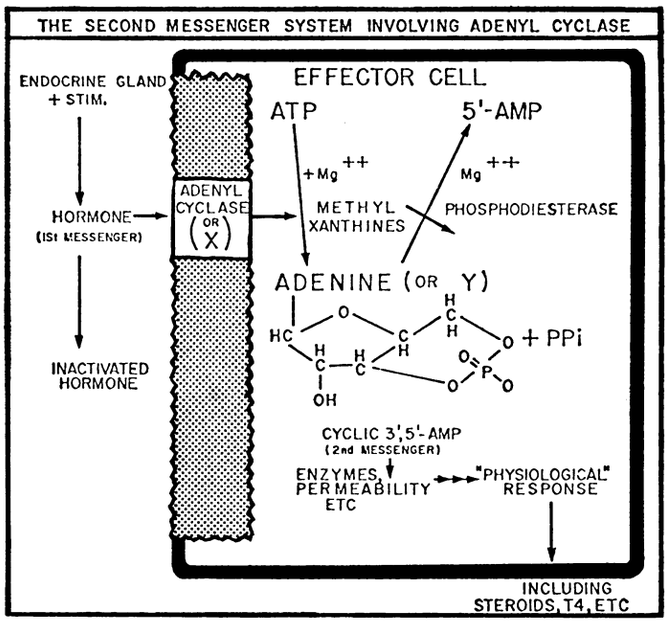
A second messenger

Cyclic AMP, a regulator of virtually all hormone activity, is one of biology's prime new research targets

by Barbara J. Culliton



Cyclic AMP operates through a complex metabolic network.

Fear or excitement induces a well-known response in the human body: Adrenalin begins to flow in prodigious amounts and the heart beats faster. But in truth, adrenalin deserves only partial credit for enabling man to react to stress. The hormone, according to Dr. Earl W. Sutherland, is merely the first messenger in a complex communications network. In fact, he says, direct stimulation of the heart comes from another chemical, cyclic AMP (cyclic adenosine 3′,5′-monophosphate).

Dr. Sutherland, professor of physiology at Vanderbilt University Medical School in Nashville, discovered cyclic AMP in 1958 and has pioneered in its study ever since. He describes cyclic AMP as a second messenger system, an intracellular agent that mediates the action of most, if not all, of the body's hormones. This year, he won the Albert Lasker Award for Basic Medical Research in recognition of his achievements (SN: 11/14, p. 382). The avenues he opened for exploring the processes of hormonal systems are now being followed by literally hundreds of investigators as cyclic AMP research emerges as one of the more important, and more fashionable, of new fields in biology.

Every living animal tissue makes cyclic AMP. It is a second messenger that does the work for a number of hormones. Hormones, which are produced in various glands and sent out to act on target tissues, act as intercellular communicators, delivering messages from one part of the body to another. From there, cyclic AMP takes up the communications function, acting within cells to alter membrane permeability and influence enzyme activity.

Its functions are legion, and varied. Generally, when a hormone reacts with a target cell, intracellular levels of cyclic AMP are changed—sometimes up, sometimes down. And because different cells contain different systems for responding to the chemical messages hormones deliver, changes in cyclic AMP levels produce different effects depending upon the type of cell in which they occur.

Cyclic AMP is formed in cells through a metabolic process in which the enzyme adenyl cyclase acts on the body's energy compound, ATP (adenosine triphosphate), converting it to cyclic AMP. Most of the hormones that act by raising cyclic AMP levels are thought to do so by stimulating this enzyme. Thus, cyclic levels are increased by the pituitary hormones—ACTH and thyroid-stimulating hormone—by serotonin, by histamine and, in some cases, by certain of the prostaglandins (SN: 10/10, p. 306). Insulin, melatonin and, in some cases, prostaglandins, are among agents known to decrease cyclic levels. Prostaglandins, according to Drs. Jane Shaw and Peter Ramwell of the Alza Corp. in Palo Alto, Calif., increase cyclic levels in the ovaries, corpus luteum and thyroid gland and reduce levels in fat tissues.

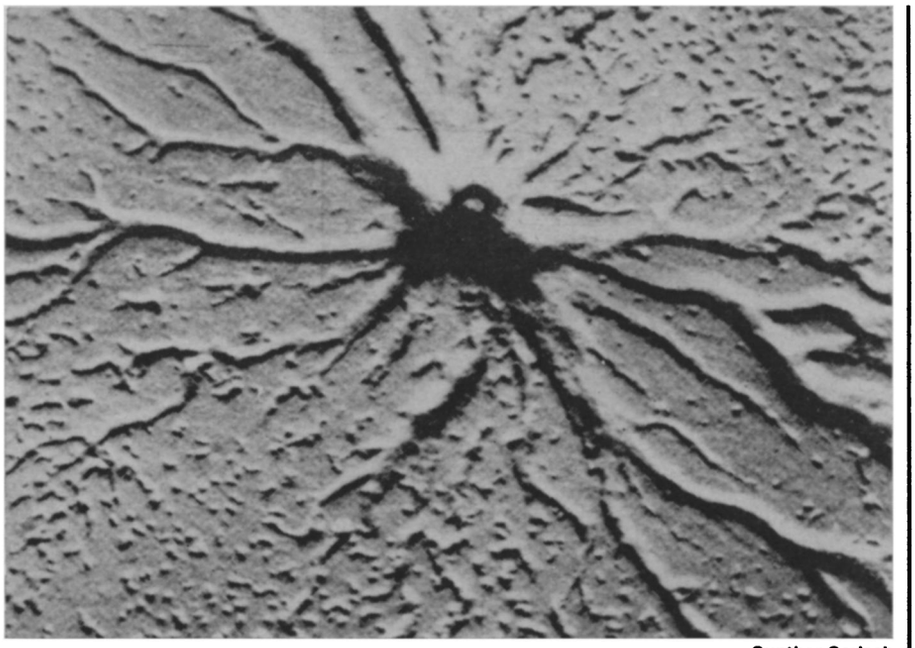
In the kidney, cyclic AMP mediates the activity of parathyroid hormone, which in turn regulates levels of calcium in blood (SN: 11/21, p. 396). Disturbances in this complex hormonal system can lead to serious bone, muscle and nervous system disorders.

Functioning of platelets or white blood cells has also been examined in relationship to cyclic AMP. At a New York Academy of Sciences symposium on cyclic AMP last month, a team of Dr. Sutherland's colleagues summarized their own work and that of other investigators. Drs. Brian Cole, G. Alan Robison and Robert Hartmann described the role of cyclic AMP in platelet aggregation. In response to stimulation by prostaglandins, intracellular levels of cyclic AMP in platelets rise, inhibiting aggregation. Thus, an association between cyclic levels and abnormal clotting or embolism formation is established. Platelets with too little cyclic AMP tend to clump together. In the reverse situation, too much cyclic in platelets could inhibit the normal patterns of blood clotting that follow injury.

The clinical implications of what is now a massive catalogue of basic knowledge about cyclic AMP are only beginning to emerge. As yet, there is no precise way to alter physiology by deliberately altering cyclic levels in a given tissue, though Dr. Sutherland forsees that eventuality. Before that, however, cyclic AMP levels will be used as indicators in the diagnosis of certain kinds of disorders.

Parathyroid diseases are an example. Patients with a relatively rare disease known as pseudohypoparathyroidism excrete too little cyclic AMP in urine after they have been given with parathyroid hormone, a known cyclic raiser in healthy individuals. Persons with hyperparathyroidism, by contrast, excrete too much cyclic AMP in their urine.

Cyclic AMP levels have also been correlated with manic-depressive disease. Individuals diagnosed as manic have been shown to have abnormally high cyclic levels. Preliminary data further indicate that lithium, a controversial drug some investigators find useful in controlling mania (SN: 4/18,



Gunther Gerisch

Cellular slime mold cells aggregate when signaled by cyclic AMP.

p. 390), inhibits the formation of cyclic AMP and thereby provides new insight into how that compound may be exerting its effect.

Dr. Sutherland himself proposes a possible connection between cyclic AMP activity and diabetes. Because insulin decreases levels of excreted cyclic AMP, he reasons, it may mean that there is an excess of the chemical in the liver, in turn leading to overproduction of glucose.

But much remains to be learned about cyclic AMP. First, while it is thought that hormones that raise cyclic levels do so by stimulating the enzymatic activity of adenyl cyclase, there is little evidence regarding the mechanisms by which cyclic-lowering hormones work. One enzyme, phosphodiesterase, has been identified as a destroyer of cyclic AMP, but there is virtually no evidence that cyclic-lowering hormones, such as insulin, operate through this channel. Again, while some hormones appear to act by releasing cyclic AMP, others seem to perform their function through a less direct, and still unclear, mechanism. "Eventually," Dr. Sutherland says, "the second messenger concept may be modified to create a more general concept."

In certain microorganisms, for example, cyclic AMP may be a first rather than a second messenger. The cellular slime mold is a case in point. Dr. Francis Bonner of Princeton University has shown that cyclic AMP is the chemical signal that initiates aggregation of individual slime mold cells in an unusual process by which single-cell organisms come together to form multicellular organisms. These creatures are being studied by several groups of scientists interested in the phenomenon of cellular differentiation (SN: 2/28, p. 215).

Vanderbilt Univ.

Sutherland: Discovered cyclic AMP.

Another unexplained piece of the cyclic AMP picture is the existence of a related substance called cyclic GMP (cyclic guanosine 3′,5′-monophosphate), the only other cyclic nucleotide known to occur naturally.

According to Dr. J. G. Hardman of Vanderbilt, cyclic GMP is about one one-hundredth as potent as cyclic AMP, occurs in tissues at levels only about 10 percent of those of cyclic AMP and seems to act independently of AMP. "All indications," he says, "are that cyclic GMP is not a physiological substitute for cyclic AMP." Indeed, although it was discovered seven years ago, virtually nothing is known about its function, except that it too appears to play some regulatory function in association with hormones. □