Bottom-up Approaches: The cAMP pathway

Each component was independently discovered, and typically connected in a binary manner

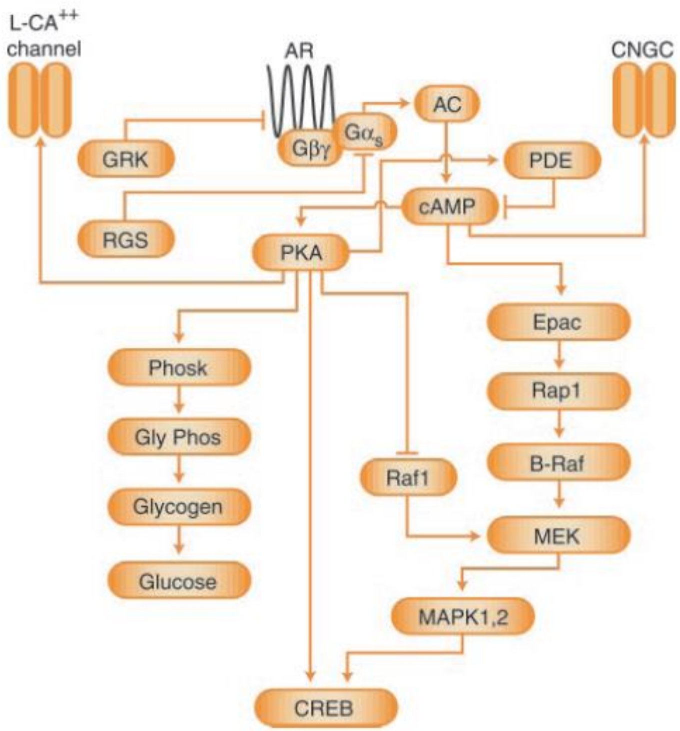
Nobel prizes for the discovery of

cAMP - Sutherland

cAMP dependent protein Kinase - Krebs and Fischer

G proteins - Gilman and Rodbell

β-adrenergic receptors - Lefkowitz and Kobilka (2012)



The cAMP pathway(s)

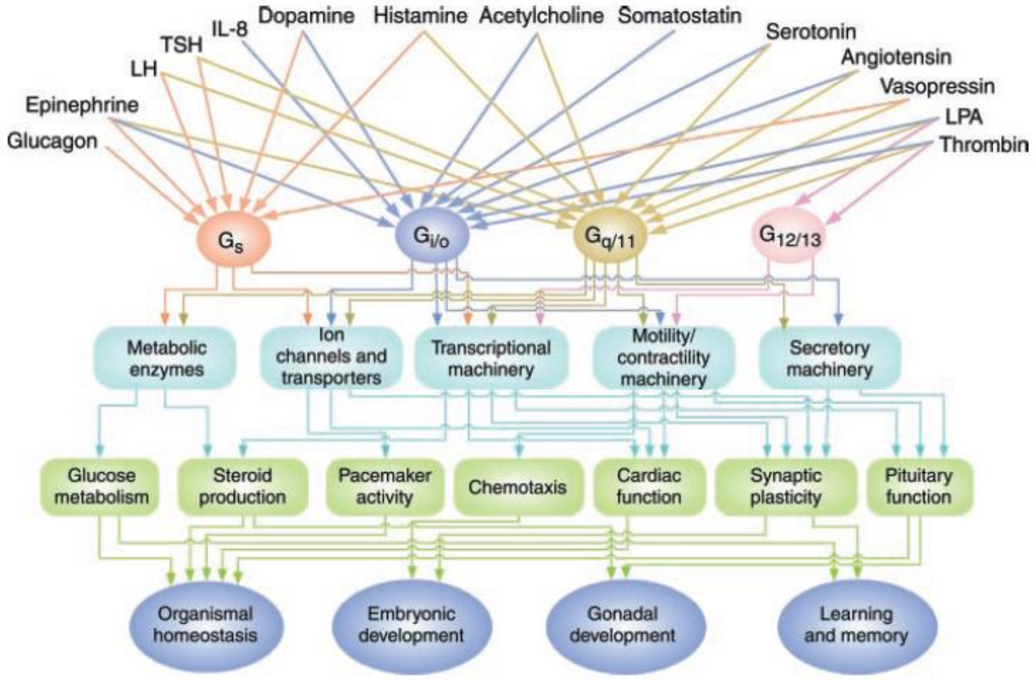
Starting at the receptor signal can flow to metabolic enzymes (phosphorylase kinase), channels (CNGC) or transcription factors (CREB)

AR – β adrenergic receptor
A class of receptor proteins that binds epinephrine or norepinephrine (also called adrenaline , noradrenaline)

Neves, Ram, Iyengar *Science* 296(5573):1636-9 (2002)

Introduction to Systems Biology
Lecture 2 - Part A-3

Iyengar



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There are many G protein receptor coupled pathways

Each hormone or neurotransmitters has its own receptors (one or more classes)
e.g. glucagon receptor , dopamine receptor etc.

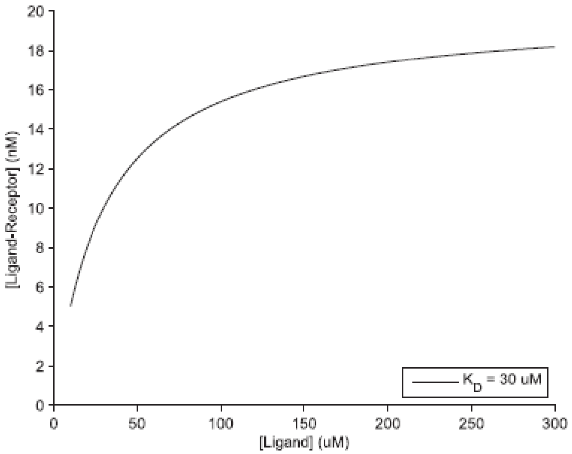
These pathways have their effects through multiple levels (scale) of organization

$$[L]+[R] \underset{k_b}{\overset{k_f}{\rightleftarrows}} [LR]$$

$$\frac{d[L]}{dt} = -k_f[L][R] + k_b[LR]$$

$$\frac{d[R]}{dt} = -k_f[L][R] + k_b[LR]$$

$$\frac{d[LR]}{dt} = k_f[L][R] - k_b[LR]$$

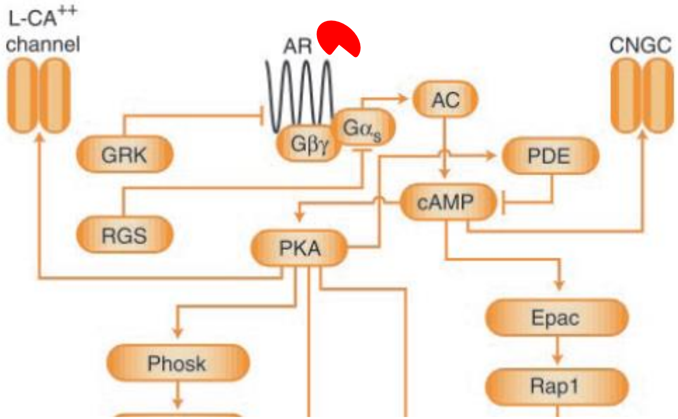


Ordinary differential equations allow us to compute how a product is formed with respect to time when the initial concentrations of reactants and forward and reverse rates are known

Deterministic models using ordinary differential equations (ODE) such as shown above can quantitatively describe the formation of ligand-receptor complex as a function of time.

The graph shows the concentration of ligand-receptor complex at various ligand concentrations when the binding reaction has reached steady state with respect to time.

So what is transduced?



A ligand such as epinephrine can only be recognized by it's cell surface receptor in this case the β-adrenergic receptor

This recognition results in production of cAMP in the cell --

The *transduction* process

Information outside the cell is transduced (converted) into a form that can regulate processes inside the cell
The transduction process can be computationally represented and studied.

The β-AR to PKA signal transduction process can be written as a series of ordinary differential equations (ODE) used to represent enzyme action

Michaelis-Menten Kinetics

$$[E] + [S] \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} [ES] \underset{k_{-2}}{\overset{k_2}{\rightleftarrows}} [E] + [P]$$

$$\frac{d[ES]}{dt} = -k_{-1}[ES] - k_2[ES] + k_1[E][S] + k_{-2}[E][P]$$

$$\boxed{V_0 = \frac{V_{\max}[S]}{K_M + [S]}}$$

$$\boxed{K_M = (k_{-1} + k_2)/\, k_1}$$

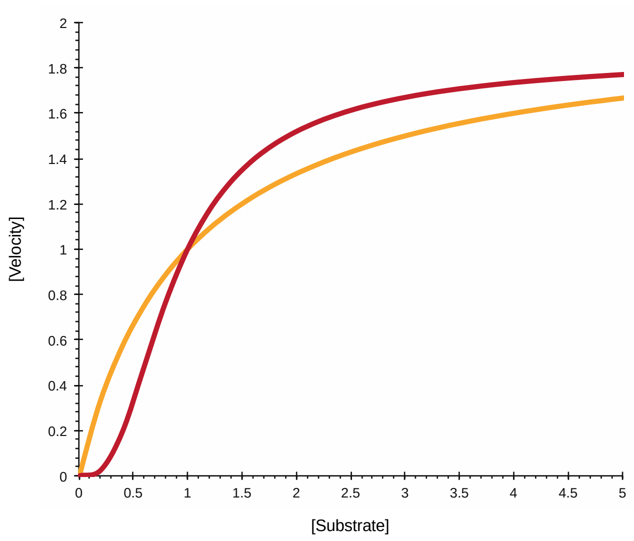
For each reaction in the signal transduction process such as:

1) LR activation of G protein
2) G protein activation of adenylyl cyclase
3) cAMP activation of PKA

We can write a set of ODEs and compute product formation

V_{max} Maximal Velocity- the maximum rate at which the enzyme can convert substrate to product

K_{cat} Turnover number V_{max} / total concentration of the enzyme



Allostery and Hill coefficients

Often there is interaction between substrate sites or a second ligand modifies the substrate affinity or velocity of the reaction – deviations from MM kinetics

Hill Equation

$$\frac{v}{V_{max}} = \frac{[S]^n}{K' + [S]^n}$$

K' is a composite coefficient representing affinity and interactions at multiple sites

n is the Hill coefficient representing the interactions between the sites

Protein kinase A , an enzyme upon activation

phosphorylates (transfers the γ-phosphate from ATP) to substrates like enzymes, channels and transcription factors to change their activity

Thus adrenaline binding to its receptor and through a series of coupled enzymatic reactions led to glucose production in liver, and muscle

Glucose from the liver released in the bloodstream

Provides energy for the fight or flight response

Information → Physiological Response