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Review Article

The Role of Second Messengers in the Functioning of the Cell

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Abstract

Secondary intermediaries, or secondary messengers, are intracellular signaling molecules released in response to stimulation of receptors. They are the initiating elements in many intracellular signaling cascades and cause the activation of primary effector messenger proteins. This triggers a cascade of physiological changes that are important for the growth, development, differentiation of cells, gene transcription, protein biosynthesis, secretion of hormones, neurotransmitters or cytokines, changes in bioelectric activity and cell migration, and apoptosis induction. Several universal secondary signaling systems exist in the cell, which are mediated by the main three types of mediators: hydrophobic molecules: water-insoluble molecules (diacylglycerol, phosphatidylinositol) that bind to cell membranes and diffuse across intermembrane spaces to organelle membranes, reaching and acting with membrane-bound secondary effector proteins; hydrophilic molecules: water-soluble molecules (cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate (cGMP), inositol triphosphate, calcium), which are distributed in the aqueous medium of the cytoplasm; gases: nitric oxide (NO), carbon monoxide (CO), hydrogen sulfide (H2S), which pass through the cell membrane and diffuse into the cytoplasm.

The purpose of this review is to generalize and systematize literature data on the mechanisms for the implementation of the functions of secondary messengers in the intercellular signaling system. The study of their functioning and regulation can serve as a fundamental basis for the study of normal brain and experimental pathology, creating the basis for subsequent clinical studies.

Keywords: secondary mediators; intercellular signaling; effector proteins; receptors; ligands; brain

Introduction

Signal transmission (signal transduction, signaling) is the process of transformation by a cell of one type of signal into another. The cell's response to external signals is due to the interaction of the cytoplasmic membrane and organelles by activating receptors. There are two mechanisms of transduction: indirect (mediated through cytolemma receptors) and direct (associated with the penetration of substances into the cell with subsequent activation of intracellular receptors). Hormones, mediators, cytokines, growth factors, neuromodulators, etc. can act as primary mediators acting through membrane receptors. Primary messengers are not able to cross the membrane in order to directly initiate a cascade of intracellular physiological changes, as they are usually hydrophilic or large polypeptide molecules [9, 13, 16, 23].

The formation of the receptor-ligand complex provides a specific transmembrane signal due to the formation of secondary intermediaries.

Secondary intermediaries (messengers) are signaling molecules of the cytosol, the output of which occurs when the cytolemma binds to the ligand. They participate in numerous processes of intracellular signaling, potentiating the primary molecules of signal-transmitting proteins. Secondary signaling molecules are important in regulating the processes of ontogenesis, tissue specialization, changes in gene activity, synthetic processes, cell cycle, neurotransmitter and amino acid metabolism in the central nervous system [16, 23].

The purpose of this review is to generalize and systematize the literature data on the mechanisms of implementing the functions of secondary messengers in the intercellular signaling system.

There are several universal secondary (messenger) signaling systems in the cell, which are mediated by the main three types of intermediaries:

1. Hydrophobic molecules: water-insoluble molecules (diacylglycerol, phosphatidylinositol) that bind to the cytolemma and diffuse through the intermembrane spaces to the membranes

of organelles, reaching and acting with membrane-bound secondary effector proteins;

2. Hydrophilic molecules: water-soluble molecules (cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate (cGMP), inositol triphosphate, calcium), which are distributed in the aqueous medium of the cytoplasm;
3. Gases: nitrogen oxide (NO), carbon monoxide (CO), hydrogen sulfide (H2S), which pass through the cell membrane and diffuse into the cytoplasm.
4. General properties of secondary intermediaries:
5. can be rapidly synthesized, isolated and removed or inactivated using specific catalytic enzymes;
6. some (calcium ions) are stored in granules or vacuoles and are quickly released if necessary;
7. production, isolation, removal and inactivation are under the control of intracellular negative feedback systems that do not allow excessive amplification of the signal coming from outside, or its excessive duration and prevent self-injury of the cell during signal processing; the exchange is limited, which allows the cell to localize in space and limit the signal transmission process in time [9, 13, 16, 23].

There are 3 classes of cytolemma receptors:

1. conjugated with G-proteins (metabotropic);
2. associated with ion channels (ionotropic);
3. associated with enzymes that have their own enzymatic activity (protein tyrosine kinases, platelet growth factor receptors, epidermal and nerve cells).

G-protein-coupled receptors (metabotropic)

G-proteins are universal mediators of signal transmission from membrane receptors to effector proteins. There are several species, each of which performs a specific function:

Gt protein (transducin) - participates in signal transmission in photoreceptors;

Gs-protein – conjugates membrane receptors with adenylate cyclase;

Gq protein regulates the activity of phospholipases C and A2.

G-protein coupled receptors have seven transmembrane sites. They are involved in the activation of intracellular signal transmission pathways [19].

Depending on the ligand binding site and the nature of the ligand, the receptors are divided into three main classes – A, B and C. Receptors of classes A and B bind low molecular weight ligands and peptides in the transmembrane region, and receptors of class C bind low molecular weight ligands in the region of extracellular loops connecting transmembrane domains.

The signal transmission pathway by G-protein-coupled receptors includes a number of steps:

1. The ligand binds to the membrane receptor. Inactive G-protein is associated with GDF;
2. The receptor associated with the ligand, interacting with the G-protein, causes its activation;
3. Activated G-protein interacts with intracellular enzymes (adenylate cyclase, guanylate cyclase, phospholipases C, A, D), changing their activity and modulates the functioning of cytoplasmic membrane channels;
4. Activation of the intracellular enzyme changes the level of secondary mediators (cAMP, cGMP, Ca2+, inositol triphosphate, diacylglycerol, etc.);
5. A change in the concentration of secondary mediators leads to activation or inhibition of dependent protein kinases or channels of the cytoplasmic membrane;

changes in the phosphorylation level of target proteins [13, 16, 19, 23]. Regulation of G-protein activity.

G-proteins consist of 3 subunits: α, β and γ. The alpha subunit participates in the binding and hydrolysis of GTP, as well as in interaction with the receptor, β-dimer and effector.

The β and γ subunits are combined into a β-complex and are associated with α-subunit. The β-complex is bound to the cell membrane and stabilizes the α-subunit.Metabotropic receptors, ion channels, phospholipase A2 and some isoforms of phospholipase C are activated through the β-complex.

The binding of the receptor to the ligand leads to an interaction between the receptor and the G-protein and activates the dissociation of GDF to form a complex: agonist-receptor-protein. By binding to this complex, GTP reduces the affinity of the receptor to the G-protein, the complex dissociates and releases the receptors. The α-subunit released from the βγ-complex, together with GTP, interacts with the effector, activating or inhibiting it.Then hydrolysis of GTP occurs and the α-GDF complex re-interacts with βy, forming a trimeric G-protein [18, 19].

Receptors associated with ion channels (ionotropic) The ion channel penetrates the cytolemma, providing ion transport. Ligand-activated ionotropic receptors open when special receptor centers of the channel are activated. Some of them are sensitive to neurotransmitters and are directly involved in the transmission of information in synaptic structures.

Diacylglycerol is a membrane-bound glycerin formed when phosphoinositol diphosphate is released by phospholipase C. In the same reaction, it forms inositol triphosphate that penetrates through the membrane into the cytoplasm of the cell. Diacylglycerol causes activation of protein kinase C, increasing its affinity for calmodulin and facilitates the translocation of the enzyme from the cytoplasm into the membrane.

Phosphatidylinositol is a phospholipid that plays an important role in intracellular signaling pathways. Its phosphorylation is catalyzed by specific enzymes phosphoinositide-3-kinase, whose activity is regulated by growth factors. Located on the cell membrane, phosphatidylinositol activates proteins involved in intracellular transport [9, 13, 16, 23].

Adenylate Cyclase signal transmission system Adenylate cyclase is a membrane glycoprotein and is a key enzyme of adenylate cyclase signaling. Adenylate cyclase is capable of forming dimeric or tetrameric complexes that can move along the cytoplasmic membrane.

There are several isoforms of adenylate cyclase.

Thus, isoform 1 is expressed in the dentate gyrus and the hippocampal CA2 field, isoform 8 – in the hippocampal CA1 field, Ca2+-sensitive adenylate cyclase – in the localization sites of NMDA-inotropic glutamate receptors and potential-dependent Ca channels, isoforms 3-5 – in the folds of the cytolemma.

The basal activity of adenylate cyclase increases when the α-subunit binds to stimulating Gs protein (Gsa), corticoliberin, somatoliberin, glucagon, norepinephrine and is inhibited when binding to Gia protein, protein kinase A, adenosine, somatostatin, angiotensin II, acetylcholine, dopamine and opioids [20]. Binding of the primary messenger to the receptor leads to the activation of adenylate cyclase. An increase in the level of cAMP leads to the opening of cAMP-activated cationic ion channels in the receptor membrane and depolarization of the membrane.

The adenylate cyclase intercellular signaling system stimulates protein kinase reactions, cytoplasmic membrane channel activity, and protein phosphorylation [24].

Protein kinases are enzymes that catalyze the transfer of the phosphate terminal residue from ATP to protein. Their activity is regulated by cAMP and cGMP.

There are several classes of protein kinases.

A-G-C-class. A-G-C-class enzymes transfer phosphate to alcohol groups of amino acids. When their enzymes are activated, either a change in the structure or a reversible association of regulatory and catalytic subunits occurs.

Protein kinase A is cAMP-dependent, mediates most intracellular effects of cAMP and regulates the activity of many other enzymes [14].

In the absence of cAMP, protein kinase A is inactive. Its activation occurs when two cAMP molecules bind to each of the β-subunits of the enzyme, followed by dissociation of the catalytic subunits.When the catalytic subunit is released, phosphorylation of substrate proteins occurs: protein kinases, phosphatases, enzymes of protein, carbohydrate and lipid metabolism, nuclear proteins and histones. Phosphorylation of proteins is the main way of transmitting signals that control intracellular processes.

The regulation of protein kinase A activity is carried out by binding them to "anchoring proteins" that localize the enzyme in a certain cell compartment. Some of the "anchoring proteins" are located in the region of the cytoplasmic membrane channels, where the concentration of cAMP is especially high [24].

Guanylate Cyclase signal transmission system

Cyclic GMF is synthesized from GTP with the participation of soluble and membrane-associated guanylate cyclase [1, 15]. Soluble guanylate cyclase is located in the cytoplasm and participates in inhibition of platelet aggregation, smooth muscle relaxation, vasodilation, neuronal signal transduction and immunomodulation [8].

The activity of soluble guanylate cyclase regulates NO, CO, Mn2+, Mg2+ and Ca2+ ions. Membrane guanylate cyclases are activated by peptides (natriuretic peptide, thermostable enterotoxin E.coli, and endogenous intestinal peptide guanylin) [11, 12]. Cyclic GMF mediates the effects of a number of hormones, natriuretic peptides, gaseous messengers, Ca2+ ions and pharmacological agents, plays an important role in the processes of exo- and endocytosis, regulation of contractility, growth and differentiation of organelles and cells in general, neuromuscular transmission [3].

Protein kinase G is a serine/threonine kinase consisting of receptor, catalytic and regulatory domains. The targets for protein kinase G are inositol-triphosphate receptors, phospholambane, vimentin, G-proteins, thromboxane A2 receptors, calcium-activated K-channels, L-type Ca-channels, Ca-dependent cytosolic phospholipase A2 and tyrosine hydroxylase.Under the influence of cGMP with a receptor domain, the catalytic domain is activated and serine/threonine residues of target proteins are phosphorylated. A certain intracellular localization of protein kinase G is provided by skeleton and "anchoring proteins" [5, 17].Phosphodiesterases are involved in the regulation of intracellular signaling by the metabolism of cAMP and cGMP. They limit their effects and serve to cross-link between cAMP- and cGMP-dependent signaling systems. Activation of the cAMP- or cGMP-dependent signaling pathway will depend on the activity of adenylate cyclase, guanylate cyclase, intracellular localization of enzymes and their targets of action [10].

Thus, cyclic nucleotides cAMP and cGMP control a wide range of metabolic processes, the activation process of which is influenced by a complex of interconnected intracellular signaling systems [4, 11, 12, 25]. Ca2+-calmodulin-dependent protein kinases contain a catalytic subunit with which calmodulin interacts and a regulatory subunit. Their activity depends on the concentration of AMP.

The C-M-G class includes cyclin-dependent protein kinases (C-subclass), mitogen-activated protein kinases (M-subclass) and protein kinases capable of phosphorylating the enzyme glycogen synthase (G-subclass). Regulation of the activity of these protein kinases is carried out by autophosphorylation or phosphorylation, as well as changes in the concentration of a number of intracellular metabolites (polyamines). Tyrosine kinases – phosphorylate tyrosine residues in target proteins. Enzymes of this class are membrane-bound. The heterogeneous class includes all other protein kinases. Their activity is mainly regulated by low molecular weight intracellular metabolites [9, 13, 16, 23].

The role of Ca2+ in intercellular signaling

The depolarization of membranes and the action of certain hormones promotes the opening of ion channels for Ca2+. There are Ca2+-binding proteins in cells, such as annexin, calmodulin and troponin [2, 6, 23]. Annexin is a calcium–binding protein synthesized in immune cells under the influence of glucocorticoids. Annexin mediates the immunosuppressive, anti-inflammatory and antiallergic effects of glucocorticoids, inhibits the activity of phospholipase A2 and cyclooxygenase 1 and 2, reducing the synthesis of eicosanoids and prostaglandins. Calmodulin is activated by the action of calcium ions, regulating the functions of transport and structural proteins.

Troponin is associated with tropomyosin and is located in the myocytes between the actin filaments, blocking the site of attachment of the myosin head to actin during muscle relaxation. During contraction, Ca2+ is released into the cytoplasm from the sarcoplasmic reticulum. Some of them attach to troponin, it changes its conformation, opening the myosin head access to the actin filament [2, 6, 23].

Inositol triphosphate system.

The inositol triphosphate system consists of: receptor, phospholipase C, cytolemma and cytoplasm enzymes. After binding the cytolemma receptor to the ligand, phospholipase C is activated, which leads to the cleavage of phosphatidylinositol-4,5-biphosphate of the cytolemma into diacylglycerol and inositol triphosphate (IF3). 3 promotes the release of Ca2+ into the cell, and diacylglycerol potentiates the activity of protein kinase C. Under the action of secondary messengers, phosphorylation and alteration of cytosol proteins occur [9, 13, 16, 23].

Gaseous secondary messengers.

These include gases such as NO, CO and H2S. They carry out intercellular and intracellular signaling, affect the channels of the cytoplasmic membrane, exocytosis processes, activate enzymes. The action of gaseous messengers is provided by cyclic nucleotides. Nitrogen monoxide passes through cytoplasmic membranes without binding to cytolemma receptors, but directly interacting with the cytosol. NO binds to heme by soluble intracellular guanylate cyclase, promoting the formation of cGMP from GTP, which, in turn, activates cGMP-dependent protein kinase, which provides phosphorylation of cytosol proteins and ion channels [21, 22].

Under the action of nitrogen monoxide, the activity of adenylate cyclase decreases, as a result of which the amount of cAMP also decreases. In neuromuscular synapses, NO reduces the release of mediators. NO diffuses from the cytosol, where it is synthesized, into the extracellular space. Its isolation is not tied to any cell compartment. Nitric oxide is formed when necessary with appropriate stimuli, and the intracellular

content is very low. Synthesis of NO in the brain, as in other organs, comes from the amino acid L-arginine, which is a substrate of NO synthase (NOS).

The functions of NO in the brain are to regulate the maturation of neurons and glia, blood supply and vascular tone, mediator exchange and impulse transmission processes [21]. Carbon monoxide (CO) also causes the activation of soluble guanylate cyclase. Increasing the level of cGMP stimulates protein kinase G. In neuromuscular synapses, CO increases the release of acetylcholine by increasing intracellular cAMP levels. Regulates the activity of glutamatergic neurons and sensory cells of carotids, contributing to vasodilation.

Hydrogen sulfide (H2S) potentiates cAMP-dependent protein kinase, suppresses synaptic impulses when excessive, and supports long–term action potential in hippocampal neurons in physiological conditions [5, 16, 23]. Thus, secondary messenger systems play an important role in the vital activity of cells. The study of their functioning and regulation can serve as a fundamental basis for the study of the brain in normal and experimental pathology, creating a basis for subsequent clinical studies.

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