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Review Article

Cyclic Nucleotides Signaling Pathways and Human Diseases: Potential Therapeutic Agents in the Management of Such Disease States

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Abstract

Every activity a cell is involved with is regulated by signals originating at the surface of the cell. Chemical substances that convert these extracellular signals received by cell surface receptors to intracellular signals are called second messenger molecules (second messengers). Activation by diffusible second messenger molecules and activation by recruitment of proteins to the plasma membrane constitute two major mechanisms of signal transduction pathways of a cell. Intracellular protein kinases or intracellular ligand-gated channels are activated by second messengers. The degradation of these second messengers results in signal termination. Protein kinase A (PKA) and protein kinase G (PKG) are involved in numerous human biological cellular processes. Cyclic nucleotides namely cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) are among the second messengers. A number of human diseases are associated with cyclic nucleotide signal pathways some of which are Alzheimer's disease, asthma, topic dermatitis, attention deficit hyperactivity disorders, bipolar disorders, chronic obstructive pulmonary diseases, cirrhosis of the liver, Cushing's syndrome, diabetic diseases albinism, Barrter's disease, cancer, Down's syndrome, erythermalgia, Fanconi anaemia, glaucoma, Huntington's disease, infertility etc. Numerous chemical substances such as cyclic nucleotide activators and/or inhibitors, protein kinases activators and/or inhibitors, phosphodiesterases inhibitors have been used as therapeutic agents against these diseases arising from defects in the signal pathways of the cyclic nucleotides.

Keywords: *Cyclic Nucleotides Signaling Pathways; Human Diseases; Therapeutic Agents*

Introduction

Many human biological processes and functions are achieved by cells communicating with one another and coordinating cell activities by a process called cell signaling. Every activity a cell gets engaged with is regulated by signals originating at the surface of the cell. Cell signaling affects almost every aspect of cell structure and functions and contributes to cells responding in an appropriate manner to a specific environmental stimulus [1,2]. Cells response to the external stimuli involves the utilization of complex molecular signaling cascades to transmit information from the external environment into the cell.

Cell signaling can be autocrine signaling or paracrine signaling [3].

With autocrine signaling, the message released by the cell will either stimulate or inhibit itself by messenger molecules and the receptors on the cell surface respond to the messenger molecules. In general, these messenger molecules typically act on target cells located at distant sites in the body and they reach these target cells by passage through the bloodstream. On the other hand, paracrine signaling entails messenger molecules moving only short distances through the extracellular space to cells that are very close to the cell that is generating the message. Due to their inherent instability, degradation by enzymes, or binding to the extracellular matrix, paracrine messenger molecules are usually limited in their ability to move around the body.

Extracellular signals transmission occurs through two major routes namely (a) transmission of a signal by a receptor from its cytoplasmic domain to a nearby enzyme, which generates a second messenger responsible for the cellular response; (b) transmission of a signal by another type of receptor by transforming its cytoplasmic domain into a recruiting centre for cellular signaling proteins [4]. In addition to the above, other routes for extracellular signals transmission include: (i) opening plasma membrane ion channels, (ii) diffusion through the plasma membrane and (iii) binding to intracellular receptors.

Whether the signal is transmitted by a second messenger through diffusion or by protein recruitment, the result is alike namely activation of a protein that is positioned at the top of an intracellular signaling pathway [5]. Signaling pathways are information lanes of a cell involving transduction of information from extracellular environment to the intracellular environment [6].

Each signaling pathway is made up of a series of distinct proteins which operate in sequence. These pathways are branched and interconnected to form complexes. Signals transmitted through signaling pathways eventually get to target proteins involved in the basic cellular processes [7]. Depending on the type of cell and message, the response initiated by the target protein may include: (a) increase or decrease in cell mobility, (b) alteration of the activity of metabolic enzymes, (c) change in ion permeability, (d) reconfiguration of the cytoskeleton, (e) change in gene expression, (f) cell death, and (g) activation of DNA synthesis.

Messenger molecules ("first" and "second") relay signals received to target cytosol and nucleus molecules at cell surface receptors. While the first messenger binds exclusively to a single receptor species at the outer surface of the cell, the second messenger often stimulates a variety of cellular activities [8]. First (extracellular) signals may come from hormones, neurotransmitters, alternations in ionic components, change in pH in the environment. Second signals may come from (i) cyclic nucleotides (within cytosol), (ii) inositol trisphosphate (within cell membranes), (iii) phosphoinositides (within cell membranes), (iv) diacylglycerol (within cell membranes), (iv) calcium ion (within and between cellular compartments); and (v) nitric oxide and carbon monoxide (gases) [9-11]. These transduce intercellular and intracellular signals which enable cells to mount huge coordinated response following stimulation by a single extracellular messenger.

Inositol trisphosphate, phosphoinositides and diacylglycerol are hydrophobic molecules while calcium ions are hydrophilic molecules. The objectives of the study were to (i) examine the characteristics of one of the dominant signaling pathways encountered in human body (ii) evaluate diseases linked to these signaling pathways and (iii) present potential therapeutic agents against such disease states.

Cyclic nucleotides signaling pathways

Cyclic nucleotides are 3′, 5′-cyclic adenosine monophosphate (cAMP) and 3′, 5′-cyclic guanosine monophosphate (cGMP) respectively.

They are second messenger molecules that link the extracellular environment to the intracellular environment and transduce first messenger signals [12].

Cyclic nucleotide signaling pathways are very vital in various biological processes and functions namely apoptosis, cell growth, myocardial contractility, inflammation, microbial pathogenesis, platelet aggregation, proliferation, transcription, and vascular smooth muscle relaxation etc [13]. The duration of action of the messenger molecules in the cell is controlled by phosphodiesterase enzymes

which are responsible for the degradation of the cyclic nucleotides [14].

Cyclic adenosine monophosphate (cAMP) generates a series of cellular reactions by utilizing a network of intracellular signaling pathways namely phosphorylation of specific target proteins. It is synthesized from adenosine triphosphate (ATP) by an enzyme named adenylate cyclase (AC). Adenylate cyclase is a transmembrane enzyme regulated by G-protein coupled receptors (GPCR). It has nine unique membrane isoforms (AC 1-9) and one soluble isoform. Adenylate cyclase signaling into the cells through GPCR can be activated or inhibited by neurotransmitters. Activation of GPCR (consisting of α, β, γ subunits) by their respective ligands (hormones or neurotransmitters) results in dissociation of the subunits into free forms.

The downstream effectors of cAMP are (i) protein kinase A (PKA), (ii) cyclic nucleotide-gated channels (CNGC) (iii) exchange protein directly activated by cAMP (Epac) [15]. These downstream effectors coordinate multitude of cellular reactions following increased concentration levels of cAMP. Protein kinase A is the most widely known effector mediating intracellular cAMP signaling. Activated PKA can phosphorylate several cytosolic and nuclear substrates leading to regulation of various specific cellular functions namely (i) cell survival pathways, (ii) gluconeogenesis, (iii) glycogen synthesis, (iv) glycolysis, (v) intestinal secretion, (vi) ion conductance, (vii) lipogenesis, (viii) renal collecting duct activities, and (ix) intracellular pathways [16]. PKA also regulate gene expression by activating cAMP response element binding protein (CREB) transcription factors. The activation of transcription factors and thus the expression of the specific downstream gene is initiated when CREB is activated through phosphorylation [17]. Furthermore, its activation through Ca^{2+}/ calmodulin kinase II (CaMKII) pathway is regulated indirectly by exchange protein directly activated by cAMP (Epac). The activity of CREB controls (a) cell growth and survival [18], (b) immune regulation [19], (c) metabolic regulation such as gluconeogenesis [20], lipogenesis [21]; and (d) development of learning and memory [22].

A transient neuron-wide form of CREB-mediated long-term facilitation can be stabilized at specific synapses by local protein synthesis [23].

The second type of cyclic nucleotide is 3′, 5′-cyclic guanosine monophosphate (cGMP). This second messenger molecule is synthesized by the action of guanylate cyclase (GC) on guanosine triphosphate (GTP). This catalytic conversion of GTP to cGMP is rapidly increased following the binding of nitric oxide to guanylate cyclase [24].

Guanylate cyclase exists in the soluble form (sGC) and the membrane bound particulate form (pGC). The pGC has seven isoforms as well as the soluble form that are distributed in the brain namely cerebral cortex, cerebellum, hippocampus, pineal gland, pituitary gland, and striatum etc [25]. Nitric oxide (NO) is the most potent activator of sGC and is synthesized from nitric oxide synthase (NOS) in response to elevated Ca^{2+} ion levels. Nitric acid as a retrograde messenger stimulates presynaptic sGC to induce production of cGMP which eventually leads to the production of protein kinase G (PKG). Cyclic GMP in the presynaptic terminal effects the release of neurotransmitters namely glutamate and dopamine [26]. The up-regulation of the cGMP/PKG pathway gives rise to phosphorylation of CREB in the postsynaptic terminal [27]. CREB phosphorylation is further facilitated by the release of Ca^{2+} ions from ryanodine-sensitive stores by PKG [27]. The intracellular effectors mediating the signals of NO-sGC are (i) protein kinase G (PKG, similarly called cGMP-dependent protein kinase, cGK), (ii) cGMP-gated cation channels, (iii) cGMP-specific phosphodiesterses and cGMP-regulated phosphodiesterses that have allosteric sites for cGMP. The cGMP pathway is a key element in the pathophysiology of the heart.

Discussion

Cyclic nucleotides signaling pathways and human diseases

Signaling pathways in human body have been linked with various diseases some of which include Alzheimer's disease, asthma, topic dermatitis, attention deficit hyperactivity disorders, bipolar disorders, chronic obstructive pulmonary diseases, cirrhosis of the liver,

Cushing's syndrome, diabetic diseases (diabetes mellitus, diabetes insipidus, diabetic nephropathy), diarrhea, drug addiction, ejaculatory dysfunction, endotoxic shock, epilepsy, erectile dysfunction, heart disease, humoral hypercalcaemia of malignancy, hypertension, irritable bowel syndrome, manic-depressive illness, metabolic syndrome, migraine, multiple sclerosis, narcolepsy, nausea, obesity, osteoporosis, pain, pancreatitis, Parkinson's disease, hyperparathyroidism (primary and secondary), manic-depressive illness, premature labour, renal disease, rheumatoid arthritis, schizophrenia, sudden infant death syndrome and Zollinger-Ellison syndrome [28,29]. These diseases are as a result of abnormal phenotypic remodelling of the signalsome. Similarly, genotypic remodelling of the signalsome leads to numerous inherited disease states in human beings namely albinism, Barrter's disease, cancer, Down's syndrome, erythermalgia, Fanconi anaemia, glaucoma, Huntington's disease, infertility, Kindler's syndrome, Liddle's disease, mental retardation, Niemann-Pick disease, osteopetrosis, polycystic kidney disease, Stargardt disease, Tangier syndrome, Usher syndrome, Van Buchem disease and Werner syndrome etc [30,31].

Cyclic nucleotides signaling pathways being part of human signaling pathways have been implicated in a number of these human diseases as a result of sensitization or desensitization of signalsome. For instance, cyclic AMP has been reported to be linked mostly with the following diseases, (i) back disease, (ii) cataract, (iii) diabetes (iv) coronary cardiac disease, (v) drug addiction, (vi) Parkinson's disease, (vii) autosomal dominant polycystic kidney disease (ADPKD), (viii) peptic ulcer, (ix) cancer, (x) bronchial asthma and chronic obstructive pulmonary disease, (xi) autoimmune diseases and erectile dysfunction [32-34].

Similarly cyclic GMP has been connected with the following diseases (i) arterial and pulmonary hypertension, (ii) atherosclerosis, (iii) heart failure (iv) thrombosis (v) erectile dysfunction, (vi) liver cirrhosis, (vii) renal fibrosis and failure, (viii) cancer [35].

In disease state, derangement of cyclic second messenger related intracellular signal transduction does occur as a result of decline in the functional integrity of the cyclic second messenger. This decline might be caused by suppression of the binding activity of protein kinase to the cyclic second messenger.

In Alzheimer's disease, the probable mode of action of cyclic second messenger may involve alteration in (i) calcium ion homeostasis, (ii) state of tau phosphorylation (iii) processing of the β-amyloid precursor protein.

As expected, to maintain normal health these diseases associated with cyclic nucleotide signal pathways have to be treated. Potential therapeutic agents have been reported and some officially reported to be potential approved.

Potential therapeutic agents

Defects in cyclic nucleotide signaling pathways are considered to be responsible for numerous human diseases. Some of these defects are as a result of interferences with signaling events by bacteria and viruses while other diseases can arise due to defects in the function of cell signaling pathways. These defects can be categorized into phenotypic remodelling and genotypic remodelling of the signalsome. Phenotypic remodelling acts by altering the behaviour of cells permitting their normal functions to be subverted, leading to disease. Genotypic remodeling acts by causing a gene in a single cell to undergo mutation leading to profound alteration of the setup of the signalsome.

Some of the therapeutic agents in clinical use for diseases that may not be linked with defects in cyclic nucleotide signaling pathways have been reported as potential active agents for defects in cyclic nucleotide signaling pathways. Therefore, in the present study we try to categorize these potential therapeutic agents against human diseases linked with cyclic nucleotide signaling pathways defects into activators and inhibitors. They include: Activators of cAMP- (i) salmeterol (clinically used for the treatment of asthma and chronic obstructive pulmonary disease) [36]; (ii) theophylline (clinically used for the treatment of obstructive airway disorders) [37]; (iii) desmopressin (clinically used for the treatment of central and nephrogenic diabetes insipidus) [38]; (iv) ranitidine (clinically used for the treatment of peptic ulcers, and gastroesophageal reflux disorder) [39]; (v) forskolin (clinically used to treat psoriasis and a potential

vascular smooth muscle relaxant) [40], (vi) pentoxifylline (clinically used for the treatment of peripheral vascular disease, cerebrovascular disease and other conditions involving a defective regional microcirculation) [41]; (vii) rolipram (clinically used for the treatment multiple sclerosis) [42]; (viii) Ibudilast and roflumilast (clinically used for the treatment of asthma and stroke) [43], (ix) Vinpocetine (clinically used for the treatment of inflammation) [44], (x) antibacterial and antiviral agents [45]. Of all the cAMP activators, phosphodiesterase inhibitors have found numerous clinical applications in (i) treatment of incontinence (ii) regulation of heart rate disorders (iii) prevention of heart failure (iv) treatment of prostate and lymphoid tissue cancers (v) treatment of nephritis and renal failures (vi) treatment of autoimmune diseases (vii) treatment of asthma and chronic obstructive pulmonary disease etc.

Inhibitors of cAMP (i) Metoprolol (clinically used for the treatment of angina, hypertension, heart failure, etc) [45] (ii) morphine (treatment of chronic pain) [46], (iii) H89 (PKA inhibitor as well as NO blocker) [47].

Activators of cyclic GMP: (i) nitric oxide releasing drugs [48]. Typical examples are nitroglycerin, sodium nitroprusside, isosorbide dinitrate, S-nitroso-N-acetylpencillinamine, and nebivolol. (ii) Phosphodiesterase-5 inhibitors acting as (a) cardioprotective agents [49]. Examples are sildenafil, dipyridamole. (b) Anti-hypertrophy agents [50]. Examples are udenafil and tadalafil. (iii) Riociguat (for the treatment of pulmonary arterial hypertension) [51]. (iv) Cinaciguat and nesiritide respectively (potential active agents for acute heart failure) [52]. These therapeutic agents represent promising therapeutic approach for acute myocardial infarction, cardiac hypertrophy, doxorubicin cardiotoxicity and heart failure.

Conclusion

Cyclic nucleotide signaling cascades through their regulations of cAMP and cGMP modulate numerous physiological and pathophysiological processes in human body. Intracellular protein kinases or intracellular ligand-gated channels are activated by cyclic nucleotides. The reversible phosphorylation of proteins by protein kinases is one of the ways in which cells transduce intracellular signals. Defects in the function of cell cyclic nucleotide signaling pathways cause numerous human diseases. Pathogenic organism interferences in cell cyclic nucleotide signaling pathways have also been implicated as causes of diseases. Of the potential therapeutic agents employed in the management of these diseases, phosphodiesterase inhibitors are of vital importance. Finally, given the developments of cAMP, cGMP and protein kinases activators and/or inhibitors, it is likely that in the near future a variety of cAMP, cGMP and protein kinases-modulating drugs will be available in the clinic.

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