Second messenger: by definition. For second SEM.

Dr. Sarmishtha Chanda

Second messenger, molecule inside cells that acts to transmit signals from a receptor to a target. The term second messenger was coined upon the discovery of these substances in order to distinguish them from hormones and other molecules that function outside the cell as “first messengers” in the transmission of biological information. Many second messenger molecules are small and therefore diffuse rapidly through the c

ytoplasm, enabling information to move quickly throughout the cell. As elements of signaling pathways, second messengers can serve to integrate information when multiple independent upstream inputs influence the rates of synthesis and degradation of the second messenger. In addition, second messengers can have multiple downstream targets, thereby expanding the scope of signal transmission.

In cells the stimulatory effects of epinephrine are mediated through the activation of a second messenger known as cAMP (cyclic adenosine monophosphate). The activation of this molecule results in the stimulation of cell-signaling pathways that act to increase heart rate, to dilate blood vessels in skeletal muscle, and to break down glycogen to glucose in the liver.

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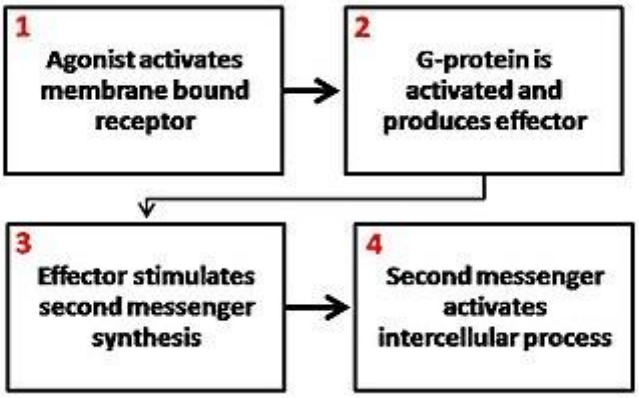
Second messengers are intracellular signaling molecules released by the cell in response to exposure to extracellular signaling molecules—the **first messengers**. (Intracellular signals, a non-local form or cell signaling, encompassing both first messengers and second messengers, are classified as juxtacrine, paracrine, and endocrine depending on the range of the signal.) Second messengers trigger physiological changes at cellular level such as proliferation, differentiation, migration, survival, apoptosis and depolarization. They are one of the triggers of intracellular signal transduction cascades.[1] Examples of second messenger molecules include cyclic AMP, cyclic GMP, inositol trisphosphate, diacylglycerol, and calcium.[2] First messengers are extracellular factors, often hormones or neurotransmitters, such as epinephrine, growth hormone, and serotonin. Because peptide hormones and neurotransmitters typically are biochemically hydrophilic molecules, these first messengers may not physically cross the phospholipid bilayer to initiate changes within the cell directly—unlike steroid hormones, which usually do. This functional limitation necessitates the cell to devise signal transduction mechanisms to transduce first messenger into second messengers, so that the extracellular signal may be propagated intracellularly. An important feature of the second messenger signaling system is that second messengers may be coupled downstream to multi-cyclic kinase cascades to greatly amplify the strength of the original first messenger signal[3][4]. For example, RasGTP signals link with the Mitogen Activated Protein Kinase (MAPK) cascade to amplify the allosteric activation of proliferative transcription factors such as Myc and CREB.

Earl Wilbur Sutherland, Jr., discovered second messengers, for which he won the 1971 Nobel Prize in Physiology or Medicine. Sutherland saw that epinephrine would stimulate the liver to convert glycogen to glucose (sugar) in liver cells, but epinephrine alone would not convert glycogen to glucose. He found that epinephrine had to trigger a second messenger, cyclic AMP, for the liver to convert glycogen to glucose.[5] The mechanisms were worked out in detail by Martin Rodbell and Alfred G. Gilman, who won the 1994 Nobel Prize[6][7].
Secondary messenger systems can be synthesized and activated by enzymes, for example, the cyclases that synthesize cyclic nucleotides, or by opening of ion channels to allow influx of metal ions, for example Ca^{2+} signaling. These small molecules bind and activate protein kinases, ion channels, and other proteins, thus continuing the signaling cascade.

Common mechanisms of second messenger systemsEdit



General Schematic of Second Messenger Mechanism

There are several different secondary messenger systems (cAMP system, phosphoinositol system, and arachidonic acid system), but they all are quite similar in overall mechanism, although the substances involved and overall effects can vary.
In most cases, a ligand binds to a membrane-spanning receptor protein molecule. The binding of a ligand to the receptor causes a conformation change in the receptor. This conformation change can affect the activity of the receptor and result in the production of active second messengers.
In the case of G protein-coupled receptors, the conformation change exposes a binding site for a *G-protein*. The G-protein (named for the GDP and GTP molecules that bind to it) is bound to the inner membrane of the cell and consists of three subunits: alpha, beta and gamma. The G-protein is known as the "transducer."
When the G-protein binds with the receptor, it becomes able to exchange a GDP (guanosine diphosphate) molecule on its alpha subunit for a GTP (guanosine triphosphate) molecule. Once this exchange takes place, the alpha subunit of the G-protein transducer breaks free from the beta and gamma subunits, all parts remaining membrane-bound. The alpha subunit, now free to move along the inner membrane, eventually contacts another membrane-bound protein - the "primary effector."

The primary effector then has an action, which creates a signal that can diffuse within the cell. This signal is called the "second (or secondary) messenger." The secondary messenger may then activate a "secondary effector" whose effects depend on the particular secondary messenger system.

Calcium ions are one type of second messengers and are responsible for many important physiological functions including muscle contraction, fertilization, and neurotransmitter release. The ions are normally bound or stored in intracellular components (such as the endoplasmic reticulum(ER)) and can be released during signal transduction. The enzyme phospholipase C produces diacylglycerol and inositol trisphosphate, which increases calcium ion permeability into the membrane. Active G-protein open up calcium channels to let calcium ions enter the plasma membrane. The other product of phospholipase C, diacylglycerol, activates protein kinase C, which assists in the activation of cAMP (another second messenger).

Calcium Ion as a Second Messenger With Special Reference to Excitation-Contraction Coupling

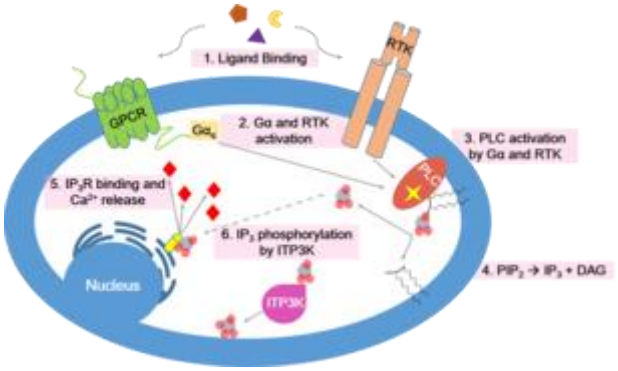
Calcium ion (Ca(2+)) plays an important role in stimulus-response reactions of cells as a second messenger. This is done by keeping cytoplasmic Ca(2+) concentration low at rest and by mobilizing Ca(2+) in response to stimulus, which in turn activates the cellular reaction. The role of Ca(2+) as a second messenger was first discovered in excitation-contraction coupling of skeletal muscle. The history of the discovery was reviewed. Characteristics of Ca(2+) as a second messenger, diversity of target molecules, capability of rapid and massive mobilization and also of oscillatory mobilization, tendency toward localization, and on the other side, ability to cause generalized cell response were described. The possible bases for these characteristics was discussed. Ca(2+) itself induces release of Ca(2+) from the sarcoplasmic reticulum (Ca(2+)-induced Ca(2+) release [CICR]). The Ca(2+) release channel, ryanodine receptor, incorporated into lipid bilayer shows CICR activity. Ca(2+) release induced by inositol trisphosphate also has an apparent CICR nature. The significance of CICR or apparent CICR with its inherently regenerative nature in physiological contractions of skeletal, cardiac, and smooth muscles was discussed.

Membrane Depolarization Increases Ryanodine Sensitivity to Ca2+ Release to the Cytosol in L6 Skeletal Muscle Cells: Implications for Excitation-Contraction Coupling

The dihydropyridine receptor in the plasma membrane and the ryanodine receptor in the sarcoplasmic reticulum are known to physically interact in the process of excitation-contraction coupling. However, the mechanism for subsequent Ca(2+) release through the ryanodine receptor is unknown. Our lab has previously presented evidence that the dihydropyridine receptor and ryanodine receptor combine as a channel for the entry of Ca(2+) under resting conditions, known as store operated calcium entry. Here, we provide evidence that depolarization during excitation-contraction coupling causes the dihydropyridine receptor to disengage from the ryanodine receptor. The newly freed ryanodine receptor can then transport Ca(2+) from the sarcoplasmic reticulum to the cytosol. Experimentally, this should more greatly expose the ryanodine receptor to exogenous ryanodine. To examine this hypothesis, we titrated L6 skeletal muscle cells with ryanodine in resting and excited (depolarized) states. When L6 muscle cells were depolarized with high potassium or exposed to the dihydropyridine receptor

agonist BAYK-8644, known to induce dihydropyridine receptor movement within the membrane, ryanodine sensitivity was enhanced. However, ryanodine sensitivity was unaffected when Ca(2+) was elevated without depolarization by the ryanodine receptor agonist chloromethylcresol, or by increasing Ca(2+) concentration in the media. Ca(2+) entry currents (from the extracellular space) during excitation were strongly inhibited by ryanodine, but Ca(2+) entry currents in the resting state were not. We conclude that excitation releases the ryanodine receptor from occlusion by the dihydropyridine receptor, enabling Ca(2+) release from the ryanodine receptor to the cytosol.

Calcium signaling



Shows Ca^{2+} release from the endoplasmic reticulum through phospholipase C (PLC) pathway.

Calcium signaling is the use of calcium ions (Ca^{2+}) to communicate and drive intercellular processes often as a step in signal transduction. Ca^{2+} is important for cellular signalling, for once it enters the cytosol of the cytoplasm it exerts allosteric regulatory effects on many enzymes and proteins. Ca^{2+} can act in signal transduction resulting from activation of ion channels or as a second messenger caused by indirect signal transduction pathways such as G protein-coupled receptors.

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