antitumor activity (Tortorella et al., 2016; Vitate et al., 2016; Pannunzio and Coluccia, 2018),

COX-independent mechanisms of antitumor activity of NSAIDs are related to their ability to influence Wnt signaling pathway, DNA mismatch repair systems, to down-regulate proto-oncogenes (such as c-myc), transcription factors (such as nuclear factor kappa B - NF-kB, peroxisome proliferator-activated receptor delta - PPAR-δ), to induce oxidative stress, etc (Adachi et al., 2007; Rigas and Tsioulias, 2015; Osafo et al., 2017; Gunaydin and Bilge, 2018).

COX-2 plays an important role in cancer stem cell biology (Pang et al., 2016). Experimental data indicate that the antitumor/chemopreventive action of aspirin and other NSAIDs may be due to the selective induction of apoptosis in human intestinal stem cells with an altered Wnt signaling pathway (Qiu et al., 2010). PGE2 has been shown to stimulate stem cell survival in adenomas and colon cancers (Al-Khariusi et al., 2013).

In their attempts to elucidate the antitumor effect of NSAIDs, many researchers emphasize that the mechanism of action should also involve to some degree DNA, and consecuently affect the processes of transcription and translation (Subbaramaiah and Dannenberg, 2003). However, most NSAIDs are anions at physiological pH – an obstacle which would make their access and interaction with the polyanionic strands of DNA more difficult. That is why this interaction between DNA and NSAIDs is reported only by a limited number of studies (Neault et al., 1996). The combination of NSAIDs and metal ions could help overcome the electrostatic repulsion between DNA and the deprotonated negatively charged form. In 2006 Roy et al. reported that meloxicam and piroxicam can form complexes with Cu(II) at physiological pH and proposed a hypothetical model of interaction between these new compounds and DNA, which most likely involves intercalation (Roy et al., 2006).

There have been various complexes of Cu(II) with NSAIDs synthesized and characterized. It has been found that these compounds express a more pronounced anti-inflammatory and antitumore activity, but possess side effects (reduced gastrointestinal toxicity) to a lesser extent compared to the individual initial compounds (Weder et al., 2002; Dillon et al., 2003; Bonin et al., 2010, Puranik et al., 2011).

Many studies report that the tandem intake of copper and NSADs has a synergetic action (Crouch et al., 1985). It is also obsverved that that inflammation carries the need for more Cu(II), which is compensated though the increased intestinal absorbtion and/or decreased

intestinal excretion of Cu(II) (Milanino et al., 1993). The mechanism of action of many NSAIds probably includes chelation of some biologically activve metal ions (Samara et al. 1998), like Cu(II), Zn(II) and Co(II), which helps the metal navigate to the site of inflammation and pain,

Challenges

Some of the major challenges regarding anticancer activity of NSAIDs are listed below:
- to establish the NSAIDs with the most promising antitumor properties as well as the most effective doses, suitable/reasonable regimens and schedules;
- to investigate if they could be used in combination(s) with other anticancer agents and/or radiotherapy;
- Safety – in order to express their cancer prevention potential the NSAIDs will be used for a long period of time, which would require to carefuly weigh the risks versus the benefits and possibly search for suitable new solutions to already known negative effects from long-term usage of NSAIDs;
- to determine the scope of action that current NSAIDs can effectively contribute in cancer preventation/ treatment
- rational selection of the target population groups that may benefit from antitumor prevention and/or treatment with NSAIDs.

One of the main advantages of NSAIDs is the fact that these drugs have been used intensively in the treatment of inflammation, pain and fever for many years (more than 100 years in the case of aspirin), they have well-studied and established pharmacokinetics, pharmaco-dynamics and toxicological profile, which will facilitate their entry (with proven efficacy) into other branches of medicine, including oncology. Such “repurposing” of non-cancer drugs for the treatment of neoplastic diseases is one of the most promising strategies in the fight against cancer.

Last, but not least. NSAIDs are a very good example of the so-called multitargeted agents that could be effective in the treatment of various diseases. For example, aspirin is used also for prevention of cardiovascular diseases, cancer and neurodegenerative disorders (such as Alzheimer’s disease) - the most common, significant and deadly pathologies, especially in elderly people. That is why further research in this area could not only give new insight into the complex molecular relationships between these diseases, but may also have a wider impact on future multi-target drug development.

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