

Secondary messengers

1. Introduction:

Multicellular organisms cannot survive without efficient communication among cells, tissues and organs. Regulation and coordination of metabolism, growth, morphogenesis depends of chemical signals from one part of the plant to another. German botanist Julius von Sachs is credited for originating this idea in the late nineteenth century [1].

Typically the end result of any signaling pathway is alteration in gene expression via regulating the transcription factors. Signal transduction pathways often involve the generation of second messengers, transient secondary signals inside the cell that greatly amplify the original signal. Binding to a receptor initiates a signal transduction pathway, often involving the generation of second messengers, such as cyclic nucleotides, inositol trisphosphate, and calcium. Such pathways normally lead to changes in gene expression. Chemical signals specifically bind protein receptors found either on the plasma membrane or in the cell's cytoplasm [2].

Second messengers are molecules that relay signals received at receptors on the cell surface such as the arrival of protein hormones, growth factors, etc. to target molecules in the cytosol and/or nucleus. In addition to their job as relay molecules, second messengers serve to greatly amplify the strength of the signal. Binding of a ligand to a single receptor at the cell surface may end up causing massive changes in the biochemical activities within the cell.

There are 3 major classes of second messengers:

1. cyclic nucleotides (e.g., cAMP and cGMP)
2. inositol trisphosphate (IP₃) and diacylglycerol (DAG)
3. calcium ions (Ca²⁺)

There are three basic types of secondary messenger molecules:

- Hydrophobic molecules: water-insoluble molecules such as diacylglycerol, and phosphatidylinositols, which are membrane-associated and diffuse from the plasma membrane into the intermembrane space where they can reach and regulate membrane-associated effector proteins.
- Hydrophilic molecules: water-soluble molecules, such as cAMP, cGMP, IP₃, and Ca²⁺, that are located within the cytosol.
- Gases: nitric oxide (NO), carbon monoxide (CO) and hydrogen sulfide (H₂S) which can diffuse both through cytosol and across cellular membranes.

These intracellular messengers have some properties in common:

- They can be synthesized/released and broken down again in specific reactions by enzymes or ion channels.

- Some (such as Ca^{2+}) can be stored in special organelles and quickly released when needed.
- Their production/release and destruction can be localized, enabling the cell to limit space and time of signal activity.

2. Secondary messengers

2.1 3',5'-cyclic AMP (cAMP)

Adenosine 3':5'-monophosphate, commonly known as cAMP, is a key second messenger in living organisms ranging from *Dictyostelium* to *Homo sapiens*. cAMP was first described as a regulator of glycogen breakdown in the liver and is now known to be a second messenger for a wide variety of cellular responses in animals.

2.2 3',5'-cyclic GMP (cGMP)

It has been shown that the second messenger cyclic guanosine 3,5-monophosphate (cGMP) is an important signalling component with multiple biological functions in plants similar to the situation in animals. In plants, there is some biochemical evidence supporting the existence of plant cGMP-responsive kinases (Newton and Smith, 2004), and the *Arabidopsis* genome contains sequences that encode gene products with both a cyclic nucleotide binding domain and a protein kinase (Meier and Gehring, 2006). However, specific cGMP targets in plants are largely unknown and in particular there is little molecular evidence available of bonafide cGMP-dependent kinases.

2.3 Nitric oxide (NO)

Nitric Oxide has multifunctional roles in plants: stomatal movement, host-pathogen interactions, hormonal signaling during growth/development and adaptation to abiotic/biotic stress. NO in guard cells plays a very important role as a secondary messenger during stomatal closure induced by effectors.

2.4 Cyclic ADP-ribose (cADPR)

There is wide range of physiological functions are signalled and regulated by mobilization of intracellular Ca^{2+} stores. The generally accepted view is that cells possess multiple types of stores that can be mobilized by specific messenger molecules. Two unrelated nucleotides with Ca^{2+} -mobilizing activity was identified viz. cyclic ADP-ribose (cADPR) and nicotinic acid adenine dinucleotide phosphate (NAADP). The action of cADPR on the channel is temperature-dependent, and proposed to be as a temperature sensing mechanism in cells.

2.5 1,2-diacylglycerol (DAG)

Diacylglycerol (DAG) has unique functions as a basic component of membranes, an intermediate in lipid metabolism and a key element in lipid-mediated signaling.

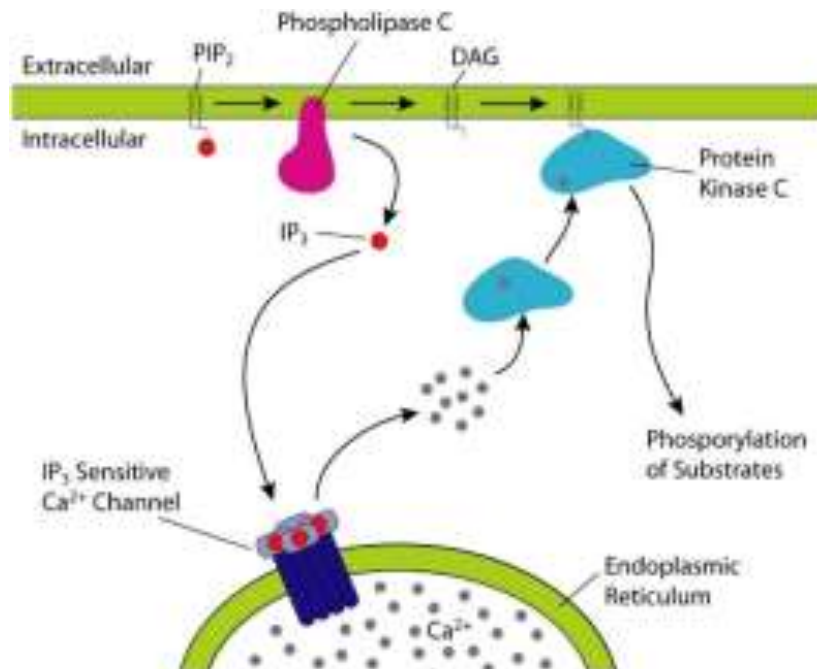
2.6 Inositol trisphosphate (IP₃)-

Inositol trisphosphate or **inositol 1,4,5-trisphosphate** (also commonly known as **triphosphoinositol**; abbreviated **InsP₃** or **Ins3P** or **IP₃**), together with **diacylglycerol** (DAG), is a **secondary messenger** molecule used in **signal transduction** and **lipid signaling** in **biological cells**. While DAG stays inside the membrane, IP₃ is soluble and diffuses through the cell. It is made by **hydrolysis** of **phosphatidylinositol 4,5-bisphosphate** (PIP₂), a **phospholipid** that is located in the **plasma membrane**, by **phospholipase C** (PLC).

Increases in the intracellular Ca²⁺ concentrations are often a result of IP₃ activation. When a **ligand** binds to a **G protein-coupled receptor** (GPCR) that is coupled to a Gq **heterotrimeric G protein**, the α-subunit of Gq can bind to and induce activity in the PLC **isozyme** PLC-β, which results in the cleavage of PIP₂ into IP₃ and DAG.^[10]

If a **receptor tyrosine kinase** (RTK) is involved in activating the pathway, the isozyme PLC-γ has **tyrosine** residues that can become phosphorylated upon activation of an RTK, and this will activate PLC-γ and allow it to cleave PIP₂ into DAG and IP₃. This occurs in cells that are capable of responding to **growth factors** such as **insulin**, because the growth factors are the ligands responsible for activating the RTK.^[11]

IP₃ (also abbreviated Ins3P) is a **soluble** molecule and is capable of **diffusing** through the cytoplasm to the ER, or the **sarcoplasmic reticulum** (SR) in the case of **muscle cells**, once it has been produced by the action of PLC. Once at the ER, IP₃ is able to bind to the Ins3P receptor (Ins3PR) on a ligand-gated Ca²⁺ channel that is found on the surface of the ER. The binding of IP₃ (the ligand in this case) to InsP3R triggers the opening of the Ca²⁺ channel, and thus release of Ca²⁺ into the cytoplasm.^[11] In heart muscle cells this increase in Ca²⁺ activates the **ryanodine receptor**-operated channel on the SR, results in further increases in Ca²⁺ through a process known as calcium-induced calcium release. IP₃ may also activate Ca²⁺ channels on the cell membrane indirectly, by increasing the intracellular Ca²⁺ concentration.



2.7 Ca⁺⁺

Evolution has adopted positively charged calcium as the primary signaling element of cells. Ca²⁺ is one of the principal second messengers for functioning as a central node in the overall “signaling web” and plays an important role in providing stress tolerance to plants.

Analysis of [Ca²⁺] in dynamics has demonstrated its signaling role in plant cells in response to a wide array of environmental cues. In general, the stress leads to increased cytosolic Ca²⁺, which initiates the stress signal transduction pathways for the stress tolerance. Ca²⁺ is the most tightly regulated ion within all membrane-bound organisms and binds to several proteins to effect changes in localization, association, and function. It is now clear that Ca²⁺ signaling affects almost every aspect of the cellular metabolism of living organisms.

In fact, an indirect increase in [Ca²⁺] cyt in plant cells is mediated by the increase in intracellular concentrations of other second messengers such as cyclic GMP, cyclic AMP, and IP3, in response to stimuli. The elevation of Ca²⁺ concentration in cytoplasm is found to be a key event in the plant cell for transduction of various signals to a biological effect [3].