COPPER COMPLEXES OF NON-STERoidal ANTI-INFLAMMATORY DRUGS

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Abstract

Plasma concentrations of low molecular weight copper-containing components are known to increase in response to various diseases such as arthritis, epilepsy, and cancer. Each of these diseases is recognized as having inflammatory components. Experiments on animals have shown that administration of low molecular weight copper complexes produced anti-inflammatory effects. Based on these results it was confirmed that the elevation of plasma copper-containing components represents a physiologic response which may lead to remission. Promotion of this physiologic response is a valid approach to the treatment of the diseases with inflammatory components. It was thus confirmed that copper complexes, a unique class of potentially more therapeutically useful anti-arthritic agents have both anti-inflammatory and antiulcer activities. However, the use of discrete coordination complexes in drug delivery is at a very early stage of development mainly because of the chronic ingestion of NSAIDs which in turn increases the risk for gastrointestinal complications, ranging from dyspepsia to gastrointestinal bleeding, obstruction, and perforation. On the other hand, there has been significant progress in the use of coordination copper complexes in drug delivery revealing their unique advantages over many other drug delivery systems.

Key words: copper, NSAID, anti-inflammatory drugs, cyclooxygenase, prostaglandine (PG)

1 NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs) are also known as non-steroidal anti-inflammatory agents/analgesics (NSAIAs) or non-steroidal anti-inflammatory medicines (NSAIMs). These drugs among a broad range of other effects have a similar eicosanoid-depressing and anti-inflammatory action as steroid drugs (Hawkey, 1999). Until recently, the non-steroidal anti-inflammatory drugs included some of the most commonly used drugs worldwide. These drugs have proved to be effective in the treatment of acute and chronic painful and inflammatory musculoskeletal conditions (Simon et al., 2005).

In this contribution, we shortly summarise current knowledge about copper based non-steroidal anti-inflammatory drugs (Cu-NSAIDs), their chemical composition, suggested mode of action, the fields of medical applications as well as the possible adverse effects of their use.

2 NSAIDs - mechanism of action

NSAIDs act by preventing the conversion of arachidonic acid to intermediate and terminal prostaglandins (PG) (Figure1). The terminal prostaglandins are extremely pro-inflammatory and interface with other pain-producing mechanisms. Prostaglandin inhibition occurs because the NSAIDs affect the converting enzyme cyclooxygenase (COX) (Polisson, 1996; Gasparini et al., 2004). Different variants of COX have been described: COX-1, which is constitutively expressed in nearly all tissues and it possesses mainly ‘housekeeping’ functions; COX-2, which is induced at injury sites by inflammatory stimuli and play a key role during inflammation; and finally the recently identified COX-3, whose function is still unknown. Based on this general functional distinction, an effort was made to design drugs which selectively inhibit COX-2 and thereby are devoid of the adverse effects associated with the blockade of both COX-1 and COX-2, e.g. gastrointestinal lesions.
Fig. 1 Schematic diagram for the conversion of arachidonic acid to eicosanoids (PG-prostaglandins, TXA-thromboxane) by the cyclooxygenase (COX) and the major site of action of the NSAIDs (non-steroidal anti-inflammatory drugs), (Dubois et al., 2005, modified).

Polisson (1996) has divided NSAIDs according to their abilities to inhibit specific types of COX-isoenzymes. Flurbiprofen, ibuprofen, and meclofenamate are the NSAIDs judged to be equally potent against COX-1 and COX-2. Those NSAIDs that preferentially inhibited COX-1 (10-30 times greater than COX-2) were piroxicam, indomethacin, and sulindac. Methoxynaphthyl acetic acid, which is the active moiety of nabumetone, preferentially inhibited COX-2 (about 7 times greater than COX-1). While non-selective NSAIDs inhibit both COX-1 and COX-2 enzymes to a significant degree, selective NSAIDs inhibit COX-2 enzymes found at sites of inflammation (COX-2) more than the type that is normally found in the stomach, blood platelets, and blood vessels (COX-1), (Mizushima, 2010).

Basha et al. (2011) have suggested the classification of NSAIDs based on chemical structure to the six groups– salicylates, acetic acids, oxicams, propionic acids, fenamates, pyrazoles, (Figure 2).

Fig. 2 Structural classes of NSAID: A – salicylates (e.g. Salicyl salicylate / Salsalate), B – acetic acids (e.g. Indomethacin), C – oxicams (e.g. Ampiroxicam), D – propionic acids (e.g. Ibuprofen), E – fenamates (e.g. Tolfenamic acid), F – pyrazoles (e.g. Phenylbutazone), (Basha et al., 2011).
3 Copper-based NSAIDs

Transition metals have been used as anti-inflammatory and anti-arthritic agents. Due to the physiological importance of copper (Cu) and its unique redox activity, many different Cu complexes and Cu chelators have been synthesized and investigated for their therapeutic and diagnostic potential in human disease (Angelusiu et al., 2009; Duncan, White, 2012; Švorec et al., 2009). Copper complexes of NSAIDs represent a large group of coordination compounds, interesting from various perspectives that find their application in various fields, especially in medicine, pharmacology, and the material industry. NSAID acids bind to the central atom Cu (II) mainly due to the carboxyl group(s). The copper carboxylates drugs constitutes an important element of anti-inflammatory and anticancer agents, some of which are a part of several commercially available drugs (Weder et al., 2002).

Sorenson (1976) found out that Cu chelates were the intermediates responsible for the observed anti-inflammatory activity of both cupric acetate and chelating compounds. The Cu chelates were more active than Cu in the form of cupric acetate and the parent chelating compounds, that’s why they were considered as the active forms of the anti-inflammatory agents. The authors have confirmed that Cu chelates are active forms of anti-arthritic drugs. In 1984 Sorenson et al. affirmed hypothesis that the elevation of plasma copper-containing components represents a physiologic response which may lead to remission. It was confirmed as a valid approach to the treatment of arthritis, epilepsy, cancer, and other diseases with inflammatory components.

Copper(II)-complexes, including Cu-NSAIDs, exhibit significant anti-inflammatory activities as well as SOD mimetic activity. Some researchers propose that NSAIDs, in addition to their inhibitory effects on the synthesis of PGs, may also inhibit the production, or act as scavengers of free radicals in vivo. Whatever the mechanism of anti-inflammatory action of Cu(II)-complexes in vivo, their beneficial function has long been recognized and their clinical effect has been investigated extensively over the last 50 years (Weder, 2002).

Duncan and White (2012) have also confirmed the ability of copper complexes to increase SOD activity, leading to relief of oxidative stress. It is obvious that the ability of Cu to participate in redox reactions combined with the ability of the complex to allow enhanced Cu delivery results in many efficacious compounds. Omoto et al. (2005) studied utilization of tetrathiomolybdate (TM) in a rat model of adjuvant arthritis. TM administration resulted in decreased severity, as demonstrated by a reduction of inflammatory cell invasion into joint tissues. Ma and Moulton (2011) demonstrated that Cu-NSAIDs exhibited enhanced efficacy and reduced side effects as their parent drugs. They first developed an approach to rationally modify the lipophilicity and solubility of Cu-NSAIDs species by forming mixed-ligand coordination complexes. By tuning the lipophilicity and solubility of a drug complex, its drug delivery pattern should be modified accordingly. Bombardier et al. (2000) attested that in patients with rheumatoid arthritis, treatment with rofecoxib, a selective inhibitor of COX-2, is associated with significantly fewer clinically important upper gastrointestinal events than treatment with naproxen, a nonselective inhibitor.

4 Applications in medicine

Inflammation is a protective response of the body to infection, injury, or a chronic medical problem. Anti-inflammatory medicines are available in two categories, steroidal and non-steroidal, and are prescribed to reduce inflammation. Steroid anti-inflammatories are powerful medications, which are based on hormonal substances, like cortisone. These medications have a stronger anti-inflammatory response than the non-steroidal medicines. The steroidal anti-inflammatories can have these side effects: loss of bone, cataract, problems with the ability to fight infection, swelling and weight gain, mood changes, high blood pressure and problems with the bone marrow. Yajima et al. (2007) described the history of discovery NSAIDs when
aspirin was synthesized as the first NSAID a century ago, and since then several types of NSAID have been developed. They have excellent analgesic action with high safety; therefore, they are used to treat pain associated with many diseases. In the area of orthopedics, long-term therapy of these drugs is prescribed not only for patients with acute conditions, such as trauma, but also for the treatment of chronic diseases, such as arthropathies, including rheumatoid arthritis and low back pain. However, gastric mucosal lesions have long been identified as a side effect of NSAIDs.

Most people tolerate NSAIDs without any difficulty. A major factor limiting their use is gastrointestinal toxicity. Although endoscopic studies reveal that gastric or duodenal ulcers develop in 15 to 30 percent of patients who regularly take NSAIDs—the chief concerns are clinically important gastrointestinal problems, such as bleeding. It has been estimated that more than 100,000 patients are hospitalized and 16,500 die each year in the United States as a result of NSAID-associated gastrointestinal events (Bombardier et al., 2000). Huski and Simon (2002) in their research also referred that from 5 to 7 percent of hospital admissions are related to adverse effects of drugs, and of these hospitalizations, those that result from gastrointestinal, nervous system, renal, or allergic effects of aspirin or the non-aspirin NSAIDs (NS-NSAIDs) are responsible for approximately 30 percent. Simon et al. (2005) observed that all drugs which inhibit COX-2 activity, both COX-2 selective inhibitors and NS-NSAIDs, may increase the risk for thromboembolic events through very complex physiologic and pathologic mechanisms, there remains the important clinical decision making process which should reside with the patient and their health care provider in deciding which therapies are most important for their unique problem. Kukanich et al. (2012) confirmed that the newer veterinary approved NSAIDs have a lower frequency of gastrointestinal adverse effects in dogs compared to drugs such as aspirin, ketoprofen and flunixin, which may be due to differential effects on the COX isoforms. NSAIDs remain the cornerstone of oral therapy for osteoarthritis unless contraindicated by intolerance, concurrent therapies or underlying medical conditions. NSAIDs are also effective and frequently used for the management of post-operative pain.

Dimiza et al. (2011) confirmed chemo-preventive and anti-tumourigenic activity of NSAIDs by reducing the number and size of carcinogen-induced colon tumours and exhibiting a synergistic role on the activity of certain antitumour drugs. Many studies have also reported that NSAIDs induce the apoptosis of colon, breast, prostate, human myeloid leukaemia and stomach cancer cell lines. Phospho-nonsteroidal anti-inflammatory drugs (Phospho-NSAIDs) represent novel NSAID derivatives with improved anticancer activity and reduced side effects in preclinical models. Wong et al. (2011) studied the metabolism of phospho-NSAIDs by carboxylesterases, and assessed the impact of carboxylesterases on the anticancer activity of phospho- NSAIDs in vitro and in vivo. Their results showed that carboxylesterase mediates that metabolic inactivation of phospho-NSAIDs, and the inhibition of carboxylesterases improves the efficacy of phospho-NSAIDs in vitro and in vivo.

5 Conclusion

The Cu complexes of NSAIDs appear to be promising for veterinary and medical use due to the reduced gastrointestinal toxicity documented by the successful long term veterinary applications and the anti-inflammatory activity. The mode of action of the NSAIDs is primarily attributed to blockage of PG synthesis as a result of inhibition of COX-enzyme system. However, a number of other potential sites of action are discussed as well. In view of the presented current achievement in the field of NSAID drugs, it appears rational to prepare less toxic and effective Cu-NSAIDs. The more complex approach to open new horizons in this field including calculations on structure – activity relationships is awaited. In our work we plan to prepare a series of copper (II) complex compounds with carboxylate ligands and to
study their SOD-mimetic activity spectrophotometrically using Nitro-Blue tetrazolium (NBT) assay with the xanthine-xanthine oxidase system. For the complexes where a suitable monocrystal is obtained, X-ray structural analysis will be performed. Quantitative structure-activity relationship (QSAR) analysis will be employed to determine physico-chemical properties of complexes relating to their biological activity.

6 References


