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STUDY OF CYCLOOXYGENASE-3 ON THE BASES OF ITS FACTS AND CONTROVERSIES

Suman Sharma *, Amrita Verma, Rajani Chauhan, Manisha Kedar and Rakhi Kulshrestha

Department of Pharmacy, Banasthali University, Banasthali - 304022, Rajasthan, India.

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Correspondence to Author:
Suman Sharma

M. Pharma (Research Associate), Department of Pharmacy, Banasthali Vidyapith, Banasthali - 304022, Rajasthan, India.

E-mail: suman.bagra24@gmail.com

ABSTRACT: Prostaglandin endoperoxide synthases, usually known as cyclooxygenases (cyclooxygenase-1 and cyclooxygenase-2), catalyze a key step in the formation of biologically effective prostaglandins. In recent times, a cyclooxygenase-1 variant protein, called cyclooxygenase-3 used to be found and characterized. COX-3 is studied recent along with significant margin for the formation of anti-inflammatory, analgesic and anticancer agents. In a pharmaceutical area, various drugs targeted on this enzyme are Acetaminophen, Dipyrone, Antipyrine, Dimethylaminopyrene, Diclofenac, Aspirin, Ibuprofen, Thalidomide and Caffeine. It is a new era for COX family that contains numerous significant applications that's the reason it is the center of attraction for researchers. Currently, the role of COX-3 in human is unclear, but scientists continue to do work in this area. The objectives of this review article are to gather all newest data literature related to developments in the structural and biochemical features of the cyclooxygenase-3 isoenzyme along with discussing its application for the various pharmacological effects of drugs.

INTRODUCTION: In human history, cyclo-oxygenase (COX) reported the most common therapeutic drug target for the various drugs. COX-1 and COX-2 are the most common in research but now a day's researcher's focus on new cyclo-oxygenase that is cyclooxygenase-3 (COX-3). Cyclooxygenase-3, (COX-3) is commonly known as a splice variant of COX-1 (COX-1b or COX-1v). Chandrasekharan *et al*., in 2002 isolated COX-3 from the heart and the cerebral cortices of dog. A huge number of controversies estimated in opposition to the cyclooxygenase-3 hypothesis.

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Selective COX-2 inhibitors loosely bound on the enzymatic target site of COX-3, because the site is similar to the COX-1 site, but their effect is more potent to reducing the fever as compare to older NSAIDs. The effect of fever has also been markedly related to an active introduction of COX-2 expression as well as linked with an increase production level of prostaglandin E2, along with no significant functions of COX-1 or a COX-1 gene product (*e.g.*, COX-3).

Lastly, those target sites which are responsible for fever, that sites do not fit into the target well of COX-3 expression, and the protein should be present within the hypothalamus rather than the cerebral cortex [1]. Literature revealed that all these studies give quarrel against COX-3, being the site for NSAIDs (antipyretic action) as well as selective COX-2 agents. On the other hand, the consequences might exist to examine as shows that

Paracetamol (NSAIDs) acts on different target site rather than the other NSAIDs category drugs and more than single, COX isoform contributes to the fever response. For the reduction of all that arguments need to discovered some new mechanism that is useful in further studies and finally, the researcher discovered the frame-shift mechanism, it extremely improbable that COX-3 acts an important function in fever and inflammation in humans.

The inducible cyclooxygenase-3 is not too much action and produces a smaller amount of PGE2 as compare to either COX-1 or COX-2. NSAID shows the various inhibitory effects on COX-3, inhibition depends upon their penetration power. They have the ability and polarity to penetrate the blood-brain barrier. So, in case of antipyretic and analgesic drugs (*e.g.,* Paracetamol), which shows the weak inhibitory effect on cyclooxygenase-1 and -2, can easily penetrate the central nervous system *via* blood-brain barrier, could describe their pharmacological action of inhibiting COX-3 [2, 3]. Literature reveals that COX-3 might contain a capacity to remission phase in chronic inflammatory ailments and might be participating in the growth of cervical, ovarian, leukemia and colonic cancer [2].

This review article aims to explain the COX-3 origin, molecular structure, biochemistry, physiology and pharmacological action with the various drugs. In a present research world, for all researchers, it might be a new target with some new pharmacological actions.

Structure and Chemistry: COX-3 is considered a novel as well as a significant target for the production of analgesic and anti-inflammatory agents. On the other side, a cause of the frame-shift mechanism is to absolute retention of intron 1 in the human protein series; this plays a significant role in human pathophysiology. In humans, expression of COX-3 mRNA was found to be expressed as an about 5.2 kb transcript, and it also found to be most abundant in heart and cerebral cortex [4]. mRNA of COX-3 occurs into the various tissues such as human cerebral cortices, canine, human aorta and endothelium, heart, kidney and neuronal tissues of rodents [5]. This mRNA protein is different as pharmacologically to cyclooxygenase-1 and -2, however, this is derivative of the cyclooxygenase-1 gene [1, 6]. Major difference is the retention of an extra intron [7] (non-coding deoxy ribonucleic acid (DNA) segments with the unidentified role) made up by 90 nucleotides. In a common method of splicing, introns are detached as well as exons (encoding regions of the gene that creates protein) be attached collectively to make a nonstop RNA coding series, which consequences in the retention of this intron resulted in the insertion of 30 amino acids into the canine COX-3 enzyme **Fig. 1** [8].

The difference between COX-1 and COX-3 at the protein level, insertion of 30-40 amino acids, depends upon the mammalian species, in the hydrophobic signal peptide [9]. Protein of cyclooxygenase-3 is glycosylated, and it shows COX activity, but COX-3 signal peptide is not cleaved. In a human, a cyclooxygenase-3 protein made by 633 amino acids, is a membrane-bound protein as well as shows all the structural and catalytic properties are same as cyclooxygenase-1 and -2 [1]. This is made up of 94 nucleotides in its mRNA and is made by COX-1 gene which retains 1 intron [1, 2, 5].

Formation of COX-3 from COX-1 gene by retention of intron 1 in its mRNA; initially this was reported into the cerebral cortex of canine along with some small quantity was analyzed in other tissues. Repeatedly, the first report explains that relative assays of murine COX-2, canine COX-3, and murine COX-1, indicates by transfected insect cells established selective inhibition of COX-3 to occur by using various antipyretic/analgesic drugs such as Phenacetin, Dipyrone, Acetaminophen, antipyrine and nonsteroidal anti-inflammatory drugs (NSAIDs). It was suggested that COX-3 inhibition might show a peripheral and central mechanism with the help of this mechanism, drugs represent their actions in the form of reducing pain and possibly fever. Literature shows the location of COX-3 in human as well as in animals but although, cyclooxygenase-3 is not relevant to human species, as it appears we might be improbable to state cyclooxygenase-3. The initial literature reports revel [1]; there is a single nucleotide difference in intron 1 between human and canine that consequences in a shift in the reading frame.

This would make it unfeasible for a full-length, catalytically active form of cyclooxygenase-3 to live in human species. Similarly, although cyclooxygenase-3 expression might be present in the rats, this could not straightly provide go up to COX-3 protein as there is alike shift in the reading frame. There has been preceding information of other splice variants of the COX enzymes **Fig. 1**.

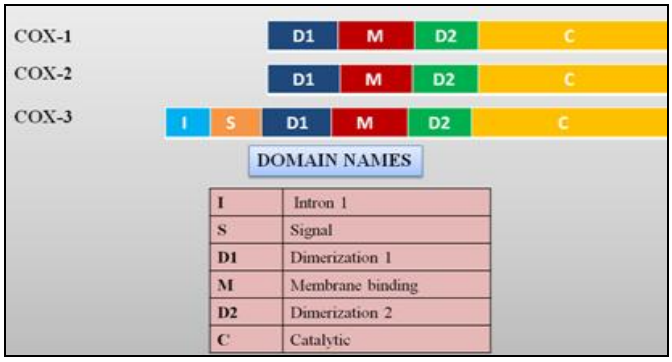

FIG. 1: STRUCTURE OF COX-1, -2 AND -3 GENES (FRAME-SHIFT MECHANISM)

Transcription of COX-3: COX-3 is transcribed from the prostaglandin-endoperoxide synthase-1gene (PTGS-1), although the resultant mRNA is spliced into a different way. The resultant protein in dogs is same as other two COX enzymes, but not in humans and mice due to a frame-shift mechanism [10, 11]. The reason behinds reported mechanism, the reality that the 93 bases of spliced intron present in the dog, resultant in the loss of 93:3 = 31 amino acids in the COX-3 amino acid series. It does not damage its functionality. In humans, 94 bases extended intron, resulting in a protein with an entirely dissimilar sequence of the amino acid as compared to cyclooxygenase-1 or -2. The resultant protein does not illustrate COX action. This is not probably to participate in functions of prostaglandin-mediated physiological responses [2, 4, 5].

Pharmacological Role of Cyclooxygenase-3: COX-3 mRNA explains 30% of COX-1 mRNA level. COX-3 mRNA is specially located in the pituitary, hypothalamus and choroid plexus. These are all main target site for binding of antipyretic drugs of NSAIDs category. Antipyretic, analgesics drugs molecule such as Paracetamol [12, 13, 14] are less active against cyclooxygenase-1 and -2 enzymes because it shows weak inhibition on cyclooxygenase-1 and -2 enzymes than to COX-3 enzyme. These drugs easily penetrate the central part of the nervous system and show pharmacological action by cyclooxygenase-3 inhibition [11]. COX-3 has been the immerging target for Alzheimer's disease, due to a higher amount of COX-3 present in the Alzheimer's patient. Long-term use of NSAIDs has lower down Alzheimer's disease [15, 16] to some extent. COX-3 is also an immerging target for the various cancers such as ovarian, cervical, colon and leukemia [17, 18, 19, 20]. Because mRNA level in COX-1 splice variant (COX-3), is raised into the mucosa of the colorectal tumor but in case of rat model when treated with NSAIDs, so after treatment COX-3 mRNA levels are decreased to normal levels as compared to cyclooxygenase-1 or -2 levels [21, 22]. This is unlikely to cyclooxygenase-3 into these species shows a significant function in prostaglandin-mediated pain, fever or chronic inflammatory disease. Paracetamol seems to be a good inhibitor of canine cyclooxygenase-3, except IC_{50} for cyclooxygenase-3 inhibitions is elevated and hard to attain with oral administer a dose of 1.0-0.5g.

TABLE 1: IC_{50} STANDARD OF NSAIDS AND ANTIPYRETIC OR ANALGESIC DRUGS [1]

Drugs	COX-3 (IC_{50})	COX-2 (IC_{50})	COX-1 (IC_{50})
Acetaminophen	460	>1000	>1000
Aminopyrine	688	>1000	>1000
Antipyrine	862	>1000	>1000
Aspirin	3.1	>1000	10
Diclofenac	0.008	0.041	0.035
Dipyrone	52	>1000	350
Ibuprofen	0.24	5.7	24
Indomethacin	0.016	0.66	0.010
Phenacetin	102	>1000	>1000
Caffeine	>1000	>1000	>1000
Thalidomide	>1000	>1000	>1000

So, in case of well-established, more fascinatingly COX inhibitors, such as Diclofenac, Ibuprofen, and Indomethacin, to be extensively used as an analgesic in current days, they all show the most potent inhibition [23, 24, 25]. Some other remarkable study has been done on those selective COX-2 drugs, and their results do not affect COX-3. A standard IC_{50} value of some NSAIDs and antipyretic or analgesic drugs shows in **Table 1**.

Presently the accurate purpose of the COX-3 protein is unidentified. In cases of rodents and humans, the COX-3 mRNA transcript has potentially targeted by nonsense-mediated decay, which described its low expression level. In a dog,

rodents and human the COX-3 proteins does not explain substantial homology. Even though cyclooxygenase-3 encoded proteins are recognized in both humans [26] as well as in rodents, but their biological functions are indistinct. The amino acid sequence of the protein encoded by rat and the human COX-3 gene has a dissimilar to cyclooxygenase-1 and-2.

Further to differentiate cyclooxygenase-3 from the known COX isoforms that differentiate as COX variant protein (COVAP), because it does not contain common COX activity [1]. In rodent studies, Acetaminophen shows a selective inhibition of COX-3, but in some evidence, it does not support any claims [26, 27, 28]. It is also important to emphasize that commercially obtainable anti-COX-3 antibodies can only be used for selective species selectively because of some substantial differences between COX-3 amino acid sequences of different species. The precise mechanism of acetaminophen remains an unknown. Therefore, study the transcription of COX genes may assist us to know the purpose of alternative splicing mechanisms in eukaryotes.

Cox Splice Variants: In recent times, cyclo-oxygenase splicing variant (COX-1), occurred in canine known as COX-3, was rise via the retention of its intron 1 and study revealed that it was differentially sensitive towards inhibition through numerous NSAIDs along with acetaminophen. Cyclooxygenase-1 retains intron 1, is seen in some human tissues at both the protein and mRNA levels. According to the molecular biology reports, in human tissues proteins, there are three separate COX-1 splicing variants are present. First one is-COX-1b_1, 1 splice variant in this the whole 94 base pair of intron-1 is retained, it will lead to a shift in the reading frame with the introduction of a stop codon approximately 249 base pair down-stream.

Consequently, that variant, encoded a small peptide this is more probably a COX-inactive protein. The second one, named as COX-1b_2, retains approximately the whole intron-1, except in a guanidine at 72 positions, again leads to a small, self-rectifying shift in the reading frame, which encodes a full length and probable COX-active protein. As the second type of splicing variant, the third type name as COX-1b_3, also retain approximately the whole intron-1 except in a cytosine at 50 base pair position, again leads to a small, self-rectifying shift in the reading frame which encodes a slightly dissimilar but full length and probable COX-active protein [29]. In acute inflammatory responses, cyclooxygenase-3 might play a role in the resolution phase, entirely different to cyclooxygenase-1 and-2. Examination of the splice variants of COX-1 mRNAs, suggests, that they might be translated in the earlier uncharacterized COX-1 associated proteins, a key protein product as cyclooxygenase-3. This is pharmacologically diverse to cyclooxygenase proteins. Still, it is a derivative of the COX-1 gene. Further, there is information of mRNA COX-3, isolation from the cerebral cortex or hippocampus of other animal species as well as humans. Discovery of other two isoenzymes known as partial COX-1a (PCOX-1a) and partial COX-1b (PCOX-1b) was isolated, but they have a lack of COX activity [30].

Drug Used on COX-3: Acetaminophen is an NSAIDs category drug, well-known as Paracetamol. It shows effective antipyretic or analgesic activity but weakly effective against the anti-inflammatory action. When Paracetamol administers to humans, prostaglandin metabolites level in urine is decreased but do not decrease prostaglandins synthesis through blood platelets or by the stomach mucosa. In case of *in-vitro* studies Acetaminophen is a less potent inhibitor for both cyclooxygenase -1 and -2 enzymes, hence there is an option to inhibit, so far anonymous form of cyclooxygenase, possibly cyclooxygenase-3.

Further, unlike other NSAIDs, acetaminophen can cross the central nervous system via the blood-brain barrier, that allowing it to attain adequate concentrations in the brain to inhibit COX-3. All of these statements use as evidence to prove that COX-3 strongly involve as the target for acetaminophen action and moderately give explanation 3 on the long-standing mystery, it is frequently more effective against a headache and fever as compared to some other NSAIDs. Further study in this particular region will lead not only to a better considerate of the function of COX enzymes in pain, fever, inflammation, and disease but also to more precise and efficient treatment of ailments involving these enzymes.

Finally, recognition of a new isozyme, COX-3, suggests that it is the active target for acetaminophen. The overall conclusion indicates that the cyclooxygenase-3 shows COX action, but pharmacologically differs from both cyclooxygenase-1 and -2, and it is more similar to cyclooxygenase-1[31]. Acetaminophen is an active metabolite of Phenacetin [32, 33]. It is a famous analgesic or antipyretic drug in the world, but nowadays it is not used widely due to the incidence of methemoglobinemia and suspected bladder and renal and carcinogenesis, renal toxicity. Phenacetin is fastly O-de-ethylated in the human body to produce acetaminophen than is again metabolized to various small and poisonous compounds. Therefore, some minute amount of Phenacetin flow in the blood.

Interestingly, Phenacetin shows active inhibition of COX-3, as compare to metabolite Acetaminophen below 30µM substrate circumstances [34, 35]. Phenacetin inhibited COX-3 on 120µM (IC50 level), as different to 460 µM for acetaminophen, tested under the parallel situation. Acetaminophen, Phenacetin is preferentially inhibiting cyclooxygenase-3.

One more analgesic or antipyretic drug is under consideration, which is Dipyrone, was considerably more effective on inhibiting cyclooxygenase-3 than both either cyclooxygenase-1 or -2. On 52µM, IC_{50} value Dipyrone inhibited COX-3, and in case of COX-1, this concentration was 6.6-fold higher. There is no evidence for inhibition of COX-2 with the help Dipyrone at below 1µM. Dipyrone is also known as pro-drug which is impulsively broken down in aqueous solution to resemble pyrazolone compounds 36 structurally. The compounds differ in their effectiveness as an analgesic or antipyretic agents. Antipyrine and dimethylaminopyrene are connected to Dipyrone and possess markedly decrease therapeutic strength like some other analgesic or antipyretic agents, preferentially inhibit cyclooxygenase-3[37, 38, 39]. By the use of selected NSAIDs, COX-3 is varying its sensitivity to inhibition. Diclofenac was the strongest inhibitor of cyclooxygenase-3 experienced and ibuprofen, Diclofenac, and Aspirin, preferentially inhibited cyclooxygenase-3 over cyclooxygenase-1 and -2 [40, 41, 42, 43]. Thalidomide and caffeine both have been reported as analgesic instead of COX-3 action.

CONCLUSION: In the past year the number of research done on cyclooxygenase -1 and -2, currently in the COX family new enzyme is the attraction point for researchers. As described in this review COX-3 isoenzyme is a new lead target for NSAIDs and some other category drugs. No more research is available on a COX-3 enzyme that's why more confusion in the scientific literature of COX-3. Currently, there remain just a handful of research papers obtainable concerning this cyclo-oxygenase splicing variant (COX-1). COX variants might ultimately lead to highly efficient anti-cancer, anti-inflammatories, pain relievers, antipyretics, agents, or treatments for Alzheimer's and additional circumstances. Certainly, all these possible indications and avenues will surely be exploited (if possible) by pharmaceutical companies in the future.

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REFERENCES:

1. Chandrasekharan NV, Dai H, Roos TL, Evanson NK, Tomsik J and Elton TS: COX-3, a cyclooxygenase -1 variant inhibited by acetaminophen and another analgesic/antipyretic drugs: cloning, structure and expression. Proceedings of the National Academy of Sciences 2002; 99(21):13926-31.
2. Kam PCA and So A: COX-3: uncertainties and contro-versies. Curr Anaes and Crit Care 2009; 20: 50-53.
3. Botting R and Ayoub SS: COX-3 and the mechanism of action of Paracetamol / Acetaminophen. Prostaglandins Leukotrienes and Essential Fatty Acids 2005; 72: 85-87.
4. Hla T: Molecular characterization of the 5·2 KB isoform of the human cyclooxygenase-1 transcript. Prostaglandins 1996; 51: 81-85.
5. Warner TD and Mitchell JA: Cyclooxygenases: new forms, new inhibitors, and lessons from the clinic. The FASEB Journal 2004; 18: 790-800.
6. Roos KL and Simmons D: Cyclooxygenase variants: the role of alternative splicing. Biochemical and Biophysical Research Communications 2005; 338: 62-9.
7. Willoghby DA, Moore AR and Colville-Nash PR: COX-1, COX-2 and COX-3 and the future treatment of chronic inflammatory disease. The Lancet 2000; 355: 646-648.
8. Kis B, Snipes JA and Busija DW: Response to comments on "Acetaminophen and the cyclooxygenase-3 puzzle: sorting out facts, fictions, and uncertainties". The Journal of Pharmacology and Experimental Therapeutics 2005; 315: 1415-16.
9. Kujubu D, Fletcher BS, Varnum BC, Lim RW and Herschman HR: TIS10, a phorbol ester tumour promoter-inducible mRNA from Swiss 3T3 cells, encodes a novel prostaglandin synthase/cyclooxygenase homologue. The Journal of Biological Chemistry 1991; 266: 12866-72.

10. Merlie JP, Fagan D, Mudd J and Needleman P: Isolation and characterization of the complementary DNA for sheep seminal vesicle prostaglandin endoperoxide synthase (cyclooxygenase). The Journal of Biological Chemistry 1988; 263: 3550-3553.
11. Qin N, Zhang SP, Reitz TL, Mei JM and Flores CM: Cloning, expression and functional characterization of human cyclooxygenase-1 splicing variants: evidence from intron 1 retention. The Journal of Pharmacology and Experimental Therapeutics 2005; 315: 1298-1305.
12. Ouellet M and Percival MD: Mechanism of Acetaminophen inhibition of cyclooxygenase isoforms. Archives of Biochem and Biophys 2001; 387: 273-280.
13. Dinchuk JE, Liu RQ and Trzaskos JM: COX-3: in the wrong frame in mind. Immunology Letters 2003; 86: 121.
14. Kis BA, Snipes JA, Isse T, Nagy K and Busija DW: Putative cyclooxygenase-3 expression in rat brain cells. Jour of Cerebral Blood Flow & Meta, 2003; 23: 1287-92.
15. Kis B, Snipes A, Bari F and Busija DW: Regional distribution of cyclooxygenase-3 mRNA in the rat central nervous system. Molecular Brain Res 2004; 126:78-80.
16. Stewart W, Kawas C, Corrada M and Metter E: Risk of Alzheimer's disease and duration of NSAID use. Neurology 1997; 48: 626-632.
17. Cui J, Kuroda H, Chandrasekharan N, Pelaez R, Simmons D and Bazan N: Cyclooxygenase-3 gene expression in Alzheimer's hippocampus and stressed human neural cells. Neurochemical Research 2004; 29: 1731-37
18. Dore M, Cote L and Sirois MA: Expression of prostaglandin G/H synthase type 1, but not type 2, in human ovarian adenocarcinomas. Journal of Histochemistry Cytochemistry 1998; 46: 77-84.
19. Sales KJ, Katz AA, Howard B, Soeters RP, Millar RP and Jabbour HN: Cyclooxygenase-1 is up-regulated in cervical carcinomas: autocrine/paracrine regulation of cyclo-oxygenase-2, prostaglandin E receptors, and angiogenic factors by cyclooxygenase-1. Can Res 2002; 62: 424-432.
20. Rocca B, Morosetti R, Habib A, Maggiano N, Zassadowski F and Ciabattoni G: Cyclooxygenase-1, but not -2, is upregulated in NB4 leukemic cells and human primary promyelocytic blasts during differentiation. Leukemia Research 2004; 18: 1373-79.
21. Vogiais D, Brown W, Glare E and O' Brien P: Rat colorectal tumors treated with a range of non-steroidal anti-inflammatory drugs show altered cyclooxygenase-2 and cyclooxygenase-1 splice variant mRNA expression levels. Journal of Carcinogenesis, 2001; 22: 869-874.
22. Shaftel S, Olschowka J, Hurley S, Moore A and O' Banion M: COX-3: a splice variant of cyclooxygenase-1 in mouse neural tissues and cells. Mol Brain Res 2003; 119: 213-15.
23. Davies NM, Good RL, Roupe KA and Yanez JA: Cyclo-oxygenase-3: axiom, dogma, anomaly, enigma or splice error?--Not as easy as 1, 2, 3. Journal of Pharmacy and Pharmaceutical Sciences, 2004; 7: 217-26.
24. Gryglewski RJ, Chlopicki S and Swies J: *In-vivo* endothelial interaction between ACE and COX inhibitors. Prost Leukotr and Ess Fatty Acids, 2005; 72: 129-131.
25. Harris RC: The macula densa: recent developments. Journal of Hypertension 1996; 14: 815-822.
26. Lucas R, Warner TD, Vojnovic I and Mitchell JA: Cellular mechanisms of acetaminophen: a role of cyclo-oxygenase. The FASEB Journal 2005; 19; 635-637.
27. Warner T and Mitchell J: Cyclooxygenase-3 (COX-3): filling in the gaps toward a COX continuum. Proceedings of the National Academy of Sciences, 2002; 99: 13371-73.
28. Warner TD, Vojnovic I, Giuliano F, Jiminez R, Bishop-Bailey D and Mitchell JA: Cyclooxygenases-1, 2 and 3 and the production of prostaglandin I2: investigating the activities of Acetaminophen and cyclooxygenase-2-selective inhibitors in rat tissues. The J of Pharmacology and Experimental Therapeutics 2004; 3109: 642-647.
29. Simmons DL: Variants of cyclooxygenase-1 and their roles in medicine. Thrombosis Res 2003; 110: 265-268.
30. Brune K: Spinal cord effects of antipyretic analgesics. Drugs 1994; 47: 21-27.
31. Ayoub SS, Colville-Nash PR, Willoughby DA and Botting RA: The involvement of a cyclooxygenase 1 gene derived protein in the antinociceptive action of paracetamol in mice. European Jour of Pharmacology 2006; 538: 57-65.
32. Kis B, Snipes JA and Busija DW: Acetaminophen and the cyclooxygenase-3 puzzle: sorting out facts, fictions, and uncertainties. The Jour of Pharmacology and Experimental Therapeutics 2005; 315: 1-7.
33. Langenbach R, Morham SG and Tiano HF: Prostaglandin synthase 1 gene disruption in mice reduces arachidonic acid-induced inflammation and Indomethacin-induced gastric ulceration. Cell 1995; 83: 483-492.
34. Mazario J, Gaitan G AND Herrero JF: Cyclooxygenase-1 *vs* cyclooxygenase-2 inhibitors in the induction of anti-nociception in rodent withdrawal reflexes. Neuro-pharmacology 2001; 40: 937-946.
35. Wickelgren I: Enzyme might relieve a headache. Science 2002; 297: 1976.
36. Bazan NG and Flower RJ: Medicine: lipid signals in pain control. Nature 2002; 420: 135-138.
37. Schwab JM, Schluesener HJ, Meyermann R and Serhan CN: COX-3 the enzyme and the concept: steps towards highly specialized pathways and precision therapeutics? Prostaglandins Leukotrienes and Essential Fatty Acids 2003; 69: 339-343.
38. Schwab JM, Schluesener HJ and Laufer S: COX-3: just another COX or the elusive solitary target of Paracetamol? The Lancet 2003; 361: 981-982.
39. Smith A: Time for a new COX. Nature Reviews Drug Discovery 2002; 1: 839.
40. Donk VD, Tsai WA and Kulmacz, RJ: The cyclooxygenase reaction mechanism. Journal of Biochemistry 2002; 41: 15451-58.
41. Botting R: COX-1 and COX-3 inhibitors. Thrombosis Research 2003; 110: 269-272.
42. Fikriye YS, Bilgin K and Kevser E: The role of cyclooxygenase enzymes in the effects of losartan and lisinopril on the contractions of rat thoracic aorta. The Eurasian Journal of Medicine 2017; 49: 16-21.
43. Xu Kang: Cyclooxygenase-2 contributes to oxidopamine-mediated neuronal inflammation and injury *via* the prostaglandin E2 receptor EP2 subtype. Scientific reports 2017; 7: 9459.

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