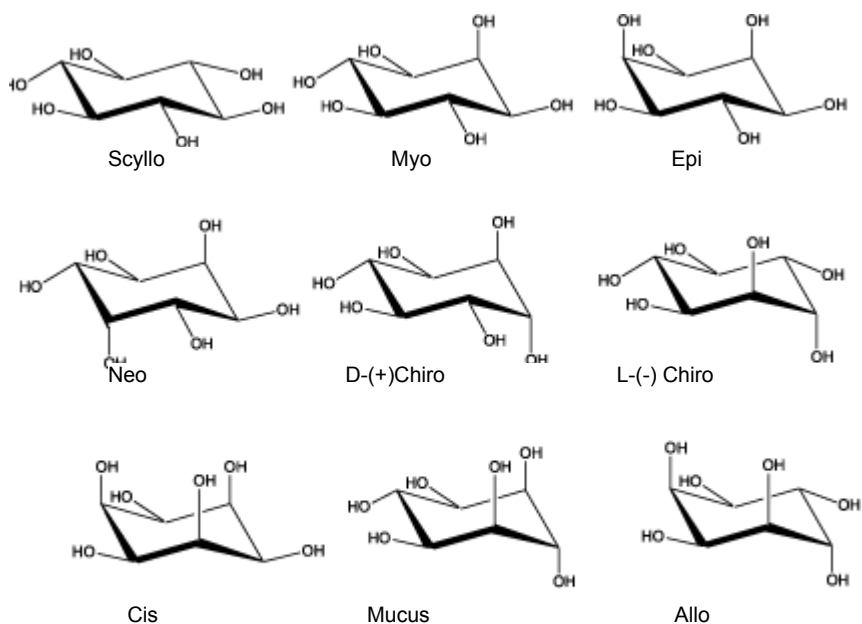


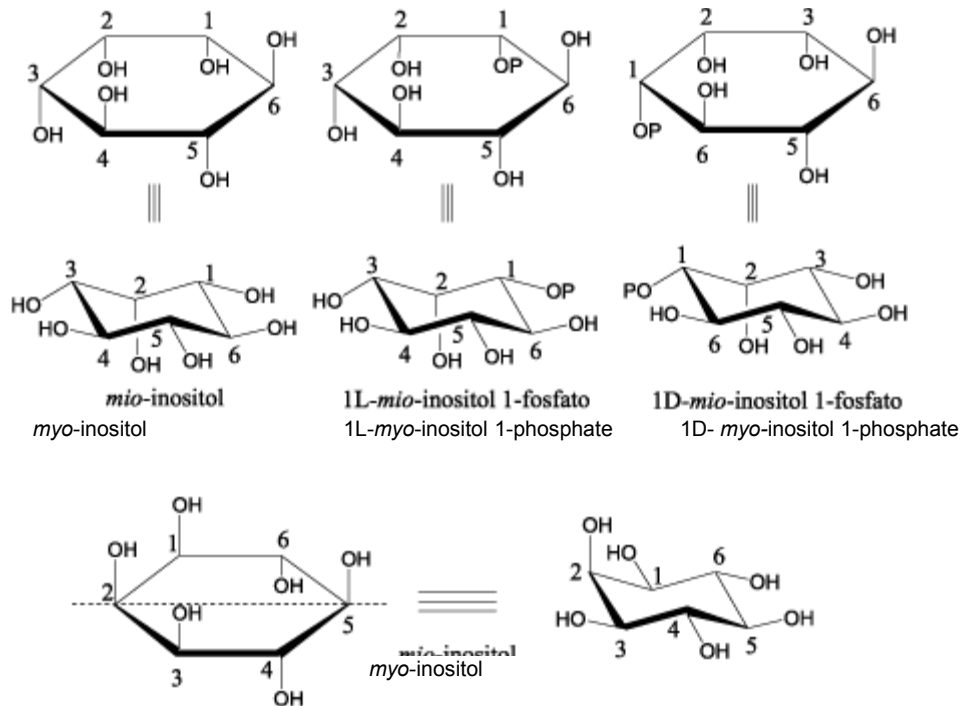
Inositols nomenclature

Inositols can be arranged in nine stereoisomers: *scyllo*, *myo*, *neo*, *epi*, D and L *chiro*, *cis*, *mucus* and *allo* ([Picture 1](#)).



Picture 1. Inositol stereoisomers

From the isomers shown in [Picture 1](#), the *myo*-inositol is the most abundant in nature, being produced from the glucose. According to the official nomenclature, the only axial hydroxyl group of *myo*-inositol (I) occupies the position C-2 in the structure ([Picture 2](#)). The phosphorylation of the *myo*-inositol in O-1 generates the 1L-*myo*-inositol 1-phosphate (II). However, the phosphorylation in the position O-3 alters the numeration of the carbon atoms, inverting C-1 with C-3, which generates 1D-*myo*-inositol 1-phosphate (III).



Picture 2. Nomenclature and symmetry plan of *myo*-inositol

The *myo*-inositol is a *meso* compound, because it presents a symmetry plan passing by the atoms C-2 and C-5 (Picture 2). Any mono-substitution in the positions 1, 3, 4 or 6 produces, therefore, a racemate.

The symbol Ins

The symbol Ins is used for the *myo*-inositol with configuration 1D. In case it has configuration L, it must be previously mentioned. The termination P_x in italic indicates the number of phosphorylations that exist in the inositol.

Example:

Ins (1,4,5) P_3 (1D-*myo*-inositol 1,4,5-triphosphate)

Ins (1,3,4,5) P_4 (1D-*myo*-inositol 1,3,4,5-tetraquisphosphate)

Ins (3,4) P_2 (1D-*myo*-inositol 3,4-diphosphate)

THE PHOSPHOINOSITIDES CASCADE

The communication in the superior organisms is necessary to the control of the development of the cells, their organisation in tissue and organs, their growth and multiplications, being also necessary to the co-ordination of their activities. In a communication system (Picture 3), a first sign called "first-messenger"¹ (hormone, growth factor, etc.) is freed and it circulates in the extra-cellular environment. The first messenger (\tilde{N}) is caught in the cell surface by receptors (R) which are specific to it. The occupation of the receptors placed in the cellular membrane initiates complex events in the plasma membrane and in the interior of the cell.

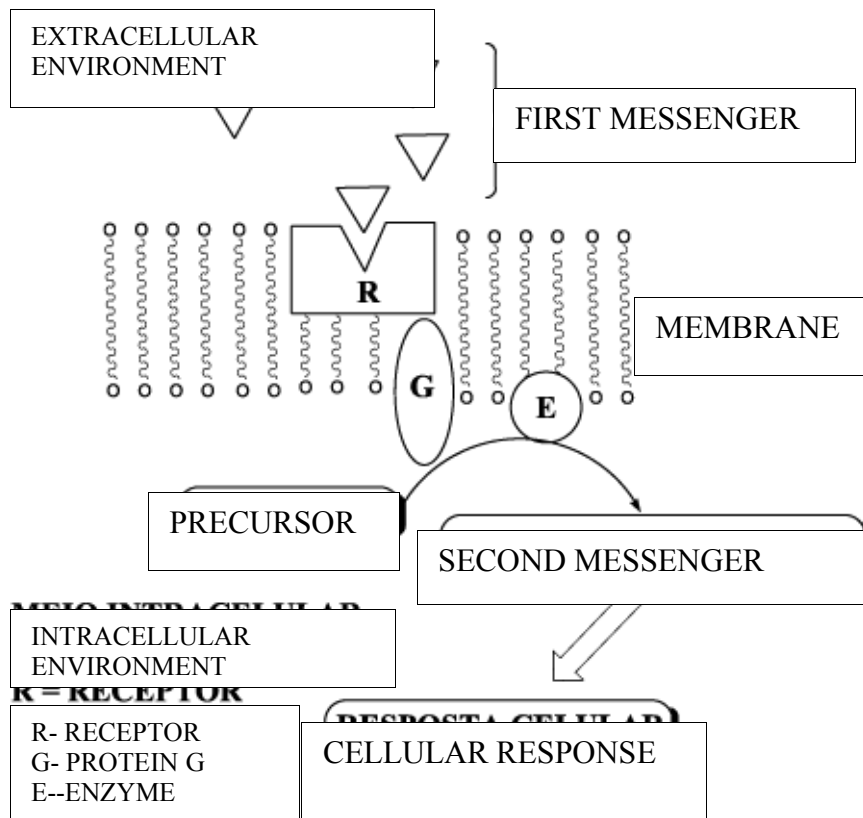


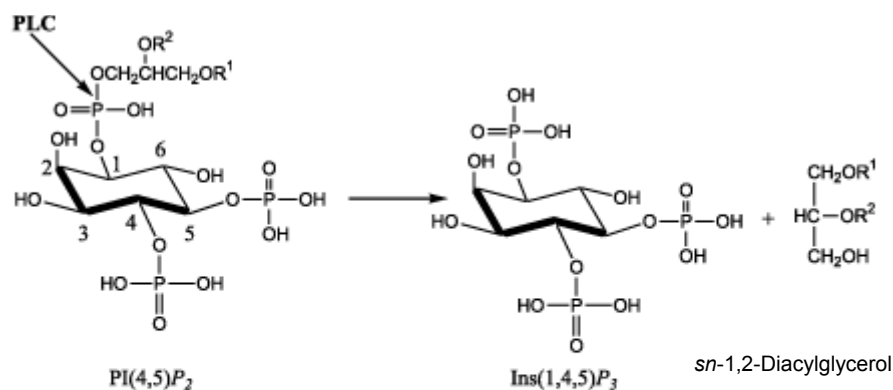
Figura 3. Mecanismo de transdução celular

Picture 3. Cellular transduction mechanism

A very important type of receptor uses a class of proteins called proteins G. These are linked to the guanines being coupled to the ion channels, or to other enzymes, controlling the liberation of other intracellular messengers². These biological molecules known as "second-messenger" (secondary messengers) constitute the last linkage of the intracellular communication chain before the physiologic response, being a point of great interest to the understanding of the signal transduction mechanisms (Picture 3).

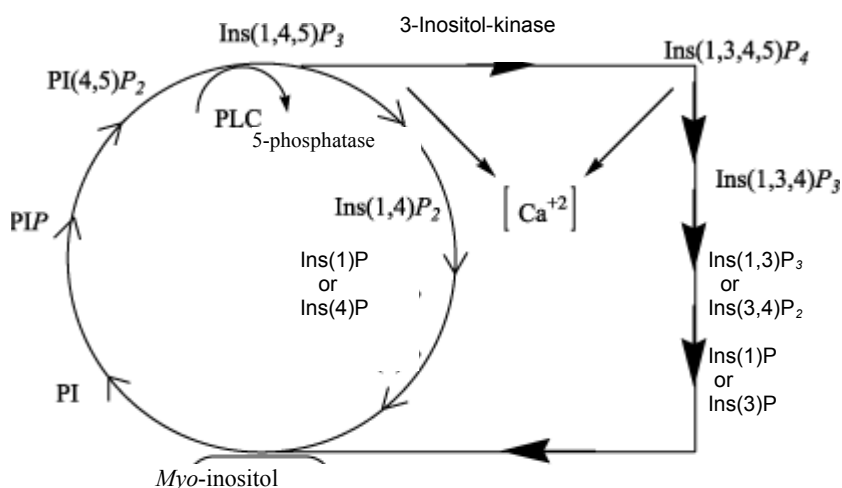
In 1975, Michell³ suggested a new way of signal transduction, which was demonstrated by Berridge and collaborators⁴ in 1983. However, only in the last years did an idea compatible with the phosphoinositides cascade^{5,6} physiologic performance appear.

With a stimulation induced by an agonist, at the level of the receptor in the membrane, a protein G activates the phospholipase C (PLC), which catalyses the hydrolysis of the phosphodiester linkage of the PI(4,5)P₂, releasing two new second-messengers in the intracellular environment: the *myo*-inositol 1,4,5-triphosphate [Ins(1,4,5)P₃] and the *sn*-1,2-diacylglycerol (Picture 4). This event triggers a series of sequential reactions called phosphoinositides cascade (Picture 5).



R¹ and R²- acyl groups originated from acids, such as stearic and arachidonic acids

Picture 4. Hydrolysis of the linkage of PI(4,5)P₂



Picture 5. Phosphoinositides cascade

The control of the hydrolysis of PI(4,5)P₂ is now recognized for being one of the basic mechanisms in the intercellular communication. A great number of neurotransmitters, hormones, etc. use this transduction /amplification mechanism to cause the cellular response.

The Ins(1,4,5)P₃, which is hydro-soluble, is connected to a specific intracellular receptor and mobilizes the Ca²⁺ present in the endoplasmic reticulum of a great number of different cellular systems. There are a certain number of substances that can blockade these receptors and the most powerful already identified is heparin⁷. The Ins(1,4,5)P₃ is responsible for regulating numerous cellular processes, like secretion, metabolism, contraction and proliferation.

The *sn*-1,2-diacilglycerol is located in the plasma membrane and it acts by activating the protein kinase C (PKC). This enzyme stimulates the phosphorylation of numerous intracellular proteins^{8,9}.

Metabolism of Ins(1,4,5)P₃

The mobilisation of Ca^{2+} by $\text{Ins}(1,4,5)\text{P}_3$ can be interrupted in two different metabolic pathways (Picture 5). In the first one, the 5-phosphatase cuts the phosphate group in C-5 to lead to *myo*-inositol 1,4-diphosphate [$\text{Ins}(1,4)\text{P}_2$]. Two other successive dephosphorylations lead to the *myo*-inositol, via *myo*-inositol 4-phosphate [$\text{Ins}(4)\text{P}$]. The *myo*-inositol is again turned into $\text{PI}(4,5)\text{P}_+$ through successive phosphorylations.

The second alternative of metabolism is the phosphorylation of the $\text{Ins}(1,4,5)\text{P}_3$ into *myo*-inositol 1,3,4,5-tetraphosphate [$\text{Ins}(1,3,4,5)\text{P}_4$] by the inositol 3-kinase (Picture 5). This one is quickly subject to dephosphorylation by the 5-phosphatase into *myo*-inositol 1,3,4-triphosphate [$\text{Ins}(1,3,4)\text{P}_3$], then into *myo*-inositol 1,3 or 3,4-diphosphate and, finally, into *myo*-inositol, via different monophosphates. $\text{Ins}(1,3,4,5)\text{P}_4$ can be weakly connected to the linkage place of $\text{Ins}(1,4,5)\text{P}_3$, but it can interfere in the mobilization of the extra-cellular Ca^{2+} through the membrane, when $\text{Ins}(1,4,5)\text{P}_3$ is present.

$\text{Ins}(1,3,4)\text{P}_3$ ¹⁰ does not stimulate the capture of Ca^{2+} . In 1987, Balla and collaborators¹¹ showed the existence of a kinase that turns this triphosphate into *myo*-inositol 1,3,4,6-tetraphosphate [$\text{Ins}(1,3,4,6)\text{P}_4$], then into *myo*-inositol 1,3,4,5,6-pentaphosphate [$\text{Ins}(1,3,4,5,6)\text{P}_5$] by phosphorylation. The existence of the inositol pentaphosphate and hexaphosphate (phytanic acid) was proved in different tissues of mammals¹².

Discussion on the Phosphoinositides cascade

In spite of numerous studies on the role of $\text{Ins}(1,4,5)\text{P}_3$ and of *sn*-1,2-diacylglycerol as second-messenger in the transduction pathway used in the Phosphoinositides cascade, no mechanism of action or a structure-activity relationship can be suggested without ambiguity.

It is known that the $\text{Ins}(1,4,5)\text{P}_3$ is a mediator in the liberation of the intracellular Ca^{2+} from the endoplasmic reticulum (ER) to the cytoplasm. It activates a receptor situated in the endoplasmic reticulum external membrane and linked to a calcium channel. This activation causes the opening of this one and consequently the liberation of the Ca^{2+} into the cytoplasm.

One also knows that the inositol phosphates capacity to cause the liberation of calcium depends on the number and on the position of these phosphate groups in the molecule. The presence of a phosphate group in the C-1 position is essential to make the linkage with the receptor. Studies made on the structure-activity relationship indicate that the presence of vicinal phosphate groups in the positions 4 and 5 of *myo*-inositol is essential to the liberation of Ca^{2+} , as Irvine had predicted in 1984¹³.

It has also been shown that the position 2 in *myo*-inositol (hydroxyl in axial) has a specific role, since this position is important for the recognition of the inositol phosphates by different enzymes¹⁴.

The recent discovery of phosphatidylinositol 3 - phosphate and of a phosphatidylinositol 3,4,5-triphosphate indicates that there are still other unknown phosphoinositides.

One does not know the physiologic importance of the transformation of $\text{Ins}(1,4,5)\text{P}_3$ in several phosphor compounds. One does not know if these compounds have their own biological activity or if they are only intermediary metabolites.

The *myo*-inositol 1,2,6-triphosphate $\text{Ins}(1,2,6)\text{P}_3$ is a product obtained by the enzymatic degradation of the phytanic acid (*myo*-inositol 1,2,3,4,5,6-hexaphosphate)¹⁵. This triphosphate showed pharmacological effects that are important in many pathologies, like the secondary diabetic complications, the cardiovascular diseases and the chronic inflammations such as arthritis¹⁵.