BIOCHEMISTRY OF VITAMINS, HORMONES AND OTHER MESSENGER MOLECULES

Chris Whiteley
Department of Biochemistry and Microbiology, Rhodes University, Grahamstown, South Africa

Keywords: phosphorylation, phosphorylase, dephosphorylation, hormones, hydrolyze

Contents

1. Introduction

Hormones are chemical messengers that coordinate cell activities in multicellular organisms. They are secreted by specific tissues or glands directly into the blood stream, which carries them to their sites of action where they alter the activities of responsive target tissues.

2. Adenylate Cyclase Cascade

In 1950 it was discovered that the enzyme glycogen phosphorylase was activated by a covalent phosphorylation and deactivated by dephosphorylation. Furthermore research workers established that the hormone epinephrine also activated the phosphorylase in cell free liver homogenates that contained the plasma membrane. The interaction of the hormone with the β-adrenergic receptor of the plasma membrane yielded the production of an unusual nucleotide subsequently identified as adenosine-3',5'-monophosphate or cyclic AMP (cAMP) [Figure 1]. This nucleotide is formed from ATP by the action of adenylate cyclase, an integral membrane protein, and further degraded into AMP by the enzyme phosphodiesterase. If the hormone was to be regarded as a 'first messenger' then cAMP could be seen as a 'second messenger'. The essential features of this messenger system was that the plasma membrane contains receptors for hormones that after binding lead to the activation of membrane-bound adenylate cyclase. This, in turn, lead to an increased level of cAMP in the cytosol that altered the rate of one or more cellular processes [Figure 2]. It was important to realize that the hormone need not enter the cell and variations in hormone levels were reflected in concentrations of cAMP. Researchers soon recognized that an intermediary α-subunit of a guanyl-nucleotide-binding protein was also necessary in the activation process. This α-subunit with its associated GTP molecule is released into the cytosol after the activated hormone-bound receptor had stimulated the inactive GDP-bound G-protein – exchanging the nucleotides [Figures 3 and 4] G-proteins that stimulate signal-transduction processes are referred to as G_s – proteins.

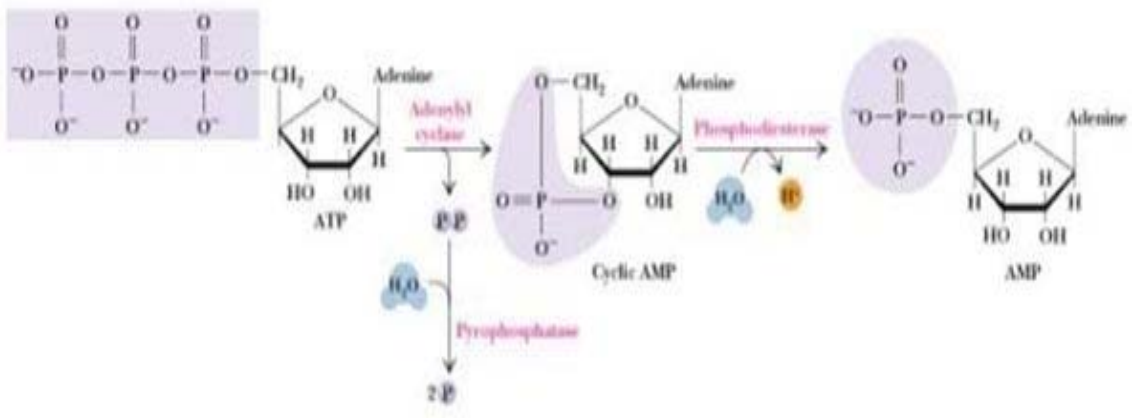

Figure1:

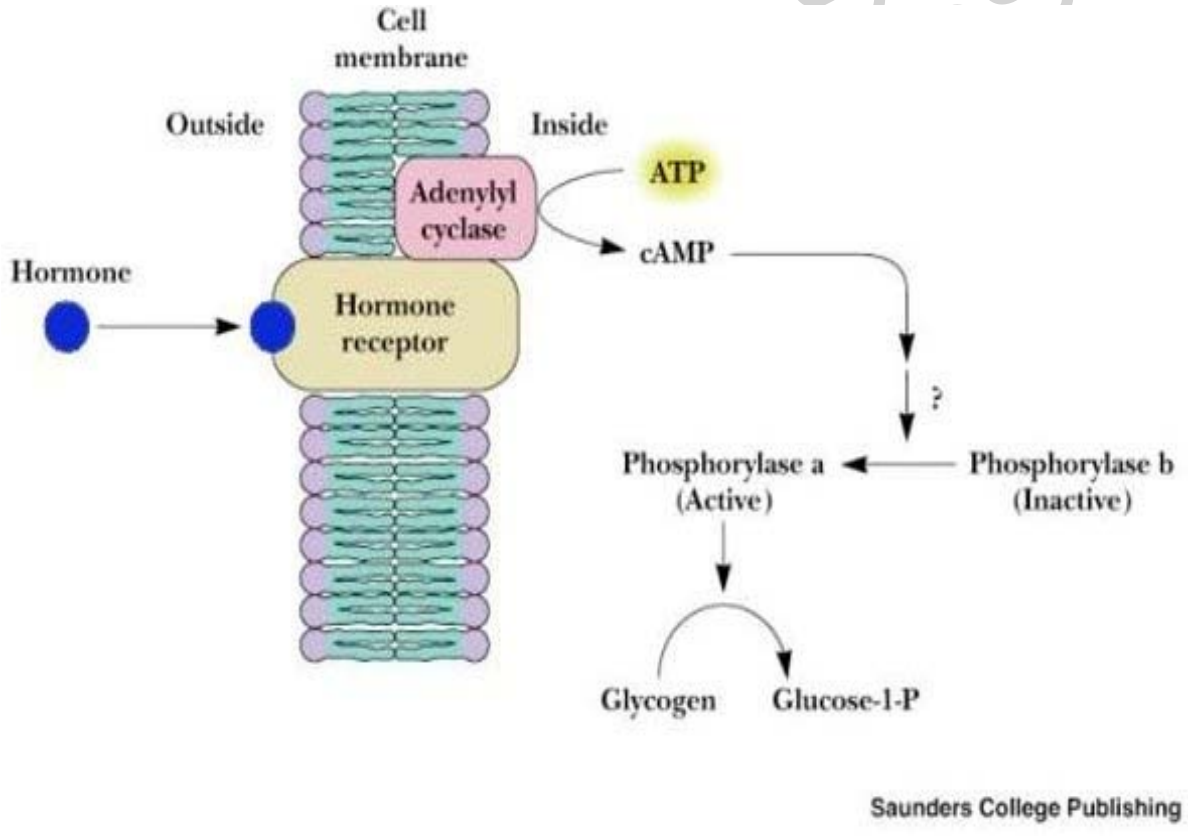

Figure2:

A trigger for the control of the activity of this enzyme comes from both the rate of exchange of GTP for GDP compared with the rate of hydrolysis of bound GTP. In the absence of hormone the rate of GTP-GDP exchange is very low and consequently all the G-protein is in the GDP form and the adenylate cyclase is inactive. The ability of G_{α} - to hydrolyze GTP to GDP then completes the hormone-triggered cycle.

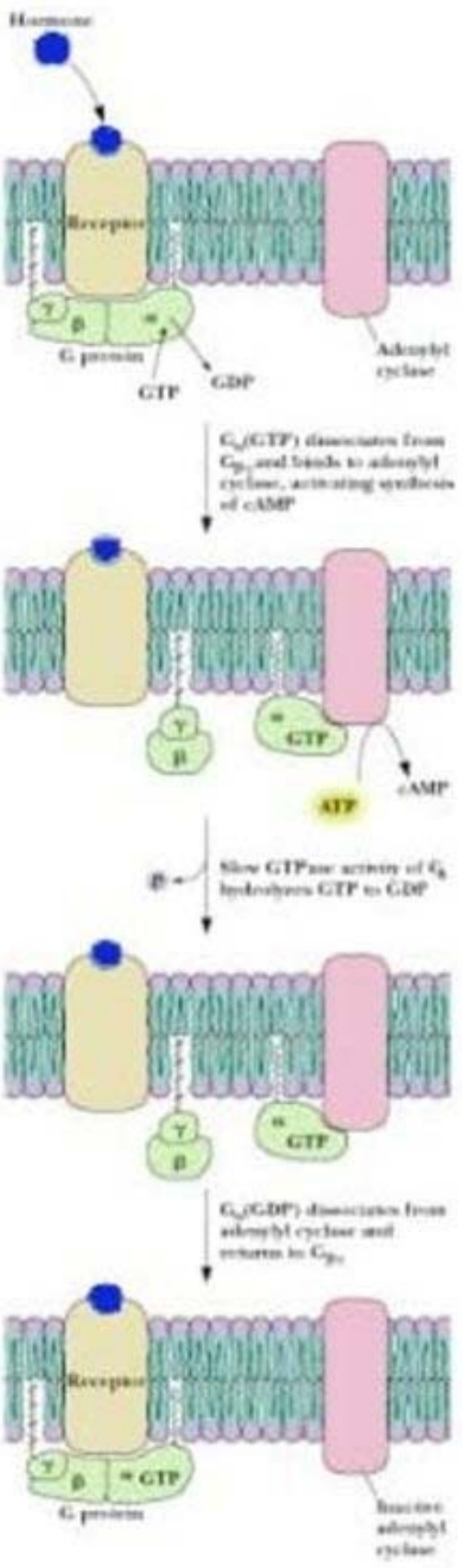
Hormone
Receptor
γ
β
α
G protein
GTP
GDP
Adenylyl cyclase
GTP
ATP
cAMP
α
GTP
γ
β
α
GTP
γ
β
α GTP
G protein

Figure3:

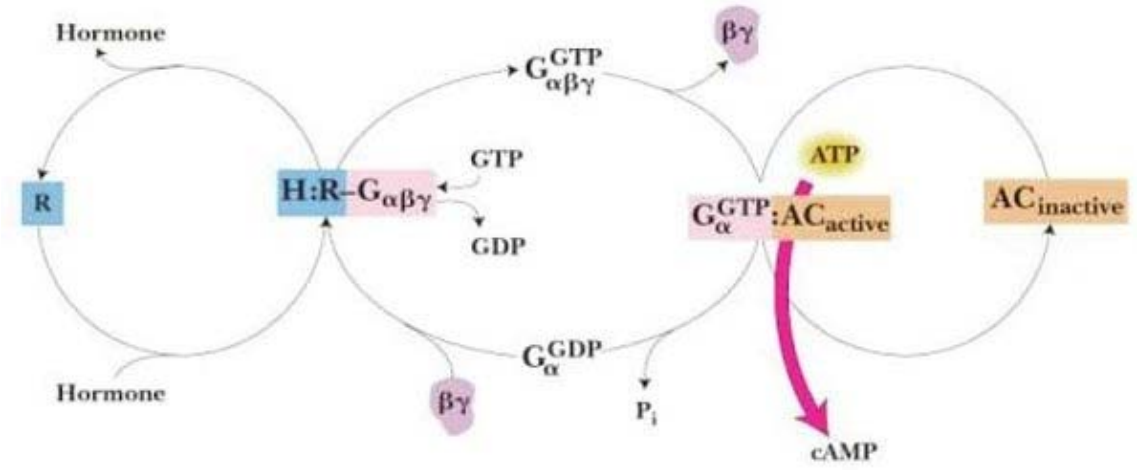

Figure 4:

The activation of G-proteins by the β-adrenergic receptor does not depend solely on whether the hormone is bound. Receptor molecules exposed to a constant level of epinephrine for an extended period no longer catalyze GTP-GDP exchange effectively and the system becomes desensitized and adapts. It should be realized that signal-transducing systems respond to changes in stimuli concentration rather than absolute concentration. Adaptation is advantageous because it enables receptors to operate over a wide range of background concentration of stimuli. Serine residues in the C-terminal region of the β-adrenergic receptor are phosphorylated by specific kinases which, by acting on the hormone-receptor complex and not on the receptor itself, prevents GTP-GDP exchange thereby blocking signal transmission. Sensitivity would be restored by a removal of the attached phosphates.

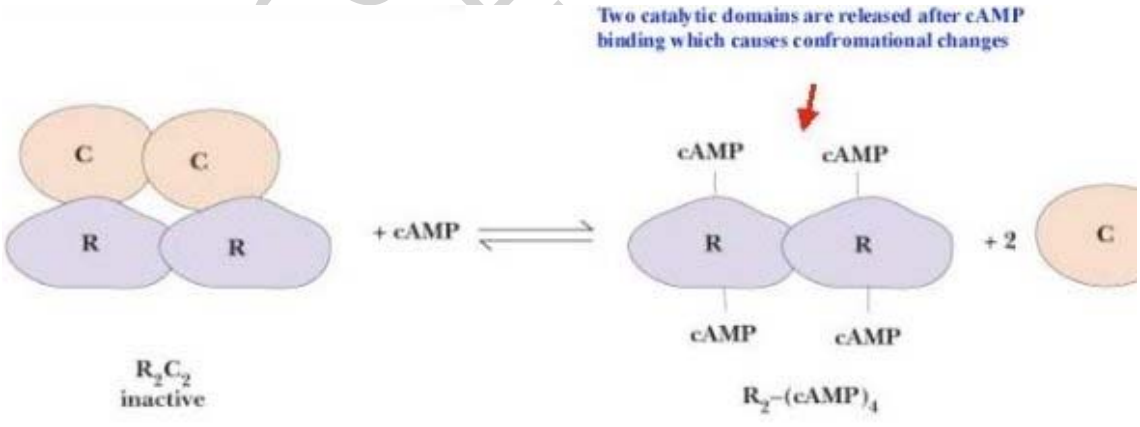

Figure 5:

The cyclic nucleotide (cAMP) perpetuates its message within the cytosol by an allosteric activation of protein kinases. In muscle and liver protein kinases are able to phosphorylate both glycogen synthase (rendering it inactive) and phosphorylase kinase (rendering it active). Four molecules of cAMP bind to the two regulatory subunits of

each inactive kinase enzyme disrupting the integrity of the enzyme and releasing two active catalytic subunits [Figure 5]. The three steps during the adenylate-cyclase cascade serve to amplify weak hormone signals. a) each hormone-receptor complex catalyses the formation of many G_α-GTP; b) many molecules of cAMP are formed by an activated adenylate cyclase; c) each cAMP-activated protein kinase can alter the activity of many molecules of each target protein.

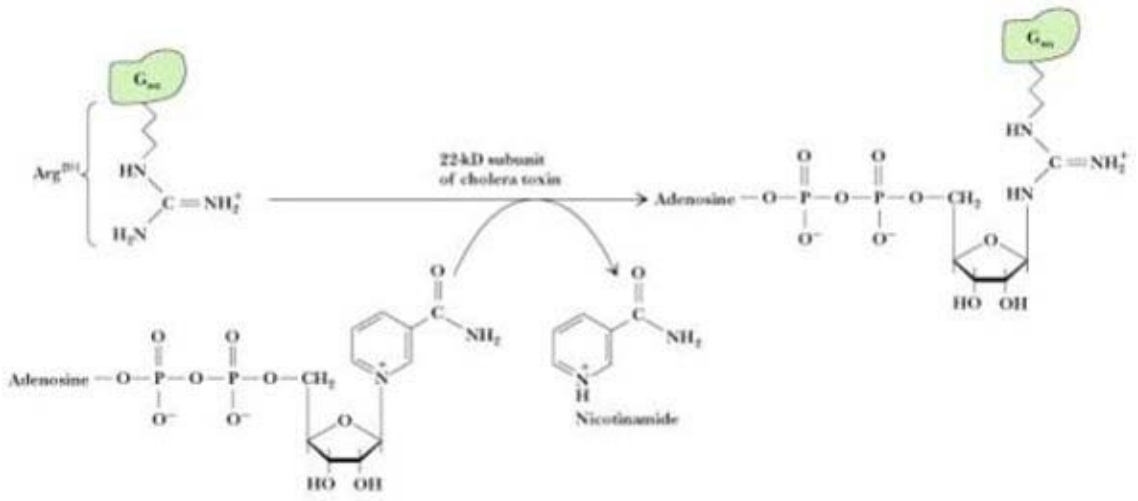

Figure 6:

Cholera toxin, a 87kd protein secreted by *Vibrio cholerae*, enters the intestinal mucosal cell and catalyses the transfer of an ADP-ribose unit from NAD^+ to a specific arginine side chain of the α-subunit of G_s.

This ADP-ribosylation of G_s blocks its capacity to hydrolyze bound GTP to GDP, and so impairs the built-in deactivation device [Figure 6]. The G-protein is locked in the active form, hence adenylate cyclase stays persistently activated and the levels of cAMP become abnormally high. This leads to a large efflux of sodium ions and water from the gut.

Certain hormones such as opiates and α_2-adrenergic amines, lower cAMP levels in target cells by stimulating GTP hydrolysis thereby reducing adenylate cyclase activity. Pertussis toxin, produced by *Bordetella pertussis* (a bacterium causing whooping cough), blocks the inhibition of adenylate cyclase by covalently modifying an inhibitory G_i- protein.

Both the G_s and the G_i have similar α,β,γ-subunit structures and the action of these two G-proteins are linked. As the hormone-triggered exchange of GTP for GDP in unmodified G_i splits it into α and βγ subunits the released βγ subunits then bind the α-subunit of the G_s reversing its activation of adenylate cyclase. Pertussis toxin catalyses the ADP-ribosylation of a specific cysteine side chain on the α-subunit of G_i locking it in the GDP form.

-
-
-