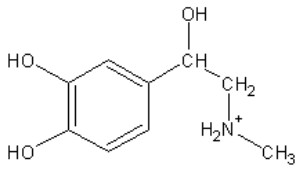
Hormones & Signal Transduction



Epinephrine:

- also called noradrenaline
- has a Tyrosine base
- increases your heart rate, your blood pressure and widens your bronchi
- increases glucose production, starch breakdown and fatty acid metabolism
- Works by binding to a receptor which sets off a kinase.

Kinase:

- Something that uses ATP to add a phosphate to a substrate's OH.

We looked at Serine/Threonine Kinases

They have the consensus sequence Arg-Arg-X-Ser/Thr-Hydrophobic

PKA (A caused it was Amazing!)

How Earl found it (remember the car and the sledgehammer)

- He takes epinephrine and gives it to liver tissue and notices glucose production
- So then he centrifuges the cells and separates in a soluble fraction (which contains the enzyme for making glucose) and the pellet (containing the membranes)
- He mixes (in vitro) Epinephrine with the Soluble Fraction and gets nothing
- He mixes (in vitro) Epinephrine with both fractions and gets glucose
- tells him must be a messenger system!

So now we get lots of research and we find the system where:

1. Epi binds to a receptor
2. The receptor, a β-AR, is a 7 membrane spanning receptor. It signals to a G protein. NOTE Allostery.
3. The G protein consists of 3 parts, α (45 KDa) β (35 KDa) and γ (7 KDa). The α subunit has GTPase activity and when triggered by the receptor binds GTP and disassociates from the β and γ subunits. NOTE Allostery!
4. The Gα-GTP then binds to Adenylate Cyclase which turns ATP into cAMP. NOTE Allostery!
5. cAMP then binds the PKA-inhibitor complex, forcing a conformation change in the inhibitor, which releases the active PKA. NOTE Allostery!
6. PKA (A ser/thr kinase) then goes out and parties by phosphorylating all kinds of proteins.

Take home message. ALLOSTERY IS IMPORTANT.

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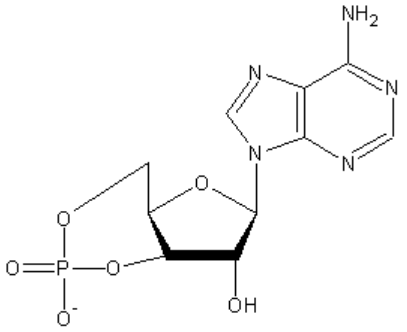
One last thing, how do we shut all this off?

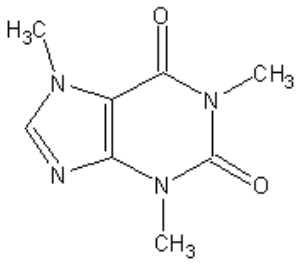
1. Phosphodiesterase eats cAMP
2. Gα's GTPase converts GTP to GDP making it inactice

Sidenote of major significance:

cAMP:



Caffine:



Note any similarities?

Amplification of Signals:

If we were to assume that each step "X" of the next molecule was activated:

1 Homone = X Gα activated.
1 Gα = X Adenylate Cyclases activated
1 Adenylate Cyclase = X cAMP
1 cAMP = X PKA
1 PKA = X phosphorylated proteins

So: we had 5 amplification steps or X^5. If we set X at 2, that means we had 32 phosphylations. 3: 243. 5: 3125…you see where this is headed.

Self-Regulation:

PKC was interesting in the ability for it to be regulated via 3 different manners:

1) It had its own pseudo substrate. If it Y-P wasn't displaced, it blocked the active site. (Displacement of SH2)
2) If dephosphylated the Tyrosine, then we had active enzyme as active site was no longer blocked.
3) If displaced the SH3 which bound to the SH1-SH2 linker, then it would change the conformation.

Take home message: ALLOSTERY IS IMPORTANT!