

Glossary

Gary D. Lopaschuk

Calmodulin

Calmodulin is a calcium-binding protein expressed in all eukaryotic cells. Calmodulin binds to and regulates many different protein targets. Calmodulin often acts as a calcium sensor, and can modulate the activity of proteins in response to changes in cellular calcium. Binding of calcium to calmodulin alters the proteins conformation, allowing calmodulin to interact with a number of other proteins. In the heart, calcium binding to calmodulin can facilitate excitation contraction coupling by facilitating the interaction of calmodulin with a number of proteins involved in excitation contraction coupling.

EDHF; Endothelium-derived hyperpolarizing factor

EDHF is secreted by endothelial cells, which leads to nitric oxide- and prostacyclin-independent vasodilation. EDHF relaxes vascular smooth muscle cells. If both NO and prostacyclin production are inhibited, arterioles still continue to dilate if they are stimulated by agents such as acetylcholine or bradykinin. This observed increase in blood vessel dilation is dependent on potassium channel activity and endothelium-dependent hyperpolarization of the smooth muscle cells.

Endothelin-1

Endothelin-1 is a small peptide produced in the endothelium of blood vessels that can cause vasoconstriction. Normally the action of endothelin-1 is kept in balance with other vasoregulatory pathways, but can contribute to high blood pressure (hypertension) and heart disease if the peptide is over-expressed.

Glycocalyx

Glycocalyx is an extracellular polymeric network of polysaccharides that project from cellular surfaces, such as those of bacteria. In bacteria the glycocalyx protects the bacterium or allows the bacterium to attach itself to inert surfaces.

G_s protein

Guanine nucleotide-binding proteins, or G proteins, are a family of proteins involved in second messenger cascades. G proteins belong to the larger group of enzymes called GTPases. G proteins are inactive if guanosine diphosphate (GDP) is bound to the protein and active if guanosine triphosphate (GTP) is bound. The stimulatory G protein (G_s) links a number of receptors to intracellular action. A good example is how G_s links the β -adrenergic receptor to adenylyl cyclase.

IP₃R: inositol trisphosphate receptor

Inositol trisphosphate (IP₃) is released from a cell membrane phospholipid called phosphatidylinositol 4,5-bisphosphate (PIP₂), via the action of phospholipase C. IP₃ binds to and activates an IP₃ receptor (IP₃R), which can be found on the membrane of the sarcoplasmic reticulum. The IP₃R functions as a sensor for IP₃, resulting in the release of calcium from the sarcoplasmic reticulum. The IP₃R can be phosphorylated and regulated by kinases, such as protein kinase C, Ca²⁺ calmodulin-dependent protein kinase, and protein kinase A.

K_{ATP}

K_{ATP} is a potassium channel that is inhibited by ATP. As a result, K_{ATP} is a metabolically regulated potassium channel. For instance, K_{ATP} is one of the potassium channels responsible for pancreatic β -cell insulin release.

Phospholipase C and release of IP₃ and diacylglycerol

Phospholipase C (PLC) plays an important role in signal transduction processes. Phospholipase C participate in phosphatidylinositol bisphosphate (PIP₂) metabolism and lipid signaling pathways in a calcium-dependent manner. PLC hydrolyzes PIP₂ into two important second messenger molecules, IP₃ and

diacylglycerol. These two second messengers have many important downstream functions, which include: ion channel modification, neurotransmission, endocrine functions, vesicular trafficking, cell proliferation, cell differentiation, cell apoptosis, and cytoskeleton remodeling.

PKA; protein kinase A

Protein kinase A, sometimes called cAMP-dependent protein kinase, is activated by increases in cellular cAMP. Protein kinase A can then phosphorylate and modify the activity of a number of intracellular proteins, including those involved in muscle contraction.

PKC; protein kinase C

Protein kinase C (PKC) is a family of kinases initially identified as requiring diacylglycerol, calcium, or phospholipids for activation. The conventional PKCs require calcium, diacylglycerol, and phosphatidylcholine for activation. Novel PKCs require diacylglycerol, but do not require calcium for activation. The conventional and novel PKCs are activated through the same signal transduction pathway as phospholipase C. Some atypical PKCs have also been identified that require neither calcium or diacylglycerol for activity. The PKCs have numerous cellular targets.

PKG; protein kinase G

Protein Kinase G (PKG), sometimes referred to as cGMP-dependent protein kinase is activated by cGMP. Protein kinase G phosphorylates a number of biologically important targets, some of which are involved in the regulation of smooth muscle relaxation. Nitric oxide (NO) acts via PKG stimulation.

Protein kinases activated by G-protein receptor dependent signalling pathways

A number of different protein kinases can be activated by G protein-coupled receptors. A large number of cell membrane receptors (one example being β -receptors) are coupled to G-proteins to mediate their intracellular events. The G-proteins in turn are linked to a number of downstream kinases which initiate various signaling pathways. An example of a downstream kinase is protein kinase A. In the β -adrenergic signal-

ing pathway the stimulation of the β -receptor stimulates a Gs protein, which results in a stimulation of adenylate cyclase resulting in an increase in cAMP, and an activation of protein kinase A. Protein kinase A phosphorylates and modifies the activity of a number of intracellular proteins, including those involved in muscle contraction. This is but one example of numerous G protein receptor-dependent signalling pathways.

Rho-K; rho-kinase

Rho-kinase (Rho-K) is a serine/threonine kinase that is activated by GTP-bound RhoA. Rho-K is involved in the regulation of number of cellular activities which include smooth muscle contraction, cell morphology, formation of stress fibers and focal adhesions. Rho-K regulates smooth muscle contraction by phosphorylating the regulatory subunit of myosin light chain.

RyR: ryanodine receptor

Ryanodine receptors are intracellular calcium channels present in excitable cells, such as muscle and neurons. In sarcoplasmic reticulum of muscle cells, the ryanodine receptor a major source of calcium release that initiates muscle contraction.

Soluble guanylate cyclase

Nitric oxide (NO) is important for many physiological functions including vascular smooth muscle relaxation, neuronal signal transduction and inhibition of platelet aggregation. The primary receptor for NO is soluble guanylate cyclase (sGC), which catalyzes the conversion of GTP to the second messenger molecule cyclic GMP (cGMP). cGMP can then activate PKG to initiate smooth muscle relaxation.

Tyrosine phosphorylation

Protein kinases act by primarily phosphorylating two types of amino acids. One type are serine/threonine kinases, the other are tyrosine kinases. Tyrosine phosphorylation is involved in many cellular processes. A well known tyrosine kinase is the insulin receptor, which results in a tyrosine phosphorylation of the insulin receptor substrate to initiate the insulin-signaling pathway.