

## CLINICAL IMPLICATIONS OF BASIC RESEARCH

### G PROTEINS IN MEDICINE

THE award of the 1994 Nobel Prize in Physiology or Medicine to Alfred G. Gilman and Martin Rodbell for the discovery of G (guanine nucleotide-binding) proteins and their role in cellular signal transduction has focused attention on the manifold functions of these ubiquitous molecules and on the ways in which they can become disordered in human diseases. These molecules couple a dizzying array of receptors at the cell surface (including those for neurotransmitters such as epinephrine, hormones, odorants, and photons of light) with a variety of intracellular effectors exposed at the inner surface of the plasma membrane (including enzymes such as adenylate cyclase and ion channels). This design explains how such extracellular “first messengers” as hormones generate intracellular “second messengers” such as cyclic AMP (cAMP) — an idea originally proposed by Earl Sutherland (a previous Nobel laureate) more than 30 years ago.

As Figure 1 shows, G proteins function essentially as on-off switches for cellular signaling. They consist of three nonidentical protein subunits ( $\alpha$ ,  $\beta$ , and  $\gamma$ ) that are noncovalently associated. In the resting state, the nucleotide guanosine diphosphate (GDP) is tightly

bound to the  $\alpha$  subunit. This is the “off” position of the G-protein switch. When the membrane receptor is activated — for example, by the binding of a hormone — it interacts with the G protein, causing GDP to dissociate from the  $\alpha$  subunit. GDP is rapidly replaced by guanosine triphosphate (GTP), which activates the G protein. This in turn leads to its dissociation into  $\alpha$ -subunit and  $\beta\gamma$ -subunit complexes, either or both of which can activate effectors. The switch is now “on.” Within a few seconds the  $\alpha$  subunit, which is a guanosine triphosphatase (GTPase), hydrolyzes GTP to GDP. This inactivates the  $\alpha$  subunit, allows it to reassociate with the  $\beta\gamma$  subunit, and resets the switch to the off position. Many different G proteins mediate diverse physiologic effects by this mechanism.

Given the ubiquitous distribution of G proteins and the remarkable diversity of their functions, it should come as no surprise that alterations in their structure or expression might have serious pathophysiologic consequences. Such alterations may either increase or decrease the activity of the affected G protein.

A dramatic example of decreased function was discovered in patients with pseudohypoparathyroidism (Albright’s hereditary osteodystrophy), which is a syndrome of generalized resistance to the action of a variety of hormones combined with several dysmorphic characteristics. Most patients with this disorder have a 50 percent reduction in the activity of  $G_s$ , the G protein

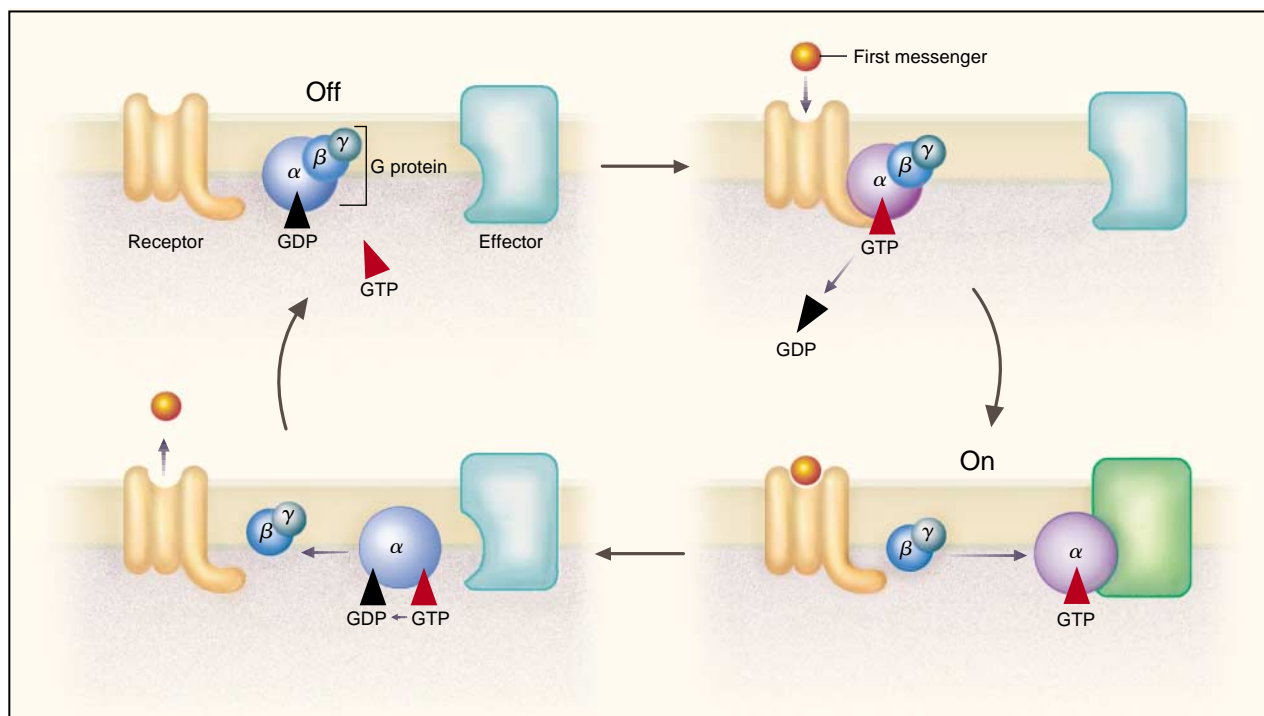


Figure 1. Mechanism of Activation and Action of G Proteins.

In the “off,” or resting, state, guanosine diphosphate (GDP) is tightly bound to the  $\alpha$  subunit of the G protein. When the membrane receptor is activated by the binding of a hormone (first messenger), it interacts with the G protein, causing GDP to dissociate from the  $\alpha$  subunit. GDP is replaced by guanosine triphosphate (GTP), which activates the G protein and leads to its dissociation into  $\alpha$ -subunit and  $\beta\gamma$ -subunit complexes, either of which can activate effectors (the “on” state). The  $\alpha$  subunit quickly hydrolyzes GTP to GDP, an action that inactivates the  $\alpha$  subunit, allows it to reassociate with the  $\beta\gamma$  complex, and resets the switch to the off position.

that mediates the activation of adenylate cyclase in response to hormones such as parathyroid hormone, thyrotropin, and gonadotropins. A number of distinct germ-line mutations affecting the  $\alpha$  subunit of the  $G_s$  protein ( $G_s\alpha$ ), which disrupt either the protein or the synthesis of its messenger RNA, are responsible for the defect.

The activity of the G protein is increased in intestinal epithelial cells of patients with secretory diarrhea caused by infection with *Vibrio cholerae*. The bacteria secrete an exotoxin that catalyzes the adenosine diphosphate ribosylation (a specific chemical alteration) of a specific arginine in  $G_s\alpha$ . This drastically reduces the GTPase activity, which normally functions to turn off the G-protein switch, thereby causing continued activation of  $G_s$  and formation of cAMP and ultimately leads to the increased fluid and electrolyte transport that causes the diarrhea.

Somatic mutations that activate G proteins are also known. Up to 40 percent of patients with acromegaly due to pituitary somatotroph tumors have constitutively activated adenylate cyclase in the tumor cells because of mutations affecting  $G_s\alpha$  that reduce GTPase activity. The resultant elevation of intracellular cAMP levels leads to hypersecretion of growth hormone and cellular proliferation. Some autonomously functioning thyroid adenomas have similar mutations.

The McCune–Albright syndrome consists of hyperfunction of one or more endocrine glands (pituitary somatotrophs, adrenal cortex, thyroid, and gonads) coupled with café au lait spots and polyostotic fibrous dysplasia. It also appears to be caused by activating mutations in the gene for  $G_s\alpha$ , which probably occur early in embryonic development. Affected persons express this mutation in a mosaic pattern that correlates with the cellular abnormalities observed.

Finally, two patients have been described with the seemingly paradoxical pairing of “testotoxicosis” (precocious puberty due to the hypersecretion of testosterone by Leydig cells) and pseudohypoparathyroidism (hormone resistance). This is caused by a single mutation in the gene for  $G_s\alpha$  that activates  $G_s$  (by enhancing the rate of release of GDP), leading to increased secretion of cAMP and testosterone by the Leydig cells. However, the altered protein is unstable at 37°C, explaining the pseudohypoparathyroid phenotype in all tissues except the testes, which are generally 3°C to 5°C cooler than the rest of the body.

Similar syndromes involving abnormalities in G protein–coupled signal transduction pathways can also be caused by alterations in either the upstream (receptor) or downstream (effector) partners of the G proteins or even by other proteins that regulate their function. Several examples due to constitutively activated mutant receptors have already been described. Thus, the basic discoveries of Gilman and Rodbell have already laid the foundation for new insights into the pathogenesis of various human diseases.

Howard Hughes Medical Institute  
Durham, NC 27710

ROBERT J. LEFKOWITZ

#### RECOMMENDED READING

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