THE SCIENCE WORLD
A Monthly e Magazine
ISSN:2583-2212
June, 2025 Vol.5(6), 7433-7437

Popular Article

The Serpentine Signalers: Decoding the Body's Master Communicators

*[1] Surjith K.P., [3] Rajani C.V., [2] Ranjith D., [1] Patki H.S., [4] Bijula Balakrishnan.
[1] Assistant Professor, Department of Veterinary Anatomy, College of Veterinary and Animal Sciences, Pookode, Wayanad,Kerala.
[2] Assistant Professor, Department of Veterinary Pharmacology and Toxicology, College of Veterinary and Animal Sciences, Pookode, Wayanad, Kerala.
[3] Associate Professor, Department of Veterinary Anatomy, College of Veterinary and Animal Sciences, Pookode, Wayanad,Kerala.
[4] Medical Officer (AYUSH), District Ayurveda Hospital, Kalpetta Wayanad, Kerala.
DOI:10.5281/ScienceWorld.15772280

Introduction

Receptors are the biological transducers of the body that detect stimuli and trigger specific responses. Upon receiving a signal, they initiate cellular signal transduction pathways, resulting in a cascade of molecular events that produce a physiological effect. Their functions include signal detection and transmission, maintaining homeostasis, facilitating neural communication, regulating endocrine responses, supporting immune surveillance and enabling sensory perception. Biological transducers function in coordination with the autonomic nervous system, operating through enteric, sympathetic or parasympathetic pathways. Sympathetic activation, typically associated with the "fight or flight" response, is triggered by various sensory inputs processed in the posterior hypothalamus and the limbic system. These signals are transmitted to the spinal cord via polysynaptic pathways and relayed through the thoracolumbar outflow to elicit specific cellular responses. In contrast, parasympathetic activity, which governs "rest and digest" functions, originates primarily from the anterior hypothalamus and is mediated through craniosacral outflow, facilitating restorative and energy-conserving physiological actions.

Types of receptors

Receptors can be broadly classified based on their mechanism of action. These include ligand-gated ion channels (ionotropic receptors), G protein-coupled receptors and enzyme-linked receptors, all of which are transmembrane proteins located in the plasma membrane. In contrast, intracellular receptors are found either in the cytoplasm or in the nucleus. Additionally, receptors are categorized

Official Website
www.thescienceworld.net
thescienceworldmagazine@gmail.com
Published 29 /06/2025

according to the type of stimulus they detect such as mechanical, thermal, chemical, light or noxious stimuli (nociceptors).

Receptors typically possess two binding domains: an external (extracellular) domain and an intrinsic (intracellular) domain. The external domain, also known as the ligand-binding domain exhibits affinity for certain proteins, hormones, chemicals, drugs, metabolites or neurotransmitters that initiate or modulate biological activity. Ligands may vary in their properties some are small, lipid-soluble molecules capable of diffusing across the plasma membrane to exert effects within the cell, while others are larger, polar molecules that cannot readily cross the membrane and thus interact with cell surface receptors to trigger intracellular responses. Ligands such as large peptide hormones including insulin, growth hormone, FSH, LH, and TSH have high molecular weights and therefore interact with receptors located on the cell surface. Similarly, polar or charged ligands like catecholamines, acetylcholine, serotonin and prostaglandins also bind to membrane-bound receptors, as they are unable to cross the lipid bilayer of the cell membrane. In contrast, lipid-soluble ligands such as steroid hormones, vitamin D, retinoic acid and thyroid hormones, which are derivatives of cholesterol can diffuse through the plasma membrane and bind to intracellular receptors located in the cytoplasm or nucleus.

Guanine nucleotide-binding proteins

G proteins (guanine nucleotide-binding proteins) play a crucial role in cell signaling, acting as molecular switches that transmit signals from various extracellular stimuli (e.g., hormones, neurotransmitters, sensory signals) to intracellular effectors. They are vital for maintaining physiological homeostasis and coordinating a wide range of biological functions. Cell membrane receptors such as G protein-coupled receptors (GPCR), play a critical role in maintaining physiological homeostasis by regulating complex intracellular signaling cascades. GPCR **spans the cell membrane seven times**, making the receptor loops **in and out of the plasma membrane seven times hence,** known as seven pass receptors. It is also known as serpentine receptors due to its **snake-like, coiled arrangement** of the seven transmembrane helices giving it a **"serpentine" appearance** when visualized in 3D structural models.

GPCRs possess an extracellular ligand-binding domain that typically interacts with large, polar molecules to initiate a cellular response. These receptors also feature an intracellular effector-binding domain that activates downstream signaling pathways.The intracellular domain is coupled to a heterotrimeric G protein complex composed of three subunits: alpha (α), beta (β) and gamma (γ). In the inactive state, the α-subunit is bound to guanosine diphosphate (GDP). G proteins are sometimes referred to as biological switches. Upon ligand binding, the receptor undergoes a conformational change that promotes the exchange of GDP for guanosine triphosphate (GTP) on the α-subunit, thereby

Official Website
www.thescienceworld.net
thescienceworldmagazine@gmail.com
Published 29 /06/2025

activating the G protein. This activation results in the dissociation of the α-subunit (now bound to GTP) from the β and γ units. Both the activated α-subunit and the detached β and γ units can then interact with various intracellular effectors to propagate the signal and elicit specific cellular responses.

All serpentine receptors operate through G protein-coupled mechanisms. Catecholamines such as epinephrine, norepinephrine, and dopamine exert their effects via GPCR pathways. Similarly, muscarinic acetylcholine receptors, as well as receptors for histamine, serotonin and prostaglandins also function through G protein-coupled signaling. G proteins are often referred to as biological amplifiers because a single ligand-receptor interaction can activate multiple intracellular signaling pathways, leading to a broad and amplified physiological response.

The body responds to sympathetic stimulation by activating certain organ systems to support the "fight or flight" response, while simultaneously inhibiting others to conserve energy and prioritize critical functions. This sympathetic drive involves the engagement of specific adrenergic receptors, classified broadly into stimulatory (Type I) and inhibitory (Type II) categories.

Organs that are activated during sympathetic responses typically express type I adrenergic receptors. Most of these organs possess α_1-adrenergic receptors, with the exception of the heart, adipose tissue and juxtaglomerular cells of the kidney, which express β_1-adrenergic receptors to mediate stimulatory effects. Conversely, organs that are functionally suppressed during sympathetic activation usually express type II β-adrenergic receptors (β_2), which mediate inhibitory effects. Notable exceptions to this include platelets, presynaptic nerve terminals, beta cells of pancreas and gastrointestinal glands which instead express type II α-adrenergic receptors (α_2) to facilitate inhibitory modulation.

The specific distribution of adrenergic receptors and their associated G proteins ensures a well-coordinated and efficient physiological response to sympathetic stimulation. Multiple types of G proteins exist, including Gq, Gs (stimulatory) and Gi (inhibitory), each mediating distinct intracellular signaling pathways. The cellular response to a stimulus varies depending on the type of G protein coupled to the receptor.

Molecular cascade of G protein coupled receptors

α_1-adrenergic receptors, upon binding with ligands such as norepinephrine or epinephrine activate the Gq protein pathway. This leads to the stimulation of phospholipase C (PLC), which hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP_2) in the plasma membrane into two secondary messengers as inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG). DAG contributes to the activation of protein kinase C (PKC), which phosphorylates various target proteins, including ion channels and transcription factors. Meanwhile IP_3 facilitates the release of calcium ions from intracellular stores within the smooth endoplasmic reticulum. The elevated cytosolic calcium binds to

Official Website
www.thescienceworld.net
thescienceworldmagazine@gmail.com
Published 29 /06/2025

calmodulin, activating calmodulin-dependent kinase (CaMK), which subsequently phosphorylates the regulatory light chains of myosin. This cascade culminates in depolarisation which ultimately leads to smooth muscle contraction. Conversely, binding to α_2-adrenergic receptors involves Gi proteins, which inhibit adenylyl cyclase activity, thereby reducing cAMP levels and exerting an inhibitory effect. This G protein receptor coupling diversity allows for precise regulation of physiological processes in response to sympathetic activation.

Epinephrine and norepinephrine bind to β-adrenergic receptors, which are coupled to Gs proteins triggers a stimulatory cascade through the activation of adenylyl cyclase and subsequent elevation of intracellular cAMP levels. β -adrenergic receptors are classified into three subtypes: β_1, β_2 and β_3, each mediating distinct tissue-specific responses. β_1- adrenergic receptors are predominantly expressed in cardiac tissue, where they play a key role in enhancing cardiac performance. Activation of these receptors increases heart rate (positive chronotropic effect) via the sinoatrial (SA) node, enhances atrioventricular (AV) nodal conduction (positive dromotropic effect) and augments excitability of Purkinje fibers and bundle branches (positive bathmotropic effect). The rise in cAMP activates protein kinase A (PKA) which phosphorylates a variety of intracellular proteins and enzymes contributing to cellular depolarization. Furthermore, PKA-mediated phosphorylation of L-type calcium channels in cardiac myocytes facilitates in increased calcium influx, promoting positive inotropic effects (enhanced myocardial contractility). PKA can also phosphorylate transcription factors, thereby influence gene expression and contribute to longer-term cellular adaptations in response to β_1-adrenergic stimulation. The effects on smooth muscle are primarily mediated by β_2-adrenergic receptors, which are coupled to Gs proteins. Activation of these receptors leads to an increase in intracellular cAMP, which in turn activates protein kinase A (PKA). In smooth muscle, PKA promotes dephosphorylation of myosin light chains of smooth muscles resulting in relaxation phase. β_3-adrenergic receptors are predominantly found on adipocytes and signal via Gs proteins. Their activation stimulates the breakdown of triglycerides into free fatty acids and glycerol, a process known as lipolysis. These breakdown products serve as substrates for gluconeogenesis thereby increasing the availability of glucose in peripheral circulation to support the body's metabolic demands during stress.

Conclusion

G protein coupled receptors (GPCRs) are true molecular multitaskers, playing a central role in how our bodies sense and respond to the world around us. From the way we perceive light, smell and taste to how our heart beats or our mood shifts, these receptors are behind the scenes translating external signals into meaningful cellular actions. Their unique seven-transmembrane structure makes them versatile and a highly responsive compound, which nearly one-third of all modern medicines work by targeting these receptors. As science continues to unlock the secrets of GPCRs, we are opening

Official Website
www.thescienceworld.net
thescienceworldmagazine@gmail.com
Published 29 /06/2025

new doors to treating diseases more precisely and effectively turning these tiny cellular gatekeepers into powerful tools for better health.

References

Rosenbaum, D. M., Rasmussen, S. G. and Kobilka, B. K. (2009). The structure and function of G-protein-coupled receptors. *Nature*, *459*(7245), 356-363.

Kroeze, W. K., Sheffler, D. J. and Roth, B. L. (2003). G-protein-coupled receptors at a glance. Journal of cell science, 116(24), 4867-4869.

Strader, C. D., Fong, T. M., Grazlano, M. P. and Tota, M. R. (1995). The family of G-protein-coupled receptors. The FASEB journal, 9(9), 745-754.

Weis, W. I. and Kobilka, B. K. (2018). The molecular basis of G protein–coupled receptor activation. Annual review of biochemistry, 87(1), 897-919.