

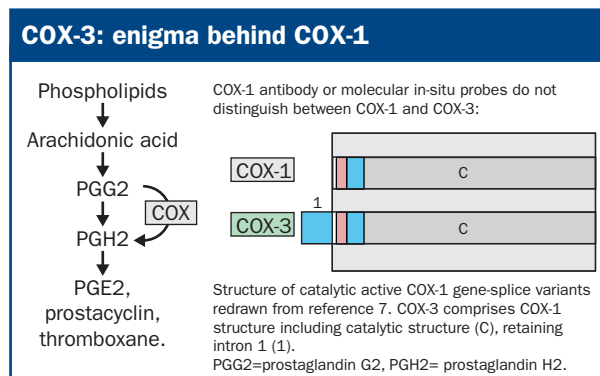
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COX-3: just another COX or the solitary elusive target of paracetamol?

In 1899, acetylsalicylic acid, aspirin, was one of the first analgesic and anti-inflammatory drugs. However, it took a further 70 years and at least a dozen new drugs, many of which are still widely used today, such as indometacin and ibuprofen, before the common mechanism of action of all these drugs was established. In 1971, John Vane identified cyclo-oxygenase (COX-1) as a molecular target.¹ Inhibition of COX-1 and consecutive reduction of prostaglandins and thromboxanes (figure) explained both the pharmacological activity (analgesic, anti-inflammatory, antipyretic, and antiplatelet) and side-effects (gastrointestinal ulceration).

However, some questions still remained unanswered. Metamizole and paracetamol (acetaminophen), two well-established analgesic and antipyretic drugs, had only weak inhibitory activity against COX and no antiplatelet effect, suggesting a distinct mode of action. In 1989–92, a new isoform, COX-2, was discovered, which offered a simple and attractive hypothesis.² The constitutively expressed COX-1 is the housekeeping enzyme, responsible for physiological activities of prostaglandins while COX-2, whose expression is induced under inflammatory conditions, is responsible for pathological prostaglandins that produce pain and high temperature. On the basis of these observations, COX-2-selective drugs were rapidly developed and became one of the most commercially successful class of drugs. However, after only a few years of clinical use, the COX-2 hypothesis turned out to be more complicated than initially thought. Both COX-1 and COX-2 have physiological and pathological roles.³ COX-2 inhibitors, which have a better gastrointestinal-safety profile (mucosal protection), were found to have cardiovascular and renal side-effects.⁴ For some years, there were rumours of the existence of further isoforms. An anti-inflammatory COX-3 was postulated by Willoughby et al⁵ as an inducible isoenzyme expressed in later, resolving stages of inflammation. During the past decade, Brune and Botting⁶ independently speculated on the existence of a COX-3 in the brain, mainly responsible for pain and high temperature. It took until 2002, and Chandrasekharan and colleagues from Dan Simmons group,⁷ to identify COX-3 (which is not a genetic isoform like COX-2) in the brain.

Alternative splicing generates at least four different mRNA variants derived from the *COX-1* gene; COX-3, COX-1, and the two truncated, partial PCOX-1 sequences, PCOX-1a and PCOX-1b—encoding novel variants of the COX-1 protein family. However, apart from COX-1, Chandrasekharan and colleagues⁷ found that only canine COX-3—a 65 kDa membrane-bound protein—has glycosylation-dependent cyclo-oxygenase activity. Human *COX-3* is a 5.2 kb transcript encoded on chromosome 9 that is expressed in specific tissues with highest levels in the brain (reaching 5% of the total amount of COX-1 mRNA) and in the heart.⁷ In the brain Chandrasekharan and colleagues find that the truncated, partial COX-1 mRNAs (PCOX-1) are equally expressed. COX-3 harbours the COX-1 structure with retained intron 1 and a signal peptide (figure). These investigators



also claim that COX-3 mRNA is abundantly expressed in the mature brain and in the spinal cord, whereas it is absent in fetal central nervous system tissue.

In earlier reports a COX-1/PGHS-1 (prostaglandin synthase 1) transcript of almost similar length (5.1 kb) to COX-3 was shown to be expressed by monocytes⁸ and endothelial cells.⁹ The presence of COX-3 mRNA in the adult human brain, but lack of expression in fetal tissue, identified COX-3 as a conserved differentiation-associated protein of the human central nervous system. Retention of intron 1 could alter folding and may affect dimerisation and the active site, mediating structural changes.⁷ Therefore, although COX-3 contains all the COX-1 transcript, the retained intron sequence could significantly alter its enzymatic properties as shown by a lower potency (1/5th) in generating PGE₂. That Chandrasekharan and colleagues find COX-3 to act differently from COX-1 is further emphasised by a 3–10 fold higher IC₅₀ for diclofenac or ibuprofen to block COX-1 compared with its ability to inhibit COX-3 (IC₅₀ is the concentration of enzyme needed to inhibit production of substrate by 50%). The different IC₅₀ values between COX-1 and canine COX-3 imply a distinct active centre in COX-3 and thus suggest the feasibility of inhibiting COX-3 specifically.

With the discovery of COX-3, attention turns back to COX-1. Was there any specific detection of COX-1 in the past, since available antibodies do not distinguish between COX-1 and COX-3, and detection proposed as specific for COX-1 also included COX-3 signals (figure)? Moreover, results from homozygous mice with a knocked-out gene locus for *COX-1*¹⁰ have to be reassessed since they also represent *COX-3* knockouts. Because COX-3 is a spliced COX-1 variant, a specific COX-3 knock-out (not distinguishing between COX-3 or PCOX-1a) is probably unachievable in practice.

The most significant implication of Chandrasekharan and colleagues' findings is that multiple COX-1 isoenzymes could be derived from just one gene providing a range of COX enzymes and products, at least in the dog.¹¹ Other than the option of inhibiting COX-1 or COX-3 at the protein level, it should be possible to modify COX-1 splicing at the RNA level, leading to the generation of enzymatically inactive PCOX-1a or PCOX-1b variants.

COX-3 inhibition by paracetamol is not specific and only weak, and therefore does not completely solve the mystery of paracetamol being analgesic without affecting COX-1 or COX-2. This finding opens up the search for further COX variants or paracetamol-inducible antipyretic and analgesic-acting proteins. COX-3 does not appear to be the solitary elusive target of paracetamol. So what does COX-3 offer for the future? The answer is

probably more insight into the analgesic activity of COX inhibition. Paracetamol seems to be an inhibitor of canine COX-3, but the IC₅₀ for inhibiting COX-3 is high and difficult to achieve with an oral dose of 0.5–1.0 g. More interestingly, well-established COX inhibitors, such as ibuprofen, diclofenac, or indometacin that are widely used as analgesics, show the most powerful COX-3 inhibition. However, the limited number of drugs tested so far allows no final conclusions. Another interesting observation is that selective COX-2 drugs have no effect on COX-3 (data not shown by Chandrasekharan and colleagues but mentioned in the text). COX-2-selective drugs are suspected to be less analgesic than unselective COX-1 or COX-2 inhibitors like ketoprofen,¹² naproxen, or diclofenac.¹³ An important future aspect of human COX-3 research might be the promise of a new target for analgesic drug discovery, enriching the oversimplified COX-1 and COX-2 debate.

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Hogwash from Hogwarts

Boys are admitted to hospital with head injuries after running luggage trolleys into a railway station wall. An American college accepts a PhD on Ovidian Metamorphosis and Post-Modernist Influences in Writings of J K Rowling. Schoolgirl hysteria follows the

leaked news that in the final adventure our hero succumbs to Dark Forces and is condemned to eternity as a retarded adolescent on the film set of *Lord of the Rings*. And a first edition fetches £25 000. Only the last is true but with pottermania, an affliction to which I am immune, anything is possible. True, the *Philosopher's Stone* film did provide a welcome diversion from plastic airline food but after a few dozen pages of the text of that and a short-lived stab at *Chamber of Secrets* it seemed reasonable to abandon both tales to a more appreciative age group. Yet otherwise sensible adults do worship at the feet of this precocious child, and numbered among the obsessed is the science correspondent of London's *Daily Telegraph*.¹

Roger Highfield draws on his considerable personal knowledge and the views of 100 consultants from the sciences to seek rational explanations for happenings that Master Potter and the Hogwarts school would see as magic. This is all good entertainment and the author's skills in getting across sometimes difficult science are amply demonstrated. However, Highfield's extrapolations often have to be as elastic as the boot of a Weasley Ford Anglia. Teleportation by Austrian physicists of the quantum state of a photon sounds far short of "Beam me up, Scottie". As a model for Quidditch we are invited to look at the ritualised violence of a low-scoring ballgame popular in Mesoamerican civilisations. From what I have read about these two bizarre pastimes the differences outweigh the similarities, and the Eton wall game would have served as well. We can—well, I can't but you know what I mean—project bricks onto a foggy screen and walk through them but what sort of fog holds up a station roof?

Highfield rightly hopes that his revelations will not disillusion the young reader. His publisher, though, sees this book as "the perfect guide for parents who want to teach their children science through the adventures of their favourite hero". No child worthy of the name would fall for that, surely. Lois Gresh and Robert Weinberg's publisher does not make this mistake.² These authors, in doing for Batman, Spider-Man, the Incredible Hulk, and other superheroes of the comic strip what Highfield does for Potter, distance themselves from Hogwarts. "Supernatural and magical characters", they declare "can't be explained by logic or scientific expertise". However, the two books are not that far apart really. "The change from high school weakling to the surprised possessor of magic powers" is a publicity quote, not for Rowling's skinny hero but on a video of Spider-Man the movie. Furthermore, both books pay tribute to the late Carl Sagan's *Contact*, a literary experiment in space/time travel, and they note the advisory role of CalTech professor Kip Thorne and the "grandfather paradox" in which you return in time and kill your grandfather before your father is conceived. Gresh and Weinberg are happy to concede when science fails to explain some fantastic deed, and this book is intriguing for the light it throws on readers' taste and the development of this type of comic strip from the first appearance of Superman in the 1930s.

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