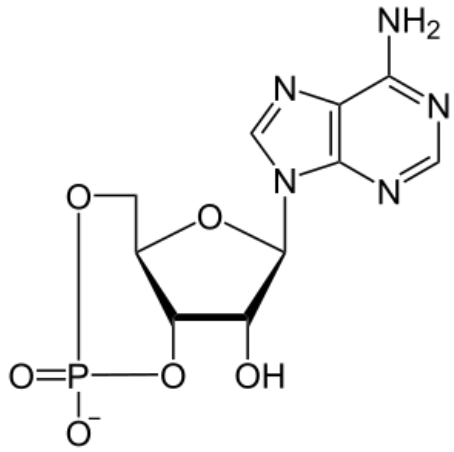
Second messengers

Second messengers are small, non-protein, in water soluble molecules. They are called second, because the first messenger is a signal molecule, which binds to the receptor protein. They are involved in transfering the signal in pathways starting by G-protein receptors as well as in pathways starting by an enzyme-linked receptors. They are made from easily accesible substrates and have a short half life. Second messengers include **cAMP, kalcium cations, cGMP, inositol-1,4,5-trisphosphate, diacylglycerol, phosphatidylinositol-3,4,5-trisphosphate** and more. Except for calcium cations, second messengers are produced by specific enzymes after stimulation of membrane receptors. Afterwards seccond messengers activate proteinkinases, which phosphorylate aminoacids serine or threonine in various intracellular proteins. Phosphorylation changes activity of these proteins in terms of activation or inhibition. Activity of second messengers is limited and they are degradated by different enzymes.

Second messenger	Substrate	Enzyme	Efector	Degradation
cAMP	ATP	adenylate cyclase (AC)	proteinkinase A (PKA)	fosfodiesterases (PDE)
cGMP	GTP	guanylate cyclase (GC)	proteinkinase G (PKG)	fosfodiesterases (PDE)
Calcium cations (Ca^{2+})	–	release from ER after stimulation IP_3	calmodulin	re-resorption to ER with help of Ca^{2+} ATP-ase
inositol-1,4,5-trisphosphate (IP_3)	phosphatidylinositol-4,5-bisphosphate (PIP_2)	phospholipase C (PLC)	proteinkinase C (PKC)	phosphatases – defosforylation to inositol
diacylglycerol (DAG)	phosfatidylinositol-4,5-bisphosphate (PIP_2)	phospholipase C (PLC)	proteinkinase C (PKC)	lipases – formation of glycerol and free fatty acids
phosphatidylinositol-3,4,5-trisphosphate (PIP_3)	phosfatidylinositol-4,5-bisphosphate (PIP_2)	phosphatidylinositol-3-kinase (PI3K)	proteinkinase B (PKB)	phosphatase PTEN – cleavage of phosphate in position 3

Cyclic adenosinmonophosphate (cAMP)

Cyclic AMP is made from ATP by enzyme adenylate cyclase, which is binded to the cytoplasmatic membrane and activated through G-protein after binding of signal molecule to it's membrane receptor. cAMP then transfers the signal from cytoplasmatic membrane to the metabolic pathways in cytoplasm. Transfer molecule following the cAMP is usually **proteinkinase A (cAMP-dependent proteinkinase)**, which phosphorylates other proteins. PKA-regulated proteins are involved for example in regulation of glycid and lipid metabolism, transport of water and ions in kideys and more. cAMP doesn't stay in cell for long and is soon transformed by *fosfodiesterase to* AMP (adenosinmonophosphate).



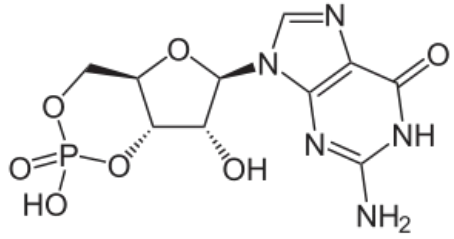
cAMP

Cyclic guanosinmonophosphate (cGMP)

Is formed similiarly to cAMP, meaning it's formed by enzyme ***guanylate cyclase*** from GTP. Guanylate cyclase is activated for example by atrial natriuretic peptid (ANP)[1]. cGMP activates **proteinkinase G (cGMP-dependent proteinkinase)**, which phosphorylates target proteins. Signal transduction including cGMP use for example rods in eye retina or smooth muscle cells in cavernous bodies of penis.

Second messengers derived from phosphatidylinositol-4,5-bisphosphate

Phosphatidylinositol-4,5-bisphosphate (PIP_2, also $PtdIns(4,5)P_2$) is a phospholipid found in cytoplasmatic membrane. From phosphatidylinositol-4,5-bisfosfate can be synthesised second messengers, which can affect two different proteinkinases.



cGMP

Phosphatidylinositol-3,4,5-trisphoshate

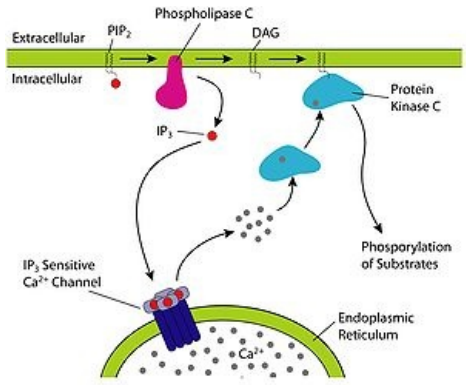
Phosphatidylinositol-3,4,5-trisphosphate (PIP_3, aslo $PtdIns(3,4,5)P_3$) is synthesised by phosphorylation of PIP_2 by enzyme ***phosfatidylinositol-3-kinase*** (PI3K). It stays binded in the inner layer of cytoplasmatic membrane and here activates *phosphatidylinositol-dependent kinase 1* (PDK1), which phosphorylates (and by that activates) **proteinkinase B**. Proteinkinase B (PKB, also called AKT) phosphorylates proteins that regulate proliferation, cell cycle and apoptosis.

Diacylglycerol a inositol-1,4,5-trisphosphate

Signal molecule binds to a receptor, which leads to an activation of enzyme phospholipase C, which splits phosphatidylinositol-4,5-bisphosphate to 1,2-diacylglycerol (DAG) a inositol-1,4,5-trisphosphate (IP_3, also $Ins(1,4,5)P_3$). Both are second messengers. IP_3 diffuses through cytosol, and binds to a calcium channel in endoplasmatic reticulum and opens it. Calcium cations are releases from endoplasmatic reticulum and therefore raise the Ca^{2+} level in cytosol. DAG stays immersed in cytoplasmatic membrane. DAG and calcium cations together activate **proteinkinase C**, which then phosphorylates proteins associated with cytoskeleton and by that affect contraction, migration and secretion in cells.

Calcium cations

Ca^{2+} is more regular second messenger than cAMP. Rise of Ca^{2+} concentration causes contraction of muscle cells or secretion of certain substances. Cells always contain certain level of Ca^{2+}, but extracelular level is much higher than intracellular. Intracellular level is raised by opening of calcium channels in endoplasmatic reticulum, which is caused by binding of IP_3 onto this channels. Calcium cations could be accounted for as third messegers. Calcium cations activate other proteins directly or with a help of **calmodulin**, protein binding Ca^{2+}. Calmodulin with binded calcium cations activates CaM-kinases, which phosphorylate other proteins.



PIP2 cleavage to IP3 and DAG

Links

Related articles

- Cell signaling
- Hormones
- G-protein
- Insulin

Reference

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