Earl W. Sutherland’s Discovery of Cyclic Adenine Monophosphate and the Second Messenger System

Formation of a Cyclic Adenine Ribonucleotide by Tissue Particles

Fractionation and Characterization of a Cyclic Adenine Ribonucleotide Formed by Tissue Particles

Earl Wilbur Sutherland, Jr. (1915–1974) was born in Burlingame, KS. After reading a book about Louis Pasteur in high school he decided to go into medical research. He obtained his B. S. from Washburn University in Topeka, KS in 1937 and his M.D. from the Washington University School of Medicine in St. Louis in 1942. He stayed at Washington University for the next 11 years, eventually obtaining the title of Associate Professor of Biochemistry. In 1953, Sutherland moved to Cleveland, OH, where he became professor and director of the pharmacology department at the Western Reserve School of Medicine and remained until 1963 when he became Professor of Physiology at the Vanderbilt University School of Medicine. In 1973 Sutherland moved to the University of Miami. There he was appointed Distinguished Professor of Biochemistry, a position he held until his death.

In 1958, while at Western Reserve, Sutherland made the discovery that would lead to his 1971 Nobel Prize in Physiology or Medicine “for his discoveries concerning the mechanisms of the action of hormones.” It was at that time that Sutherland isolated a previously unknown compound, called cyclic adenine monophosphate (cAMP) and proved that it had an intermediary role in many hormonal functions. This is the subject of the two Journal of Biological Chemistry (JBC) Classics reprinted here. These two papers by Sutherland are the first in a series of three Nobel pieces of work on epinephrine and cAMP. The next Classic in the series will explain how Edwin Krebs and Edmond Fischer showed that epinephrine and cAMP stimulate glycogen breakdown by activating glycogen phosphorylase via a protein kinase. This will be followed by Classic papers by Alfred Gilman showing how epinephrine stimulates cAMP formation.

Sutherland started his studies on hormones at Washington University in collaboration with Nobel laureates Carl and Gerty Cori, who were the subjects of a previous JBC Classic (1). With the Coris, Sutherland investigated the mechanism by which epinephrine regulates the degradation of glycogen to glucose in the liver. He discovered that epinephrine acts by activating phosphorylase, which leads to the formation of glucose from glycogen.

After moving to Western Reserve, Sutherland, joined by Ted Rall, continued to study the epinephrine-phosphorylase system. They observed that the increased formation of phosphorylase in liver was mediated by a heat-stable factor. Chemical analysis showed that the compound was an adenine ribonucleotide, but its properties were unusual. Sutherland wrote to Leon Heppel hoping that he might be able to help elucidate its structure. Around the same time, David Lipkin wrote Heppel describing a new nucleotide that was produced by treating ATP with barium hydroxide. Heppel deduced that Sutherland and Lipkin were studying the same molecule, which turned out to be adenosine 3′,5′-monophosphate, now commonly referred to as cyclic AMP or cAMP.

In the first JBC Classic reprinted here, Sutherland and Rall discuss the conditions required for the formation of cAMP and its prevalence in various organs. They discovered that the
compound was present not only in liver preparations but also could be found in the heart, skeletal muscle, and brain. Using [8,14C]ATP they also found that the formation of cAMP involves the cyclization of ATP. In the second JBC Classic reprinted here Sutherland and Rall describe the ion exchange purification and crystallization of cAMP as well as some of its properties.

Sutherland’s discovery and chemical characterization of the cAMP intermediate or “second messenger” was of crucial importance for understanding the mechanism of action of epinephrine and of many other hormones. His discovery implied that epinephrine induces the formation of cAMP in the liver cells and that the nucleotide then converts the inactive phosphorylase to the active enzyme, which leads to the formation of glucose.

However, this gave rise to the question of how the hormone stimulates the formation of cAMP from AMP. Sutherland found that this took place by way of an enzyme he called adenyl cyclase. Thus, according to Sutherland’s scheme, epinephrine binds to a cell surface receptor, which stimulates adenyl cyclase, causing the formation of cAMP, which then exerts its effect in the cell by activating phosphorylase. Sutherland later suggested that the effects of many other hormones could be explained on essentially similar lines and that the various hormones do not enter the cell but instead bind to surface receptors causing the formation of cAMP which then activates or inhibits various metabolic processes.

This general hypothesis was first met with strong criticism by scientists because it seemed to be impossible that a single substance could lead to the numerous effects caused by different hormones. However, eventually it was shown that a large number of polypeptide hormones do exert their effects by way of cAMP, and Sutherland was awarded the 1971 Nobel Prize.

In addition to the Noble Prize, Sutherland has received many honors for his research. He was elected to the National Academy of Sciences in 1966 and was awarded the National Medal of Science in 1973. Sutherland served on the National Institutes of Health Pharmacology Training Committee and the Arthritis and Metabolic Disease Program Committee. He was also active on the editorial boards of many journals, including Biochemical Preparations and the Journal of Pharmacology and Experimental Therapeutics.1

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REFERENCES


1 All biographical information on Earl W. Sutherland was taken from Ref. 2.
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