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Secondary Messengers – A Role in The Regulation of Cell Function

Bon Lizaveta I[1*], Maksimovich Nataliya Yevgenievna[2], Vihanga BT[3]

[1]Associate Professor of the Department of Pathological Physiology named D.A. Maslakova Grodno State Medical University, Republic of Belarus.

[2]Professor, Head of the Department of Pathological Physiology named D.A. Maslakova Grodno State University, Republic of Belarus.

[3]Student, Grodno State Medical University, Belarus.

Corresponding Author: Bon Lizaveta I, Associate Professor of the Department of Pathological Physiology named D.A. Maslakova Grodno State Medical University, Republic of Belarus. **Email:** asphodela@list.ru

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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.

1. Introduction

Signal transmission (signal transduction, signaling) is the process of transformation by a cell of one type of signal into another. The response of the cell to external signals occurs due to the interaction of the cytoplasmic membrane and organelles by activating receptors. There are two mechanisms of transduction: indirect (mediated through cytolemmal receptors) and direct (associated with the penetration of substances into the cell with subsequent activation of intranuclear receptors). Hormones, mediators, cytokines, growth factors, neuromodulators, etc. can act as primary messengers acting through membrane receptors. Primary messengers are not able to overcome the membrane in order to directly initiate a cascade of intracellular physiological changes, since they are usually hydrophilic or large polypeptide molecules [9, 13, 16, 23].The formation of the receptor-ligand complex ensures the conduction of a specific transmembrane signal due to the formation of second messengers. Secondary messengers (messengers) are signal molecules of the cytosol, which are released when the cytolemma binds to a ligand. They participate in numerous processes of intracellular signaling by potentiating the primary molecules of signal-transmitting proteins. Secondary signaling molecules are important in the regulation of ontogenesis processes, 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 literature data on the mechanisms of implementation of the functions of second 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 mediators:

1.Hydrophobic molecules: water-insoluble molecules (diacylglycerol, phosphatidylinositol) that bind to the cytolemma and diffuse through the intermembrane spaces to the organelle membranes, reaching and interacting 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 environment of the cytoplasm;

3.Gases: nitric oxide (NO), carbon monoxide (CO), hydrogen sulfide (H2S), which pass through the cell membrane and diffuse into the cytoplasm.

2. General Properties of Secondary Intermediaries

1.can be quickly synthesized, isolated and removed or inactivated using specific catalytic enzymes;

2.some (calcium ions) are stored in granules or vacuoles and are quickly released when needed;

3.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 cell self-damage during signal processing;

the exchange is limited, which allows the cell to localize in space and limit in time the process of signal transmission [9, 13, 16, 23].

There are 3 classes of cytolemmal receptors:

1.coupled with G-proteins (metabotropic);

2.associated with ion channels (ionotropic);

3.associated with enzymes, having their own enzymatic activity (protein tyrosine kinases, receptors for growth factors of platelets, epidermal and nerve cells).

3. G-Protein Coupled Receptors (Metabotropic)

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

Gt-protein (transducin) - is involved in signal transmission in photoreceptors;

Gs-protein - couples membrane receptors with adenylate cyclase;

G_q-белок – регулирует активность фосфолипаз С и A_2.

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

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

The G protein-coupled receptor signal transduction pathway includes a number of steps:
1. the ligand binds to the membrane receptor. The inactive G protein is associated with GDP.
2. the ligand-bound receptor, 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 modulating the functioning of cytoplasmic membrane channels;
4. activation of an intracellular enzyme changes the level of secondary messengers (cAMP, cGMP, Ca2+, inositol triphosphate, diacylglycerol, etc.).
5. a change in the concentration of secondary messengers leads to the activation or inhibition of dependent protein kinases or channels of the cytoplasmic membrane;
changes in the level of phosphorylation of target proteins [13, 16, 19, 23].

4. Regulation of G-Protein Activity

G proteins consist of 3 subunits: α, β and γ. The alpha subunit is involved in the binding and hydrolysis of GTP, as well as in interaction with the receptor, βγ-dimer, and effector.
The β and γ subunits are combined into a βγ complex and are associated with α-subunit. The βγ-complex is associated with the cell membrane and stabilizes the α-subunit. Through the β-complex, activation of metabotropic receptors, ion channels, phospholipase A2 and some isoforms of phospholipase C occurs.

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

5. Receptors Associated with Ion Channels (Ionotropic)

The ion channel permeates the cytolemma, providing transport of ions. Ligand-activated ionotropic receptors open upon activation of special channel receptor centers. Some of them are sensitive to neurotransmitters and are directly involved in the transmission of information in synaptic structures.Diacylglycerol is a membrane-bound glyceride formed during the e-phosphoinositol diphosphate by phospholipase C.

In the same reaction forms inositol triphosphate, which penetrates through the membrane into the cytoplasm of the cell. Diacylglycerol activates protein kinase C, increasing its affinity for calmodulin and facilitating the translocation of the enzyme from the cytoplasm to the membrane.Phosphatidylinositol is a phospholipid that plays an important role in intracellular signaling pathways. Its phosphorylation is catalyzed by specific enzymes, phosphoinositide-3-kinases, whose activity is regulated by growth factors.Being located on the cell membrane, phosphatidylinositol activates proteins involved in intracellular transport [9, 13, 16, 23].

6. Adenylate Cyclase Signaling System

Adenylate cyclase is a membrane glycoprotein and is a key enzyme in 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 field of the hippocampus CA2, isoform 8 is expressed in the field of the hippocampus CA1, Ca2+-sensitive adenylate cyclase is expressed in the localization sites of NMDA-inotropic glutamate receptors and voltage-dependent Ca channels, isoforms 3-5 are expressed in the folds of the cytolemma.The basal activity of adenylate cyclase increases when the α-subunit binds to the stimulatory Gs-protein (Gsa), corticoliberin, somatoliberin, glucagon, norepinephrine, and is inhibited when bound to the Gia-protein, protein kinase A, adenosine, somatostatin, angiotensin II, acetylcholine, dopamine and opioids [twenty].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 system of intercellular signaling stimulates protein kinase reactions, activity of cytoplasmic membrane channels, and protein phosphorylation [24]. Protein kinases are enzymes that catalyze the transfer of a terminal phosphate residue from ATP to a protein. Their activity is regulated by cAMP and cGMP.
There are several classes of proteincases.

1. A-G-C-class. Enzymes of the A-G-C class transfer phosphate to the alcohol groups of amino acids. Upon their activation of enzymes, either a change in the structure or a reversible association of regulatory and catalytic subunits occurs.Protein kinase A is cAMP-dependent, mediates most of the 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.Regulation of protein kinase A activity is carried out by binding to "anchor proteins" that localize the enzyme in a specific cell compartment. Some of the "anchoring proteins" are located in the region of the channels of the cytoplasmic membrane, where the concentration of cAMP is especially high [24].

7. Guanylate Cyclase Signaling System

Cyclic GMP is synthesized from GTP with the participation of soluble and membrane-associated guanylate cyclases [1, 15].

Soluble guanylate cyclase is located in the cytoplasm and is involved in the 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 E. coli enterotoxin, and endogenous intestinal peptide guaniline) [11, 12].Cyclic GMP 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 the cell as a whole, and neuromuscular transmission [3].Protein kinase G is a serine/threonine kinase composed of receptor, catalytic, and regulatory domains.The targets for protein kinase G are inositol triphosphate receptors, phospholamban, 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 phosphorylation of serine/threonine residues of target proteins occurs. A certain intracellular localization of protein kinase G is provided by framework and "anchoring proteins" [5, 17].Phosphodiesterases are involved in the regulation of intracellular signaling through the metabolism of cAMP and cGMP. They limit their effects and serve to cross-link between cAMP- and cGMP-dependent signaling and 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, cAMP and cGMP cyclic nucleotides control a wide range of metabolic processes, the activation process of which is influenced by a complex of interrelated intracellular signaling systems [4, 11, 12, 25].

2. 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.

3. The C-M-G class includes cyclin-dependent protein kinases (C-subclass), mitogen-activated protein kinases (M-subclass), and protein kinases capable of phosphorylation of the glycogen synthase enzyme (G-subclass). The 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).
4. Tyrosine kinases - carry out phosphorylation of tyrosine residues in target proteins. Enzymes of this class are membrane-bound.
5. The heterogeneous class includes all other protein kinases. Their activity is mainly regulated by low molecular weight intracellular metabolites [9, 13, 16, 23].

8. Role of Ca2+ In Intercellular Signaling

Depolarization of membranes and the action of certain hormones contribute to the opening of ion channels for Ca2+. Ca2+-binding proteins exist 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 anti-allergic 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 bound to tropomyosin and is found in myocytes between actin filaments, blocking the attachment site 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 access to the actin filament for the myosin head [2, 6, 23].

9. Inositol Triphosphate System

The composition of the inositol triphosphate system includes: receptor, phospholipase C, enzymes of the cytolemma and cytoplasm.After binding of the cytolemma receptor with the ligand, phospholipase C is activated, which leads to the cleavage of cytolemma phosphatidylinositol-4,5-biphosphate into diacylglycerol and inositol triphosphate (IP3). IP3 promotes the entry of Ca2+ into the cell, and diacylglycerol potentiates the activity of protein kinase C. Phosphorylation and changes in cytosol proteins occur under the action of second messengers [9, 13, 16, 23].

10. Gaseous Second 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, and activate enzymes. The action of gaseous messengers is provided by cyclic nucleotides.Nitrogen monoxide passes through cytoplasmic membranes without binding to cytolemmal receptors, but directly interacting with the cytosol. NO binds to heme-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 influence of nitrogen monoxide, the activity of adenylate cyclase decreases, as a result of which the amount of cAMP also decreases. At neuromuscular synapses, NO reduces the release of neurotransmitters. NO diffuses from the cytosol, where it is synthesized, into the extracellular space. Its release is not tied to any cell compartment. Nitric oxide is formed when needed with appropriate stimuli, and the intracellular content is very low. The 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 include the regulation of maturation of neurons and glia, blood supply and vascular tone, mediator metabolism, and impulse transmission processes [21].

Carbon monoxide (CO) also causes the activation of soluble guanylate cyclase. An increase in cGMP stimulates protein kinase G. At neuromuscular junctions, CO increases the release of acetylcholine by increasing the intracellular level of cAMP. Regulates the activity of glutamatergic neurons and carotid sensory cells, promoting vasodilation.Hydrogen sulfide (H2S) potentiates cAMP-dependent protein kinase, suppresses synaptic impulses in excess, and in physiological conditions it maintains a long-term action potential in hippocampal neurons [5, 16, 23].Thus, second messenger systems play an important role in the life 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 the basis for subsequent clinical studies.

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