Annals of Pharmacology and Pharmaceutics

Review Article
Published: 06 May, 2020

Earl W Sutherland (1915-1974) and the Concept of Second Messengers

*Ronald P Rubin**

Department of Pharmacology and Toxicology, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, USA

Abstract

The discovery of cAMP in the liver by Earl Sutherland in 1956 was paradigmatic and of fundamental biological significance because it revealed how hormones and neurotransmitters exert their selective effects on cells. This work spawned studies in many other cell types that demonstrated the occurrence of a signaling mechanism that regulated a variety of cell functions and metabolic processes, such as lipolysis, glycogenolysis, as well as permeability of ion channels and gene expression. Sutherland expanded his analysis of second messenger systems by focusing on cGMP, which is also widely distributed in mammalian tissues but differs from cAMP in its basic properties. By establishing the field of second messenger systems, Earl Sutherland laid the foundation of a new concept of cell regulation. He clearly ranks as a memorable figure in the annals of scientific immortals.

Keywords: cAMP; Cyclic nucleotides; Adenylyl cyclase; Second messenger systems; Cell regulation; cGMP; Phosphorylation

Introduction

Earl Sutherland was born in a small town in Kansas [1]. His father had been a farmer and a dry goods salesman, and his mother nurtured young Earl's interest in science. He was also reared to be an independent individual. Due to a financial setback in his family, Sutherland supported himself through college, working as a hospital orderly. Sutherland graduated from Washburn College in Topeka Kansas in 1937 and earned an MD degree from Washington University in St. Louis in 1942. Following an internship in medicine, Sutherland began his research career in the laboratory of Carl and Gerty Cori in the Department of Pharmacology at Washington University (Figure 1).

The Coris had created a department of excellence in which individuals worked synergistically to produce a highly productive environment. The first hormone (epinephrine) was discovered by Oliver and Schaefer during the latter part of the 19th century. Beginning in the late 1920's, the mechanism involved in glycogen breakdown to glucose during stress was investigated by the Coris. They identified phosphorylase, phosphoglucomutase, and glucose 6-phosphatase as the major enzymes involved in this process [2,3].

Young Sutherland was given the task as a student assistant to work with a graduate student named Sidney Colowick to study the enzymatic formation of glycogen. Their collaboration gave Sutherland his first two publications [1,4]. Sutherland's first publication in 1941 was a letter to the Editor of the Journal of Biological Chemistry on the enzymatic conversion of glucose-6-phosphate to glycogen. This initial work would provide the impetus for Sutherland to discover cAMP some fifteen years later at Case Western Reserve.

During World War II, Sutherland served as a physician in George Patton's army in Europe. After returning home in 1945, he considered entering clinical practice. However, Carl Cori, recognizing Sutherland's talent, convinced him to continue his career in research. So, Sutherland remained at Washington University as a pharmacology assistant in the Department of Pharmacology. He rose through the ranks to become Associate Professor and eventually became Professor of Biochemistry [1].

Early Career at Washington University

The phosphorylation-dephosphorylation reaction is a basic energy releasing process of cells. One of Sutherland's first discoveries was that glycogen phosphorylase was the rate-limiting enzyme involved in glucose release by glycogen breakdown [5,1]. He later demonstrated that the activation of the enzyme was accompanied by its conversion from an inactive to an active form [6]. By

OPEN ACCESS

Correspondence:
Ronald P Rubin, Department of Pharmacology and Toxicology, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, Buffalo, New York, 14214, USA,
E-mail: rprubin@buffalo.edu

Received Date: *09 Apr 2020*
Accepted Date: *04 May 2020*
Published Date: *06 May 2020*

Citation:
Rubin RP. Earl W Sutherland (1915-1974) and the Concept of Second Messengers. Ann Pharmacol Pharm. 2020; 5(4): 1188.

discovering early on in his career that phosphorylase was the rate-limiting step in glycogenolysis in liver and muscle, Sutherland made a fundamental advance in our understanding of metabolic processes.

In the early 1940's, Sutherland moved to the Biochemistry Department when Carl Cori became the Chair of Biochemistry. This period in the career of Earl Sutherland was an exciting one. The department created by the Coris was a Mecca for research, and Sutherland was fortunate to work side-by-side with several future Nobel-Prize winning scientists, including Severo Ochoa, Arthur Kornberg, Edwin Krebs, and Christian de Duve [1]. It was a highly competitive but synergistic environment, where contributions to biomedical science were extensive and far-reaching.

In late 1940's, when Sutherland began his studies on hormone action, the prevailing sentiment among his fellow scientists was that hormones could not be investigated in the absence of organized cell structure. However, Sutherland was resolute in his view that cell structure had to be incorporated into research protocols. So, instead of simply utilizing broken cell preparations, he developed an *in vitro* test system consisting of liver slices, cell extracts, and purified enzymes [7].

Transition to Western Reserve and the Discovery of cAMP

In 1953 Sutherland moved to the Department of Pharmacology at Case Western Reserve in Cleveland Ohio as Professor and Chair of the Department of Pharmacology. His initial work there involved adding hormones to different enzyme preparations with minimal success. However, after several modifications, Sutherland and Ted Rall [8] were able to demonstrate the stimulatory effects of hormones in broken cell preparations. This work represented a novel finding and encouraged them to continue their investigations.

By differential centrifugation, Sutherland and Rall [9] found that the addition of hormone to the particulate fraction resulted in the production of a heat stable product, which in turn activated phosphorylase when the factor was added back to the supernatant fraction. The heat stable factor was determined to be an adenine nucleotide produced by the liver, heart, brain, and skeletal muscle. In 1958 the factor was identified as cAMP (Figure 2) [10,11].

The subsequent finding by Krebs et al. [12] that cAMP-dependent kinase mediated many of the actions of cAMP by hormones and pharmacological agents complemented the studies of Sutherland and Rall. These findings, taken together, strongly supported the idea that epinephrine-induced cAMP formation converts the inactive form of glycogen phosphorylase to the active form, which leads to the release of glucose from glycogen in liver.

Many scientists were skeptical that a nucleotide that was resistant to boiling, could elicit a variety of cell-specific actions by diverse hormones. Nevertheless, the validity of this idea was brought into sharp focus by the findings of Robert Haynes, working in a neighboring laboratory. He found that cAMP served as an intermediate in the stimulation of phosphorylase and steroid hormone output from the adrenal cortex by ACTH [13,14].

After David Lipkin et al.[15] isolated cAMP from a digestate of ATP, established its structure, and described its chemical properties, Sutherland [16] felt confident enough to propose in the early 1960's that cAMP served as a second messenger for a variety of hormones and neurotransmitters [16,17]. By the late 1960's incontrovertible evidence had been compiled to establish cAMP as a cellular mediator [18,19].

The ability of cells to stimulate cAMP synthesis in a wide distribution of cell types prompted further investigation into the biochemical mechanisms involved in this process. Sutherland and his colleagues addressed this issue by identifying adenylyl cyclase as the enzyme that catalyzed cAMP synthesis [20-22]. They also discovered phosphodiesterase, the enzyme that degrades cAMP [23,24]. Both of these enzyme systems were found to be widely distributed in tissues.

There were broad implications to Sutherland's discovery. The ubiquitous presence of cAMP in tissues signified the widespread occurrence of a signaling mechanism in diverse cell types that was not previously understood in biochemical terms. Experiments using the rat heart were of particular importance since they laid the groundwork regarding the relationship between changes in cyclic AMP levels and cardiac activity [25].

Move to Vanderbilt and the Discovery of cGMP

To devote more time to research, and because of changes in the administration of the University, Sutherland decided to move to Vanderbilt University in 1963 [26]. Because he envisioned the production of multiple second messengers, Sutherland then directed his attention to cGMP. Cyclic GMP was first identified in rat urine by Price et al. [27] in 1959 and subsequently was found in many mammalian tissues by Sutherland and his co-workers [28,29]. However, the concentration of cGMP in tissues was 1-2 orders of magnitude less than cAMP, so that its quantization was delayed for several years.

Nevertheless, Sutherland and Hardman did eventually conclude that cGMP synthesis was regulated by guanylyl cyclase and that the enzyme differed from cAMP in its cellular distribution and ion activation [30]. In addition, the enzyme was stimulated by cholinergic agonists, nitroso compounds, and a number of vasoactive peptides [31]. Other studies determined that cGMP, like cAMP, was a regulator of certain ion channels [32,33].

Move to the University of Miami

In 1973, Sutherland moved to the University of Miami to become Distinguished Professor of Biochemistry [34]. By then, in addition to the role played by cAMP in cell activation, it had been established that the biochemical mechanisms of hormone action were not solely mediated by cAMP and cGMP, but also included other second messengers, such as calcium, eicosanoids, and nitric oxide, inositol trisphosphate and diacylglycerol [35].

Despite still being productive, particularly in the area of cGMP, Sutherland was in failing health. In view of the fact that he passed away at the early age of 57, the contributions made by Earl Sutherland were even more remarkable. His last two articles were published in 1976 [36,37].

An Enduring Legacy

The profound significance of Sutherland's work is underscored by the subsequent studies carried out by other Nobel Prize-winning scientists who based their work on Sutherland's contributions. Paul Greengard [38] demonstrated the activation of cAMP-dependent protein kinase in brain was a key factor in controlling neuronal excitability. Sutherland also provided the basis for the work of Robert

Figure 1: Earl W. Sutherland. (Taken from Nobel Prize.org).

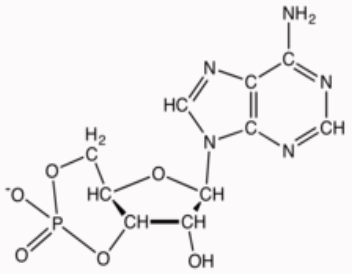

Figure 2: Cyclic adenosinemonophosphate (cyclic AMP).

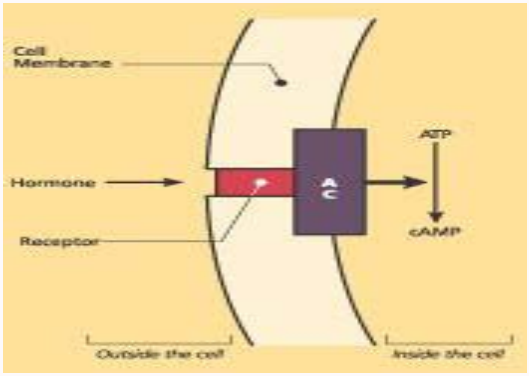

Figure 3: Schematic model depicting the generation of cAMP by hormone. (Taken from:Rodbell's Inspiration -Sutherland's Second Messenger. https://history.nih:gov/exhibits/rodbell/text/3_1_rodbell.htm.)

Furchgott, Ferid Murad, and Louis Ignarro on the role of nitric oxide-cGMP in regulating smooth muscle contraction [39,40]. Finally, the work of Alfred Gilman Jr. and Martin Rodbell on elucidating the role of G-proteins in regulating adenylyl cyclase must also be attributed to Sutherland's legacy [41].

In 1971, Earl Sutherland became first sole winner of the Nobel Prize in 11 years for elucidating the mechanisms involved in hormone action [42]. Sutherland was particularly unique in that he not only made a discovery of monumental importance, but he continued to develop a large portion of the new field himself.

Sutherland's legacy also endures in the form of the students that he trained, and who subsequently established their own successful careers. In addition to Ted Rall, these individuals included: Joel Hardman, Reginald Butcher, G. Alan Robison, and Gunter Schultz. The great interest that he took in their successful careers underscored the outstanding profile of Sutherland as a mentor, as well as a researcher.

Personal Qualities

Earl Sutherland had the ability to differentiate between important and unimportant observations, and he ventured into unknown territory to address the significant questions. Although he was highly original in developing his own concepts, Sutherland could remember important discoveries that fellow scientists had carried out in the distant past. He also had a gift for intuition, which he employed with tenacity. He was also a master of experimental design and was able to perceive the fundamental basis of a problem. Although he strongly believed in open scientific communication, Sutherland had a strong sense of independence of thought. He was always independent and direct, manifesting the person of a typical mid-Westerner. But above all, Sutherland's persistence in advancing the basic idea that the action of a hormone could be demonstrated in a cell-free system led him to scientific advances that are regarded as among the most fundamental in cell biology [43,1].

Selected Awards and Honors

In addition to the Nobel Prize, Earl Sutherland received many honors and awards for his work. He was the recipient of a Career Investigator Award and the Achievement Award from the American Heart Association. He was also a member of the US National Academy of Sciences, and received the National Medal of Science, the Lasker Award, and the Banting Memorial Lectureship. At Vanderbilt University, a Chair in Pharmacology was established in his honor, as well as a Lectureship and the Sutherland Prize for Research [44]. While it is difficult to encapsulate Sutherland's accomplishments in one brief overview, Martin Rodbell offered a fitting tribute to him in the form of an unembellished cell model depicting hormone stimulation of cAMP (Figure 3) [45].

Epilogue

Earl Sutherland went on a scientific journey that placed him in the ranks of true scientific pioneers. By establishing the concept of second messenger systems and cell signaling, he created a paradigm for research that would endure during the second half of the twentieth century and beyond. Clearly, Earl Sutherland ranks as a memorable figure in the annals of scientific immortals.

Addendum

A primary objective of this article was to be selective in summarizing the major scientific contributions of Earl Sutherland, and not to cite every one of his important publications.

References

1. Carl CF, Earl W. Sutherland (November 19, 1915-March 9, 1974). A biographical memoir. National Academy of Sciences; New York. 1978.
2. Simoni RD, Hill RL, Vaughan M. Carbohydrate metabolism: Glycogen phosphorylase and the work of Carl F. and Gerty T. Cori. 1928-1943. J Biol Chem. 2002;277(29):18e.
3. Rubin RP. Carl and Gerty Cori: A collaboration that changed the face of biochemistry. J Med Biogr. 2019;967772019866954.
4. Sutherland EW, Colowick SP, Cori CF. The enzymatic conversion of glucose-6-phosphate to glycogen. J Biol Chem. 1941;140:309-10.
5. Colowick SP, Sutherland EW. Polysaccharide synthesis from glucose by means of purified enzymes. J Biol Chem. 1942;144(2):423-37.

6. Sutherland EW, Wosilait WD. The relationship of epinephrine and glucagon to liver phosphorylase. I. Liver phosphorylase: preparation and properties. J Biol Chem. 1956;218(1):459-68.

7. Rall TW, Sutherland EW, Wosilait WD. The relationship of epinephrine and glucagon to liver phosphorylase. III. Reactivation of liver phosphorylase in slices and in extracts. J Biol Chem. 1956;218(1):483-95.

8. Sutherland EW, Wosilait WD. Inactivation and activation of liver phosphorylase. Nature. 1955;175(4447):169-70.

9. Sutherland, Earl W. Studies on the mechanism of hormone action. Nobel Lecture. In: LesPrixNobel en. Stockholm; Norstedt and Saer. 1971;5:240-57.

10. Rall TW, Sutherland EW. Formation of a cyclic adenine ribonucleotide by tissue particles. J Biol Chem. 1958;232(2):1065-76.

11. Sutherland EW, Rall TW. Fractionation and characterization of a cyclic adenine ribonucleotide formed by tissue particles. J Biol Chem. 1958;232(2):1077-92.

12. Krebs EG Walsh DA, Perkins JP. An adenosine 3'-5'-monophosphate-dependent protein kinase from rabbit skeletal muscle. J Biol Chem. 1968;243(13):2763-5.

13. Haynes RC Jr. The activation of adrenal phosphorylase by the adrenocorticotropic hormone. J Biol Chem. 1958;233(5):1220-2.

14. Haynes RC Jr, Koritz SB, Peron FG. Influence of adenosine 3'-5'-monophosphate on corticoid production by rat adrenal glands. J Biol Chem. 1959;234(6):1421-3.

15. Lipkin D, Cook WH, Markham R. Adenosine-3':5'-phosphoric acid: A proof of structure. J Amer Chem Soc. 1959;81(23):6198-203.

16. Sutherland EW Jr. The biological role of adenosine 3'5'-monophosphate. Harvey Lectures. Academic Press; New York. 1962;57:12-33.

17. Sutherland EW, Robison GA. The role of cyclic 3,5-cAMP in response to catecholamines and other hormones. Pharmacol Rev. 1966;18(1):145-61.

18. Sutherland EW, Robison GA, Butcher RW. Some aspects of the biological role of adenosine 3,5-monophosphate (cyclic AMP). Circulation. 1968;37(2):279-306.

19. Robison GA, Butcher RW, Sutherland EW. Cyclic AMP. Annu Rev Biochem. 1968;37(1):149-74.

20. Rall TW, Sutherland EW, Menon T. Adenyl cyclase. I. Distribution, preparation, and properties. J Biol Chem. 1962;237(4):1220-7.

21. Sutherland EW Jr. The biological role of adenosine 3',5'- phosphate. The Harvey Lectures. Academic Press; New York. 1962;57:17-33.

22. Klainer LM, Chi YM, Freidberg SL, Rall TW, Sutherland EW. Adenyl cyclase. IV. The effects of neurohormones on the fate of adenosine 3'5'-monophosphate from preparations of brain and other tissues. J Biol Chem. 1962;237:1239-43.

23. Butcher RW, Sutherland EW. Adenosine 3'5'- monophosphate in biological materials. I. Purification and properties of cyclic 3'5'-nucleotide phosphodiesterase and the use of this enzyme to characterize adenosine 3'5'-monophophosphate in human urine. J Biol Chem. 1962;237:1244-50.

24. Patterson WD, Hardman JG, Sutherland EW. Apparent multiple forms of cyclic AMP phosphodiesterase from rat erythrocytes. Molec Cell Endocrinol. 1976;5(1-2):51-66.

25. Robison GA, R.W. Butcher, Oye I, Morgan H, Sutherland EW. The effect of epinephrine on adenosine 3'5'-phosphate levels in isolated perfused rat heart. Molec Pharmacol. 1965;1(2):168-77.

26. Carl F. Earl W. Sutherland (November 19, 1915-March 9, 1974). A Biographical Memoir. 1978;328-33.

27. Price TD Ashman DF, Lipton R, Melicow MN. Isolation of adenosine 3'5'-monophosphate and guanosine 3'5'-monophosphate from rat urine. Biochem Biophys Res Commun. 1963;11:330-4.

28. Hardman JG, Beavo JA, Gray JP, Chrisman TD, Patterson WD, Sutherland EW. The formation and metabolism of cyclic GMP. Ann N Y Acad Sci. 1971;185:27-35.

29. Hardman JG, Robison GA, Sutherland EW. Cyclic nucelotides. Ann Rev Physiol. 1971;33:311-36.

30. Hardman JG, Sutherland EW. Guanyl cyclase, an enzyme catalyzing the formation of guanosine 3'5'-monophosphate from guanosine trisphosphate. J Biol Chem. 1969;244(23):6363-70.

31. Murad F, Mittal CK, Arnold WP, Katsuki S, Kimura H. Guanylate cyclase: Activation by azide, nitro compounds, nitric oxide, and hydroxyl radical and inhibition by hemoglobin and myoglobin. Adv Cyclic Nucleotide Res. 1978;9:145-58.

32. Yau KW. Cyclic nucleotide-gated channels: An expanding new family of ion channels. Proc Natl Acad Sci USA. 1994;91(9):3481-3.

33. Matulef K, Zagotta WN. Cyclic nucleotide-gated ion channels. Annu Rev Cell Dev Biol. 2003;19:23-44.

34. Cori Carl F. Earl W. Sutherland (November 19, 1915-March 9, 1974). A Biographical Memoir. In: Earl W. Sutherland Jr. University of Miami; School of Medicine; Calder Library. 1978;333.

35. Pollard TD, Earnshaw C, Lippincott-Schwartz J, Johnson G. Second messengers. In: Pollard TD, editor. Cell biology. 3rd ed. Elsevier Inc. 2017;443-62.

36. Zeilig CE, Johnson RA, Sutherland EW, Friedman DL. Adenosine 3'5'-monophosphate content and actions in the division cycle of synchronized HeLa cells. J Cell Biol. 1976;71(2):515-34.

37. Patterson WD, Hardman JG, Sutherland EW. Apparent multiple forms of cyclic AMP from rat erythrocytes. Mol Cell Endocrinol. 1976;5(1-2):51-66.

38. Greengard P, Kuo JF. On the mechanism of action of cAMP. Adv Biochem Psychopharmacol. 1970;3:287-303.

39. Furchgott RF. The requirement for endothelial cells in the relaxation of arteries by acetylcholine and some other vasodilators. Trends Pharmacol Sci. 1981;2:173-5.

40. Ignarro LJ, Buga GM, Wood KS, Byrns RE, Chaudhuri G. Endothelium-derived relaxing factor produced and released from artery and vein is nitric oxide. Proc Soc Natl Acad Sci USA. 1987;84(24):9265-9.

41. Rodbell M. The role of hormone receptors and GTP-regulatory proteins in membrane transduction. Nature. 1980;284(5751):17-22.

42. Gilman, Alfred G. Nobel Lecture. Nobel Prize.org. Nobel Media AB. 2020;2020.

43. Sutherland EW Jr. Facts NobelPrize.org. Nobel Media AB 2020;1971.

44. Butcher RW, Robison GA. An Appreciation of Earl Sutherland. Metabolism. 1975;24(3):237-40.

45. Kresge N, Simoni RD, Hill RL. Earl Sutherland's discovery of cyclic adenosine monophosphate and the second messenger system. J Biol Chem. 2005;280:e39.