How Aspirin Interferes with Cyclooxygenase Activity: the Work of William L. Smith

Stimulation and Blockade of Prostaglandin Biosynthesis

The Aspirin and Heme-binding Sites of Ovine and Murine Prostaglandin Endoperoxide Synthases

William L. Smith, Jr. was born in Tulsa, Oklahoma in 1945. He and his family moved to the Chicago area when he was an infant and then to Fort Collins, Colorado when he was in high school. After graduating from high school, Smith enrolled in a pre-med program at the University of Colorado in the fall of 1963, even though he had no idea what sort of career he wanted to pursue. However, this changed during the first couple years of college when he took several chemistry courses that were taught by excellent teachers. His admiration for these professors led to his decision to attend graduate school. Originally, he planned to go into physical organic chemistry but chose biological chemistry when he was told that physical organic chemistry was already a highly populated field. “Little did I know that the same thing would happen in biochemistry by the time I was searching for a position,” recalls Smith.

After graduating with a B.A. in 1967, Smith decided to attend the University of Michigan and work with William E. M. Lands. This decision was influenced by three papers by Mats Hamberg and Bengt Samuelsson (1–3) published in the *Journal of Biological Chemistry* (JBC) that Lands gave him to read. “These papers dealt with the mechanism of oxygenation of dihomo-γ-linolenic acid and other fatty acids by soybean lipoxygenase and sheep seminal vesicle cyclooxygenase (i.e. prostaglandin H2 synthase 1 or PGHS-1),” recalls Smith. “In the course of these studies they labeled the ω8 carbon (C-13) of the substrate with tritium in the
proS and proR orientations and found a distinct kinetic isotope effect in the removal of the proS hydrogen. This indicated that the rate determining step was abstraction of this hydrogen from the fatty acid. To this day, I find this to be a brilliant experiment and an exciting outcome. Almost 25 years later we provided evidence that Tyr-385 of PGHSs abstracted this hydrogen atom from the fatty acid (4).” More information on Samuelsson’s work on the prostaglandins can be found in his JBC Classic (5).

Just as Smith was finishing up his thesis work with Lands, John Vane reported that acetylsalicylic acid (aspirin) and another well known nonsteroidal anti-inflammatory drug called indomethacin blocked the biosynthesis of prostaglandins from arachidonic acid (6, 7). Smith had just set up an O2 electrode assay to measure prostaglandin production in acetone powder preparations of sheep seminal vesicle microsomes, and he and Lands immediately tested aspirin and indomethacin in this assay. As reported in the first JBC Classic reprinted here, they found that aspirin and indomethacin blocked arachidonic acid-induced O2 uptake and concluded that these drugs were blocking oxygenase activity. They also observed that the two drugs acted in a time-dependent manner, suggesting that they were causing a chemical modification of their target. Subsequently, it was shown that the acetyl group of aspirin was incorporated into a protein (8) that Smith later purified (9) in his first JBC paper as an independent scientist. The protein is now known as prostaglandin endoperoxide H synthase-1 (PGHS-1) or cyclooxygenase-1 (COX-1).

Smith completed his Ph.D. work in under 4 years, and in 1971 went to the University of California at Berkeley to work with Clinton E. Ballou. There he changed the focus of his research and worked on polysaccharide structures. Although he enjoyed this work, he decided he was more interested in solving problems that he felt were more biomedically relevant. He also realized that he still had an intense interest in prostaglandins. In 1974, Smith took a job as a senior scientist at Mead Johnson in Evansville, Indiana where he spent his time studying platelet aggregation, prostaglandin formation, and arachidonic acid mobilization.

A year later, he accepted a position in the Department of Biochemistry at Michigan State University where he remained for 28 years and served as chair for the last 8 years of his time there. At Michigan State, Smith continued to work on prostaglandins, focusing, among other things, on the acetylation of PGHS-1. Work in other laboratories suggested that aspirin was acetylating a serine residue on the enzyme (10, 11). In 1988 Smith and his long time colleague David DeWitt were able to clone and sequence PGHS-1 cDNA derived from seminal vesicles (12). They observed that the acetylated serine corresponded to Ser-530. Two years later, as reported in the second JBC Classic reprinted here, Smith and his colleagues showed that substitution of Ser-530 with alanine rendered the protein refractory toward aspirin but had relatively little effect on the kinetic properties of the cyclooxygenase. They concluded that the Ser-O-acetyl protrudes into the cyclooxygenase active site thereby interfering with arachidonic acid binding. This is the most definitive biochemical work on how aspirin works at the molecular level to interfere with cyclooxygenase activity. Smith later showed that substitutions of Ser-530 with bulkier residues such as threonine and asparagine gradually reduced cyclooxygenase activity (13).

In 2002 Smith decided to step down as Chair of Biochemistry at Michigan State, saying “My opinion is that administrators should serve no longer than American presidents.” Shortly thereafter he was given the opportunity to become Chair of the Biological Chemistry Department at the University of Michigan. Still at the University of Michigan today, he continues to work on prostaglandins.

In recognition of his many contributions to science, Smith has received several awards and honors. These include the 1991 Treadwell Award from George Washington University, the 1992 Distinguished Faculty Award from Michigan State University, the 1996 Abraham White Distinguished Scientific Achievement Award from George Washington University, the 1997 Senior Aspirin Award from Bayer Corporation, the 1999 Michigan Universities Association of Governing Boards Award, the 2004 State of Michigan Scientist of the Year Award, the 2004 Berzelius Lectureship from the Karolinska Institute, the 2004 Avanti Award from the American Society for Biochemistry and Molecular Biology, the 2006 William C. Rose Award from the American Society for Biochemistry and Molecular Biology, and the 2006 Hayaishi Lectureship from Hamamatsu University.1

1 We thank William L. Smith for providing background information for this introduction.
Smith’s co-author on the first Classic, William E. M. Lands, was a young faculty member at the University of Michigan when Smith joined his laboratory. Lands subsequently left Michigan in 1980 to become Chair of Biochemistry at the University of Illinois, Chicago, and later moved to the National Institutes of Health in 1990, where he served as the Senior Scientific Advisor to the Director of the National Institute on Alcohol Abuse and Alcoholism. Lands is the discoverer of the “retailoring” pathway for membrane phospholipid synthesis. He is an authority on essential fatty acids and is credited with recognizing the beneficial effects of balancing excess ω-6 fatty acids with dietary ω-3 fatty acids. In recognition of his work, the University of Michigan’s Department of Biological Chemistry endowed a lectureship in nutritional biochemistry in honor of Lands.

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REFERENCES