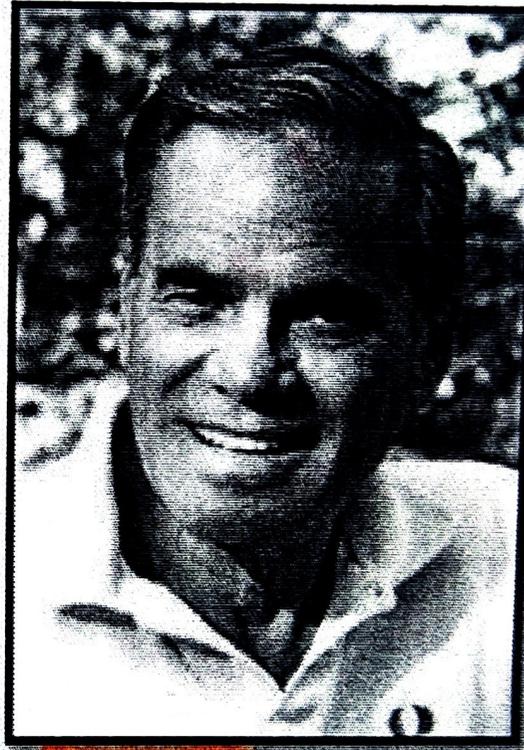




Nobel Prize in Physiology or Medicine, 1994



ALFRED G. GILMAN



MARTIN RODBELL

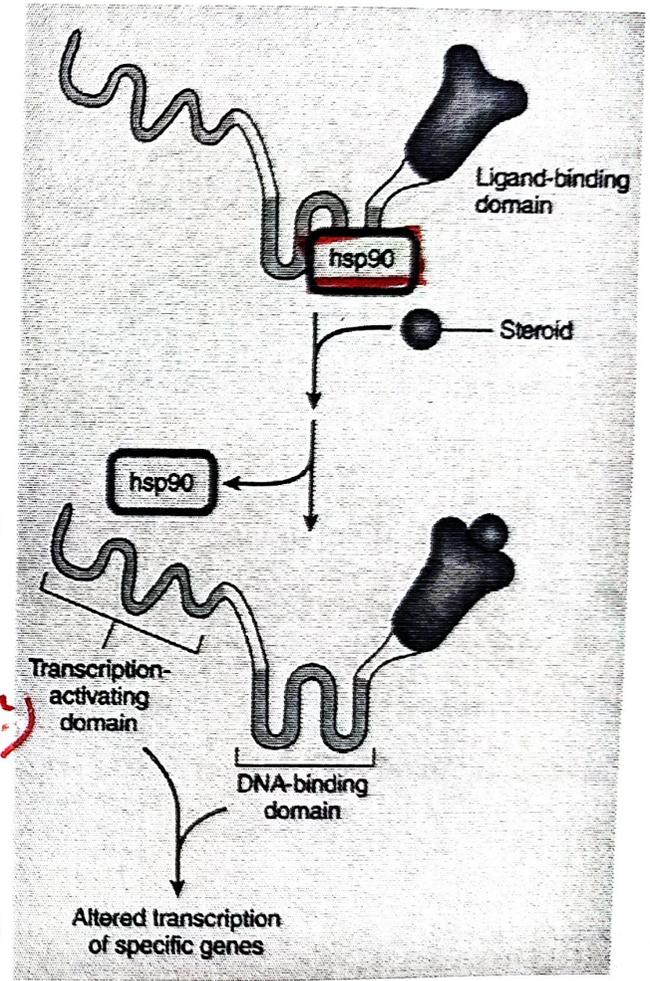
"for their discovery of G-proteins and the role of these proteins in signal transduction in cells"

أول ميكانيزم

1. Intracellular Receptors for Lipid-Soluble Agents

بخطوا response عن طريق هيا الميكانيزم

- Example: steroids and thyroid hormones.
- Stimulate the transcription of genes by binding to specific DNA sequences near the gene whose expression is to be regulated.



* نتيجة ارتباط الsteroids بـ site على الreceptor
 يحول الreceptor عن الenzym [hsp90] وبالتالي يحفز
 (Transcription-activating domain) وينتج الhormone
 ويربطها الeffect الذي يترتب عليه

* لهذا بعد عمل الhormone وقت يخطونا الeffect به فم وقت
 من ٢٠ دقيقة لعدة ساعات نسقي هاد الوقت بـ

lag period

* بعد الوقت ينص gen expression

Source: Katzung BG, Masters SB, Trevor AJ: Basic & Clinical Pharmacology, 12th www.accessmedicine.com

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- The mechanism used by hormones that act by regulating gene expression has two therapeutically important consequences:

1. All of these hormones produce their effects after a characteristic lag period of 30 minutes to several hours—the time required for the synthesis of new proteins. This means that the gene-active hormones cannot be expected to alter a pathologic state within minutes (eg, glucocorticoids will not immediately relieve the symptoms of acute bronchial asthma).
2. The effects of these agents can persist for hours or days after the agonist concentration has been reduced to zero. The persistence of effect is primarily due to the relatively slow turnover of most enzymes and proteins, which can remain active in cells for hours or days after they have been synthesized. Consequently, it means that the beneficial (or toxic) effects of a gene-active hormone usually decrease slowly when administration of the hormone is stopped.

* عند إيقاف إعطاء الهرمونات، فإن التأثيرات المفيدة (أو السامة) عادة ما تنخفض ببطء لأن بعض المستقبلات التي تم إنتاجها مسبقاً لا تزال نشطة في الخلايا.

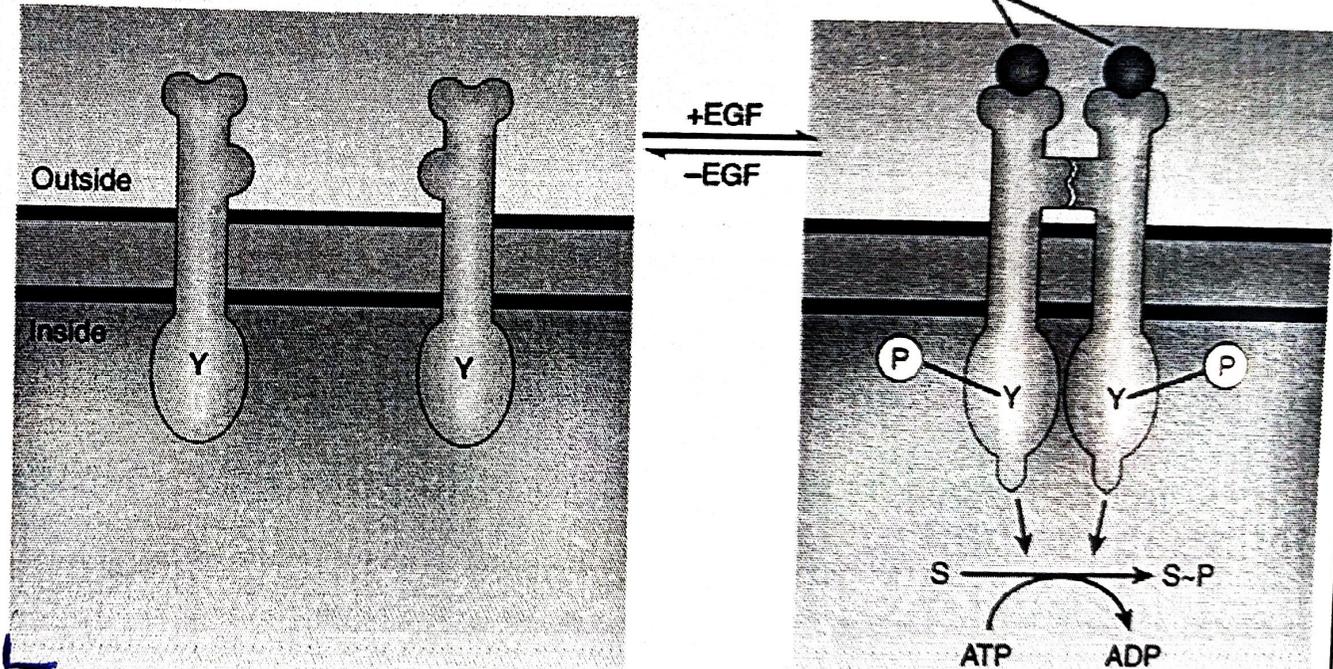
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2. Ligand-Regulated Transmembrane Enzymes Including Receptor Tyrosine Kinases

- Example:

Insulin and epidermal growth factor (EGF)



Source: Katzung BG, Masters SB, Trevor AJ: Basic & Clinical Pharmacology, 12th edition: www.accessmedicine.com

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بعضهم ligand و بعضه هورمون
 يرتبطوا بال trans membran enzyme

مع بعض combination بين ال
 two dimerizing

بالتالي ال tyrosine residues و phosphorylate بعض ال substrate-protein complexes و ينعج ال response و هو ال الالية بتساع ال energy

• Activated receptors catalyze phosphorylation of tyrosine residues on different target signaling proteins, thereby allowing a single type of activated receptor to modulate a number of biochemical processes.

نتیجہ، response، ح. پھیرنا :-

• For example, insulin uses a single class of receptors to trigger increased uptake of glucose and amino acids and to regulate metabolism of glycogen and triglycerides in the cell.

□

□

• Inhibitors of receptor tyrosine kinases are finding increased use in neoplastic disorders in which excessive growth factor signaling is often involved.

→ inhibition of receptor tyrosine kinases

نتیجہ، neoplastic disorder ← پھیر

لانہ ہونے کے باعث excessive growth factor signaling

down -
regulation

receptor
tyrosine
kinases
يعتقد على كمية (Tyrosine) Kinases
والتي في علاج تتسبب منها

- The intensity and duration of action of EGF, PDGF, and other agents that act via receptor tyrosine kinases are limited by a process called receptor **down-regulation**.
- Ligand binding often induces accelerated endocytosis of receptors from the cell surface, followed by the degradation of those receptors (and their bound ligands). When this process occurs at a rate faster than de novo synthesis of receptors, the total number of cell-surface receptors is reduced (down-regulated), and the cell's responsiveness to ligand is correspondingly diminished.

يعني يتسبب -
endocytosis of receptor
from the cell surface
degradation
receptor

و يقل عددها لهذا
down-regulated