Proceedings of the 3rd International Conference on Modern Medicine and Global Health
DOI: 10.54254/2753-8818/2025.24230

Comprehensive Overview: The History, Structure, Composition, and Mechanism of Ibuprofen

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Abstract: One typical non-steroidal anti-inflammatory medicine (NSAID) in the home is ibuprofen and this paper will discuss the aforementioned organic compound. In this work, the history, structure and composition, mechanism, binding and metabolism of ibuprofen are covered. The two researchers will attempt to explain different stages of the development of the drug as well as research surrounding the drug. Afterwards, the paper will cover functional groups, bonds, enantiomers of the drug. Lastly, the paper will delve into the more intricate workings of ibuprofen including the process of different synthesis of prostaglandin, ranging from $PGF_{2\alpha}$, PGE_2, PGD_2 to TXA_2, distribution of different prostaglandins in different human issues and functions of prostaglandins, differences between COX-1 and COX-2, how COX is binded, and primary and secondary metabolism.

Keywords: ibuprofen, structure, prostaglandin, COX, metabolism.

1. History

Nowadays, Ibuprofen is widely recognized as one of the most common household drugs. The story of ibuprofen starts when two Boots Pure Drug Company Ltd. employees, pharmacist and pharmacologist Stewart Adams and scientist John Nicholson, file a patent application for the chemical 2-(4-isobutylphenyl) propionic acid. It was granted in 1962, as mentioned in the Pharmaceutical Journal.[1]. Later, Ibuprofen first brought into the UK market in 1969 under the brand name Brufen, a prescription medication.

Since then, ibuprofen was popularized and remains a drug inside every home. Various studies have come out about additional effects of the drug. Some include trials conducted in 1995 that demonstrate how high ibuprofen dosages slow down the progression of lung disease in cystic fibrosis patients by preventing the release of lysosomal enzymes and the migration, adhesion, swelling, and aggregation of neutrophils. Later in 2005, Journal of the National Cancer Institute showed that long-term daily ibuprofen use is linked to a 51% increased risk of breast cancer [2] and Ann Neurol proposed that ibuprofen usage on a daily basis may reduce the incidence of Parkinson's disease, according to an epidemiological study [3]. In 2006, the European Medicines Agency concluded that A slight increase in the absolute risk of thrombotic events may be linked to NSAIDS. Two years later, Neurology discovered that using ibuprofen for longer than five years lowers the risk of Alzheimer's disease by 44% [4]. Most recently, European Heart Journal-Cardiovascular Pharmacotherapy have come out

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with results showing ibuprofen increases the risk of heart disease. [5] More research remains to be done on the drug and new information is found with every passing year.

2. Structure & composition

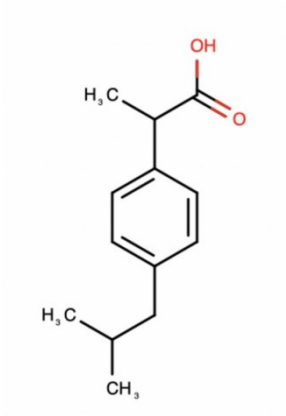

Figure 1: Structure of ibuprofen [6]

Ibuprofen is a useful and important chemical compound since it is used to moderate pain, fevers, headaches, and inflammation. NSAIDs (including ibuprofen), which is a class of drugs used to inhibit cyclooxygenase (COX) to reduce inflammation. The structure of ibuprofen is shown in figure 1. In the compound, are C-C covalent bonds.O-H bond and C-O bond. It contains three different functional groups, which are alkanes, carboxylic acid and benzene. In the benzene, each C-C bond has the same bond length, bond angle and bond enthalpy, so it is a stable structure. Benzene and an isobutyl group ($(CH_3)_2CHCH_2$) are linked to a propanoic acid, which makes ibuprofen stable and bioactive. The structure of ibuprofen enables it to block COX which can produce prostaglandins, the chemicals that lead to inflammation and pain.

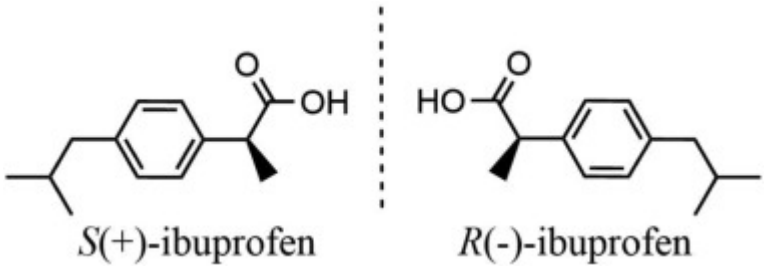

Figure 2: Enantiomers of ibuprofen [7]

There exists a chiral center with an ibuprofen molecule meaning that 2 enantiomers exist, the (R)-enantiomer and the (S)-enantiomer, which are shown in figure 2. The most typical form of ibuprofen is a racemic mixture which consists of an equi-molar combination of the two enantiomers. Obvious differences exist between the 2 isomers, when it comes to prostaglandin inhibition, the (S) isomer is 160 times more active than the (R) enantiomer. Other studies have shown that the (S)-enantiomer has the ability to inhibit both COX-1 and COX-2 while the (R)-enantiomer can inhibit COX-1, albeit to a lesser extent, and it has no effect on COX-2. For this reason, the (S)-enantiomer has been available in recent years as a separate drug.

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3. Mechanism

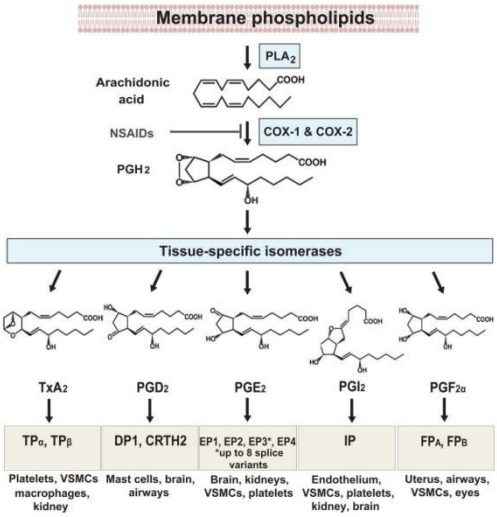

Figure 3: Process of prostaglandin synthesis [8]

Ibuprofen works by decreasing the synthesis of prostaglandins. Prostaglandin is a group of physiologically active substances that can affect hormones in animals, as mentioned by Encyclopedia Britannica. [9] As shown in figure 3, the phospholipids of the cell membrane are first hydrolyzed to arachidonic acid (AA) with the reaction of phospholipase A, (PLA). When AA is formed, it is metabolized through COX-1 and COX-2 and thus prostaglandin H (PGH,) is formed. After that, different synthases can then lead to other productions of prostaglandins. For example, the prostacyclin synthase will produce PGI_2, prostaglandin F synthase, prostaglandin E Synthase and prostaglandin D synthase can produce $PGF_{2\alpha}$, PGE_2, PGD_2, respectively, and thromboxane synthase generates TXA_2. Hence, many different forms of prostaglandins are formed.

Different prostaglandins are responsible for distinct functions. For example, PGI_2 regulates cardiovascular health. It prevents platelet aggregation and relaxes the vascular smooth muscle in blood arteries. Also, it has immunosuppressive capability, which is suggested by Mediators of Inflammation. [10] BMC Veterinary Research proposed that $PGF_{2\alpha}$, on the other hand, regulates physiology of female reproductive processes. It impacts embryo quality and morula stage development. [11] Another prostaglandin, PGE_2, is abundant in the kidney and it is important to renal function. It is responsible for renal hemodynamics, water and sodium metabolism, and blood pressure, as stated in Prostaglandins & Other Lipid Mediators. [12] TXA_2, changes vascular tone and mediates platelet aggregation. The action of TXA_2 impacts pulmonary hypertension, kidney and hepatic injury and angiogenesis. The increase in TXA_2 activity affects stroke and bronchial asthma, which is shown by PubMed. [13] Mediators of Inflammation indicates that PGD_2 regulates neurophysiological functions such as regulations of body temperature, hormone release, pain responses, and the sleep-wake cycle in mammals. [14]

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DISTRIBUTION OF PROSTAGLANDINS IN HUMAN TISSUES

Tissue		Prostaglandins E_1	E_2	$F_{1\alpha}$	$F_{2\alpha}$
Thyroid	1	—	4·5	—	50·0
	2	—	—	—	100·0
	3	—	24·5	—	—
	4	—	12·5	—	25·0
	5	—	3·5	—	4·0
Pancreas	1	—	0·75	—	2·0
	2	—	—	—	—
	3	—	1·5	—	7·5
	4	—	0·3	—	0·8
Adrenal cortex	1	—	2·5	—	3·0
	2	—	3·0	—	6·3
Adrenal medulla	1	—	45·0	—	25·5
	2	—	22·5	—	64·0
	3	—	—	—	34·0
Thymus Infant	1	11·3	—	—	—
Infant	2	19·5	—	—	—
Adult	3	9·0	—	—	—
Parotid gland	1	—	0·5	—	2·5
	2	—	5·0	—	0·5
Submandibular salivary gland	1	—	5·5	—	1·0
	2	—	10·0	—	—
	3	—	1·0	—	—
Cardiac muscle	1	—	2·25	—	—
	2	—	3·50	—	—
Rectus abdominis muscle	1	—	1·0	—	—
	2	—	10·5	—	—
Psoas muscle	1	—	1·9	—	—
	2	—	1·3	—	—
Cervical sympathetic chain	1	—	1·9	—	4·0
	2	—	3·0	—	3·9
	3	—	15·0	—	—
Vagus nerve	1	—	5·3	—	5·0
	2	—	3·1	—	9·4
Phrenic nerve	1	10·5	—	—	—
Brachial plexus	1	—	2·0	—	4·2
	2	—	1·6	—	3·9
Bronchi	1	—	4·5	—	1·0
	2	—	7·8	—	2·5
Lung parenchyma	1	—	2·4	—	50·0
	2	—	1·3	—	12·4

The figures refer to concentrations in ng/g tissue. A dash indicates that prostaglandins were not detected.

Figure 4: Distribution of prostaglandins in different human tissues [15]

Figure 4 indicates that prostaglandins are distributed in many tissues in the human body. Thus, in order to moderate inflammation, it is necessary to reduce formations of prostaglandins by inhibiting COX, the factor that leads to more being produced. COX contains two isoforms. which are COX-1 and COX-2. COX-1 regulates cellular processes, it produces prostaglandins which have homeostatic functions, such a gastric cytoprotection and platelet function. On the other hand, COX 2 produces prostaglandins which have physiological functions, such as inflammation, cell proliferation, and functions in brain, kidney, and cardiovascular systems. Ibuprofen is a NSAID, so it inhibits both COX-1 and COX-2. It is anti-inflammatory and analgesic, but since it inhibits COX-1, it blocks platelet production of thromboxane, which increases bleeding to the stomach. As a result, some damage can be done to the gut. This is one of the side-effects of ibuprofen showing that ibuprofen can be harmful to the human body. There is another class of drugs called COX-2 selective inhibitors. They do not inhibit COX-1 so that it does not inhibit TXA2 leading to an impact on platelet aggregation. Therefore, patients may have an increased possibility of heart attacks and strokes.

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4. Binding

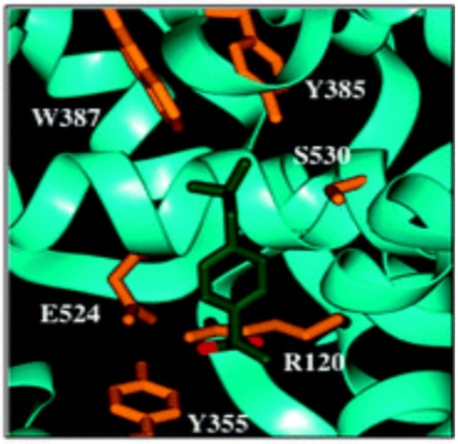

Figure 5: The binding of COX [16]

In figure 5, with carboxylate-coordinated Arg-120 and Tyr-355 at the constriction site, ibuprofen is bound in the COX-1 active site. Ibuprofen establishes a hydrogen bond with Tyr-355 as well as an ion pairing with Arg-120.

5. Metabolism

Ibuprofen can be almost fully metabolized. There is trace to non-existent amounts of the original drug in human urine and the most frequently occurring chemicals are 2-hydroxy-ibuprofen and carboxy-ibuprofen, together with the acyl glucuronides that correlate to each, which is stated in Pharmacogenetics and Genomics. [17] Once within the body, the enzyme α-methylacyl-coenzyme converts 50–65% of R-ibuprofen to the S enantiomer via an acyl-CoA thioester. Then, primary metabolism occurs through oxidative metabolism using CYP enzymes. CYP2C9 is the main CYP in charge of metabolism. It catalyzes the synthesis of 2-hydroxy- and 3-hydroxy-ibuprofen, which can subsequently be transformed by cytosolic dehydrogenases into carboxy-ibuprofen. 2C9 is shown to catalyze both enantiomers in the human body. Other CYPs such as CYP2C8 and CYP3A4 play a minor role in first pass metabolism. Ibuprofen that goes through second pass metabolism is directly glucuronidated to ibuprofen-acyl glucuronide. This can be produced with many uridine 5′ diphosphoglucuronosyltransferases (UGTs) including UGT1A3, UGT1A9, and UGT2B4. This makes up around 10 – 15% of an ibuprofen dose.

6. Conclusion

From its initial development to the modern day, ibuprofen has proven again and again that it deserves to be recognized as a widely used drug. The NSAID's inner workings are incredibly intricate but the researchers hope that this paper has been a informative guide to its structure, composition, history, and mechanism. Further research remains to be done on every aspect of the drug.

Acknowledgement

Both authors contributed equally and should be considered co-first authors.

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