

4000 Years and We Might Finally Know How Non-Steroidal Anti-inflammatory Drugs Work

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The use of non-steroidal anti-inflammatory drugs (NSAIDs) dates to approximately 2000 BC. Efforts to understand their action and improve on their potency and safety have led to the discovery of a large number of widely used drugs including Aspirin, Advil, Aleve, and Celebrex *inter alia*. A major advance was the discovery in 1971 that the enzyme cyclooxygenase (COX) is the molecular target for their pharmacological action. A subsequent advance was the discovery in 1991 of a second cyclooxygenase (COX-2) enzyme, inhibition of which appears responsible for the anti-inflammatory, analgesic, anti-pyretic, and anti-proliferative effects of NSAIDs. Our laboratory has defined the molecular determinants of the interaction of various NSAIDs with COX-2 and a case study of our approach will be presented using naproxen (Aleve) as the example. Recent results will be presented that provide a highly detailed kinetic and structural understanding of the mechanism of COX inhibition by NSAIDs.