Bernard L. Horecker's Contributions to Elucidating the Pentose Phosphate Pathway

The Enzymatic Conversion of 6-Phosphogluconate to Ribulose-5-Phosphate and Ribose-5-Phosphate


Bernard Leonard Horecker (1914) began his training in enzymology in 1936 as a graduate student at the University of Chicago in the laboratory of T. R. Hogness. His initial project involved studying succinic dehydrogenase from beef heart using the Warburg manometric apparatus. However, when Erwin Hass arrived from Otto Warburg's laboratory he asked Horecker to join him in the search for an enzyme that would catalyze the reduction of cytochrome c by reduced NADP. This marked the beginning of Horecker's lifelong involvement with the pentose phosphate pathway.

During World War II, Horecker left Chicago and got a job at the National Institutes of Health (NIH) in Frederick S. Brackett's laboratory in the Division of Industrial Hygiene. As part of the wartime effort, Horecker was assigned the task of developing a method to determine the carbon monoxide hemoglobin content of the blood of Navy pilots returning from combat missions. When the war ended, Horecker returned to research in enzymology and began studying the reduction of cytochrome c by the succinic dehydrogenase system.

Shortly after he began these investigations, Horecker was approached by future Nobel laureate Arthur Kornberg, who was convinced that enzymes were the key to understanding intracellular biochemical processes. Kornberg suggested they collaborate, and the two began to study the effect of cyanide on the succinic dehydrogenase system. Cyanide had previously been found to inhibit enzymes containing a heme group, with the exception of cytochrome c. However, Horecker and Kornberg found that cyanide did in fact react with cytochrome c and concluded that previous groups had failed to perceive this interaction because the shift in the absorption maximum was too small to be detected by visual examination.

Two years later, Kornberg invited Horecker and Leon Heppel to join him in setting up a new Section on Enzymes in the Laboratory of Physiology at the NIH. Their Section on Enzymes eventually became part of the new Experimental Biology and Medicine Institute and was later renamed the National Institute of Arthritis and Metabolic Diseases.

Horecker and Kornberg continued to collaborate, this time on the isolation of DPN and TPN. By 1948 they had amassed a huge supply of the coenzymes and were able to present Otto Warburg, the discoverer of TPN, with a gift of 25 mg of the enzyme when he came to visit. Horecker also collaborated with Heppel on the isolation of cytochrome c reductase from yeast and eventually accomplished the first isolation of the flavoprotein from mammalian liver.

Along with his lab technician Pauline Smyrniotis, Horecker began to study the enzymes involved in the oxidation of 6-phosphogluconate and the metabolic intermediates formed in the pentose phosphate pathway. Joined by Horecker's first postdoctoral student, J. E. Seegmiller, they worked out a new method for the preparation of glucose 6-phosphate and 6-phosphogluconate, both of which were not yet commercially available. As reported in the Journal of Biological Chemistry (JBC) Classic reprinted here, they purified 6-phosphogluconate dehydrogenase from brewer's yeast (1), and by coupling the reduction of TPN to its reoxidation by...
pyruvate in the presence of lactic dehydrogenase, they were able to show that the first product of 6-phosphogluconate oxidation, in addition to carbon dioxide, was ribulose 5-phosphate. This pentose ester was then converted to ribose 5-phosphate by a pentose-phosphate isomerase. They were able to separate ribulose 5-phosphate from ribose 5-phosphate and demonstrate their interconversion using a recently developed nucleotide separation technique called ion-exchange chromatography. Horecker and Seegmiller later showed that 6-phosphogluconate metabolism by enzymes from mammalian tissues also produced the same products.

Over the next several years, Horecker played a key role in elucidating the remaining steps of the pentose phosphate pathway. His total contributions included the discovery of three new sugar phosphate esters, ribulose 5-phosphate, sedoheptulose 7-phosphate, and erythrose 4-phosphate, and three new enzymes, transketolase, transaldolase, and pentose-phosphate 3-epimerase. The outline of the complete pentose phosphate cycle was published in 1955 (2). Horecker’s personal account of his work on the pentose phosphate pathway can be found in his JBC Reflection (3).1

Horecker’s contributions to science were recognized with many awards and honors including the Washington Academy of Sciences Award for Scientific Achievement in Biological Sciences (1954) and his election to the National Academy of Sciences in 1961. Horecker also served as president of the American Society of Biological Chemists (now the American Society for Biochemistry and Molecular Biology) in 1968.

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REFERENCES

1 All biographical information on Bernard L. Horecker was taken from Ref. 3.