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ALLOSTERIC MODULATORS OF GPCR & THEIR POTENTIAL THERAPEUTIC APPLICATIONS

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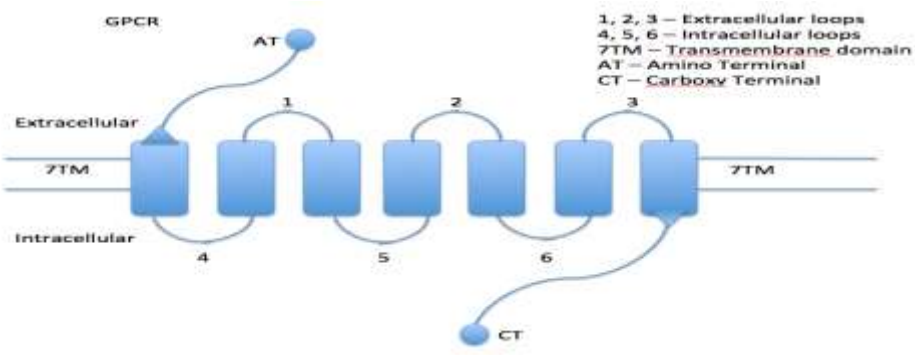
Paul Ehrlich brought in a revolution in the field of receptor biology, when he postulated that "*Corpora non agunt nisi fixata*", which translates roughly into "Agents will not act unless they are bound".[1] His postulate led on to the discovery of various regulatory proteins that are now targeted by most drugs in the market. Membrane receptors form a major chunk of these regulatory proteins. Membrane receptors are specialized integral membrane proteins to which external signaling molecules bind and trigger various functional changes. G-protein coupled receptors are the most widely distributed membrane receptors in the human body. The first G-protein coupled receptor (GPCR) was cloned way back in 1986, and this was the beta-adrenergic receptor.[2]

G-protein coupled receptors

GPCRs are a very large family of proteins, present exclusively in eukaryotes.[3] They are the largest class of cell surface receptors. The genes coding for these GPCRs constitute nearly 2 to 3% of the entire human genome.

Approximately 950 GPCRs have been identified so far, of which almost 500 have endogenous ligands acting on them.[4]



GPCRs are also known by several other names: 7TM receptors, heptahelical receptors, serpentine receptors and G-protein linked receptors (GPLRs). These names are based on the anatomical structure of the receptor molecule. Structurally, GPCRs have a central domain with 7 transmembrane alpha helices, 3 intracellular loops and 3 extracellular loops. Each alpha helix is made up of 25 to 30 amino acid residues. An amino terminal is found on the extracellular face, whereas a carboxy terminal is found on the intracellular surface.[5]

GPCR Superfamily

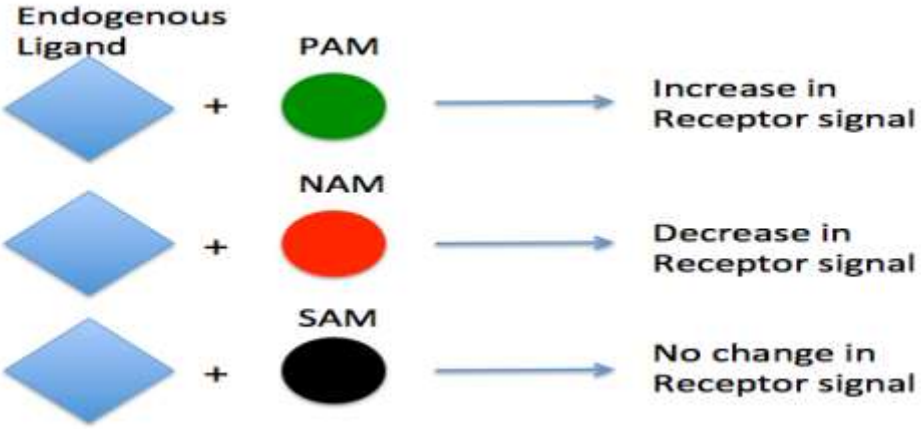
GPCRs were initially grouped into 3 different classes (A, B, C) based on the ligands which bound to them. Class A was the largest of the three, constituting almost 85% of the GPCR superfamily. Later, the classification system was scrapped and the GRAFS system was brought in. According to this system, the GPCRs were grouped into 5 classes: Glutamate-like receptors, Rhodopsin-like receptors, Adhesion receptors, Frizzled receptors and Secretin-like receptors.[6]

GPCRs may be activated by a wide variety of ligands like odorants, photons of light, hormones, neurotransmitters, ions, chemicals and drugs.[7] Hence, GPCRs are involved in nearly 70 to 90% of physiological functions. Moreover, these receptors are ubiquitous in their distribution.[8]

Allosteric Modulation

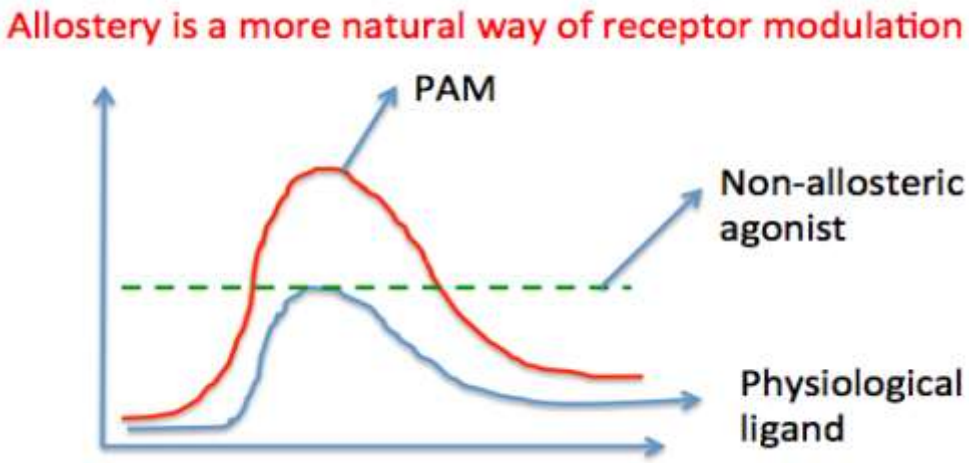
Allosteric (*Allo* = other; *Steric* = site) modulators are those agents that bind to a topographically different or distinct site from that of the endogenous or exogenous ligand. These allosteric modulators can be of three kinds: positive allosteric modulators (PAMs), negative allosteric modulators (NAMs) and silent allosteric modulators (SAMs). The allosteric modulators do not have any effect of their own, but they either increase or decrease the signal produced by the receptor, in the presence of the endogenous ligand. Agents that increase the signal are PAMs while those that decrease the same are NAMs. SAMs are those agents that bind to the receptor at an allosteric site but do not have any effect in the receptor function.

If the allosteric modulator has a function of its own, it may be termed as an ago-allosteric modulator.[9]



Merits of allostery

With the use of allosteric modulators, we do not interfere with the orthosteric sites of the endogenous ligands, hence preserving the endogenous spatial and temporal tone of the orthosteric sites. Moreover, there is just a fine-tuning of the receptor function, either increasing or decreasing the signal transduction, resulting in a more natural way of action as opposed to the orthosteric drugs.



This results in lesser side effects as compared to the orthosteric agonists or antagonists, as there is a ceiling effect seen with the use of allosteric modulators. Further, downregulation and desensitization of the allosteric receptor components are said to be very minimal or near impossible. Also, it has been studied that orthosteric sites are preserved across various families of GPCRs, leading to non-specificity of drugs acting through these orthosteric sites. This demerit is wiped off with the use of allosteric modulators.[9]

Models of allostery

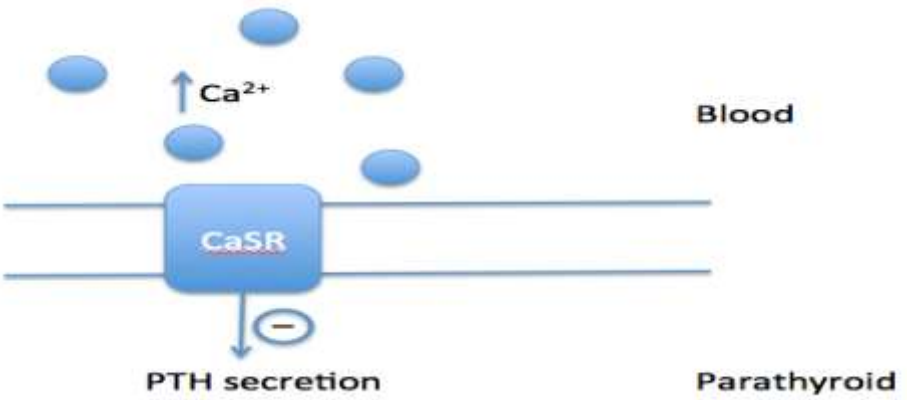
Allostery follows the two state receptor model, where the receptor is said to be in either the active or inactive form, depending on the binding of an agonist or an inverse agonist respectively. Allostery has also been studied using the symmetry or concerted model (MWC model) and the sequential model. According to these two models, the receptor is considered not as a single unit, but as a summation of two or more subunits. These models explain the possibility of allostery in the receptor interface.[10]

FDA approved allosteric GPCR modulators

Currently, there are only two FDA approved allosteric GPCR modulators: cinacalcet (a PAM) and maraviroc (a NAM). Also, FDA has approved plerixafor but there is no consensus if the drug is an orthosteric agent or an allosteric one. There are various other drugs that are in the pipeline under this category.

Cinacalcet

Cinacalcet is a positive allosteric modulator acting on the calcium sensing receptors, present mainly in the parathyroids. The calcium sensing receptor (CaSR) is a GPCR belonging to family C. The normal function of CaSR is to sense the amount of calcium in the blood and relay the information to the parathyroids. Once the blood calcium level is high, the CaSR senses it and inhibits the secretion of parathyroid hormone (PTH). The PAMs of CaSR are termed as calcimimetics while the NAMs are called cacilytics. Cinacalcet is one such calcimimetic. Currently, there are no NAMs available in the market.[9,11,12]



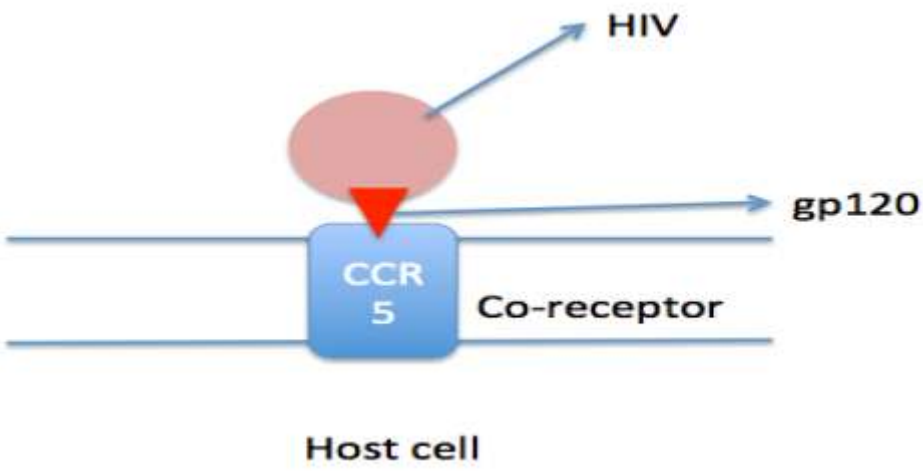
Cinacalcet, by being a PAM of the CaSR lowers the threshold at which the negative feedback is sent to the parathyroids. Hence, even at normal or high normal levels of blood calcium,

secretion of PTH is prevented or blocked. This is clinically put to use in conditions like secondary hyperparathyroidism (which is commonly due to vitamin D abnormalities or renal osteodystrophy) and hypercalcemia in parathyroid carcinoma.[9,11,12]

Potential use of calcilytics (CaSR NAMs) is seen in the treatment of osteoporosis.[9,11,12]

Maraviroc

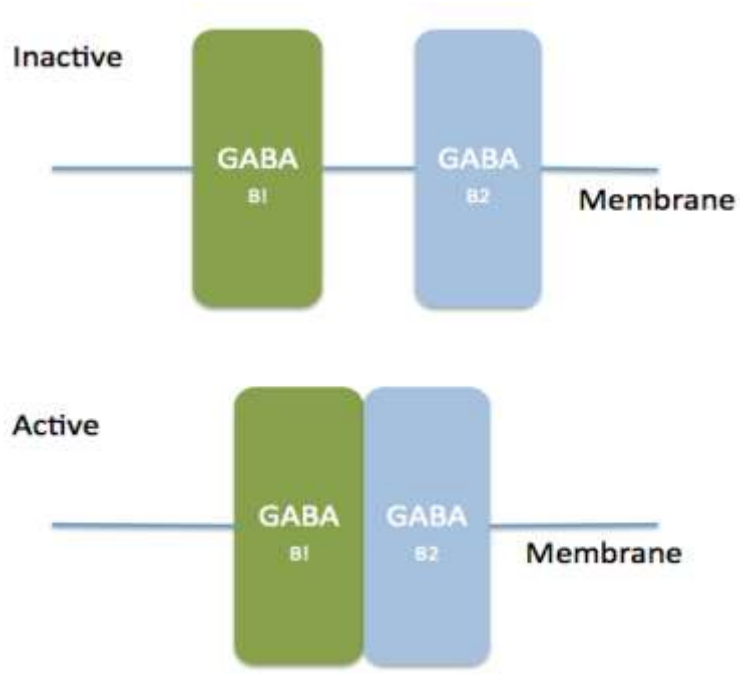
Entry of human immunodeficiency virus (HIV) into the host cell requires the function of two co-receptors, CCR5 and CXCR4. HIV may be CCR5-tropic or CXCR4-tropic or dual-tropic. The gp120 site on the HIV binds to the co-receptor on the human host cell to gain entry into the cell. By blocking these co-receptors, entry of HIV into the cell can be prevented.



Maraviroc is a NAM of the CCR5 that prevents entry of the organism into the cell. Hence, it is termed as an entry inhibitor. However, FDA does not recommend maraviroc as a first line agent against HIV, but only in treatment-experienced patients who do not respond to standard care. This drug is also being used in graft-versus-host-disease (GVHD) following bone marrow transplant in leukemias. Cenicriviroc is a similar molecule that is currently being evaluated as an entry inhibitor against HIV.[12,13]

Allostery of $GABA_B$

$GABA_B$ belongs to family C of GPCRs. $GABA_B$ receptors are known to be involved in controlling neuronal excitability and in modulating neurotransmission in the synapses. PAMs (CGP7930, GS39783) are being investigated for potential uses in anxiety disorders and in drug de-addiction therapy.



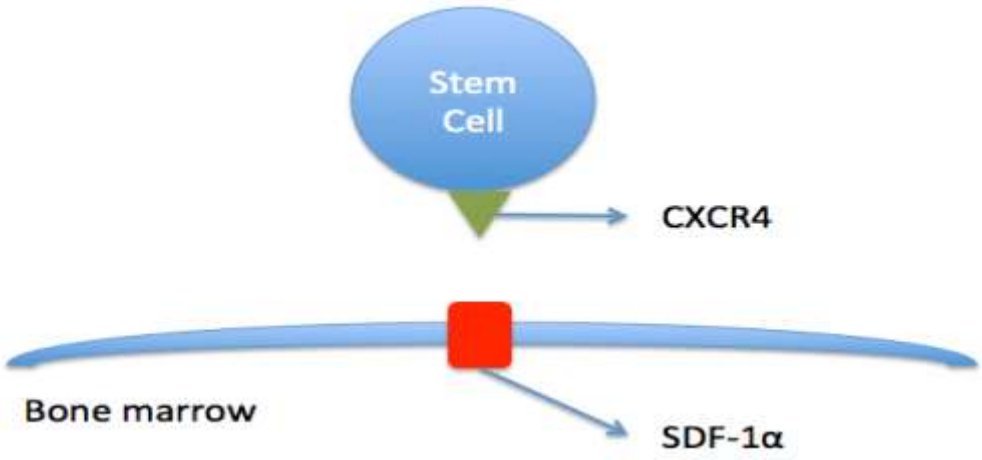
The major merit over the orthosteric drugs includes lesser side effects (especially, central and gastrointestinal), mainly because the PAM only fine-tunes the receptor function in a natural pattern. Moreover, downregulation or desensitization is not a feature of allostery, leading to the total or near absence of tolerance.[14,15]

Allostery of CCR1

CCR1 belongs to family A of GPCRs. BX471 was a NAM with anti-inflammatory properties, and was evaluated for use in multiple sclerosis but failed due to poor efficacy. It is now being studied for its anti-inflammatory potential in several conditions like pancreatitis and progressive kidney disease. A major barrier in the discovery of allosteric modulators of CCRs has been the cross modulation seen to exist among the various subgroups of CCRs.[16,17,18]

Allostery of CXCR4

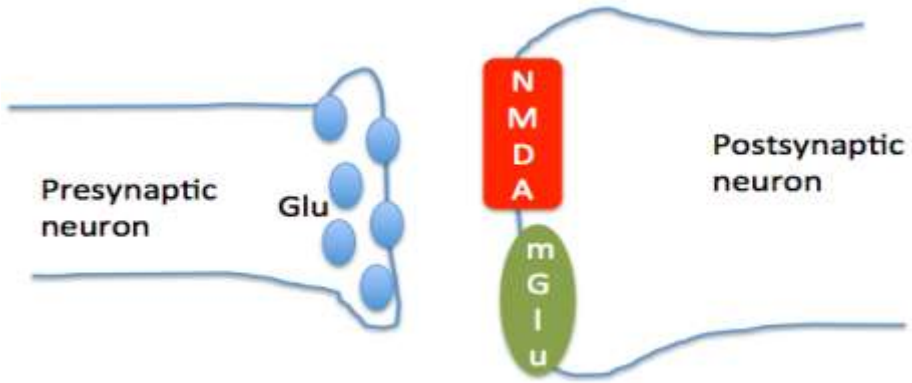
As explained above, CXCR4 is one of the two co-receptors required for HIV entry into the host cell. AMD3100 (Plerixafor) was tested as an entry inhibitor in HIV positive patients but the drug failed due to cardiotoxicity and poor efficacy. A serendipitous discovery found during this study was that this drug helped in mobilization of haematopoietic stem cells from the bone marrow to the periphery by preventing the binding of CXCR4 to SDF (Stromal Cell Derived Factor) -1α in the bone marrow.[19]



Hence, FDA approved plerixafor as an adjunctive therapy following bone marrow transplant in multiple myeloma, Hodgkin's lymphoma, etc.[19] Other potential uses could be in prophylaxis of metastasis in cancers and in opioid-induced hyperalgesia as these receptors are found in plenty in the dorsal root ganglion of the spinal cord.[20,21]

Allostery of mGluR5

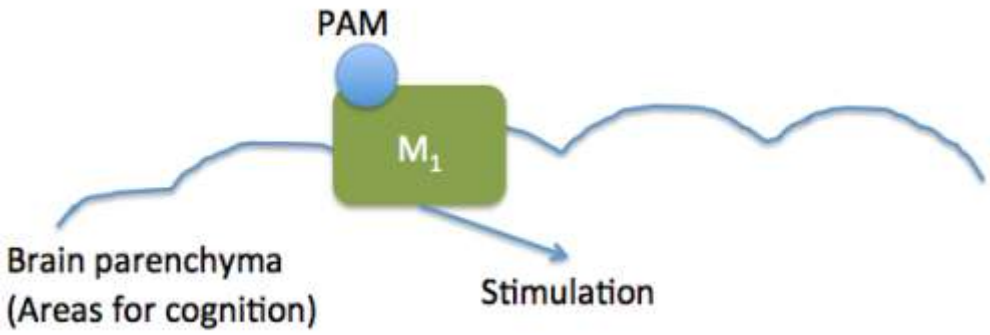
mGluR5 receptors are said to have a functional interaction with the NMDA receptors, hence having a possibility of being involved in the pathogenesis of schizophrenia.



A NAM, MPEP (6-methyl 2-[phenyethynyl] pyridine), is being evaluated in the therapy of schizophrenia.[22] Other possible applications are in gastro-esophageal reflux disease[23] (GERD) as mGluR5 is responsible for TLESR (Transient Lower Esophageal Sphincter Relaxation), acute treatment of migraine as the receptor is involved in the neurocircuitry of migraine pathogenesis and in fragile X syndrome where the receptor inactivates a protein called FMRP.[24,25]

Allostery of M_1

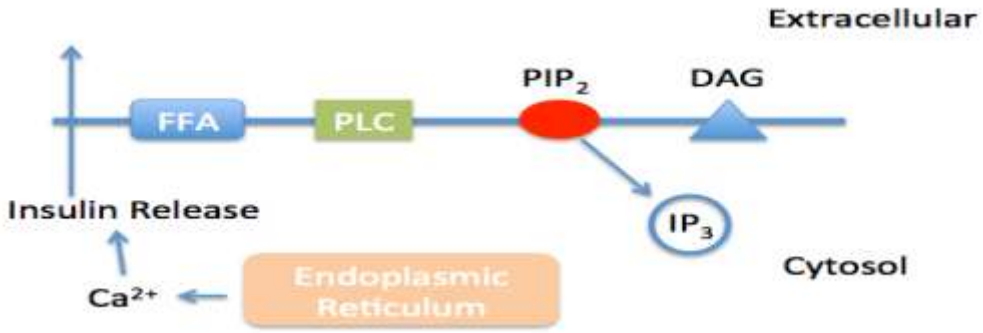
Muscarinic (M_1) receptors are found in abundance in the areas of the brain that are responsible for normal cognitive activity of a person. Also, M_1 and M_4 receptors are responsible for normal learning and memory of an individual, as they are located in the higher areas of the brain like the cortex, hippocampus and striatum. Of the two receptor subtypes, M_1 is likely to be the more critical one.



Hence, PQCA (1-((4-cyano-4-(pyridine-2-yl)piperidin-1-yl)methyl)-4-oxo-4H-quinolizine-3-carboxylic acid) which is a PAM of M_1, is being tried as an adjunctive cognitive enhancer in Alzheimer's disease, Parkinson's disease and in Huntington's chorea.[26,27]

Allostery of $FFA_{1/4}$

FFA (Free Fatty Acid) receptors are physiologically involved in release of insulin by binding to free fatty acids.



When the free fatty acid binds to the FFA receptor in the membrane of the pancreatic islets, the GPCR is activated, leading to phospholipase C activity, resulting in the generation of second messengers, inositol triphosphate (IP_3) and diacyl glycerol (DAG). The IP_3 thus

released stimulates the release of calcium from the endoplasmic reticulum, leading to a rise in the intracellular calcium concentration. This in turn stimulates the release of insulin.

Hence, PAMs of the FFA receptor are currently under trial for potential use in type 2 diabetes mellitus.[28,29]

Allostery of CRF_1

CRF_1 (Corticotropin Releasing Factor 1) belongs to family B of GPCRs. It is a physiological stress response hormone, which has been estimated to be involved in the development of depression. It has been estimated that CRF is often secreted in excess from hypothalamic and other areas in depression. This results in excessive amount of CRF in the cerebrospinal fluid. This excess of CRF neuronal activity is proposed to be one of the reasons for the various symptoms of depression. So, NAMs like antalarmin (currently in preclinical studies) are being tried out for the treatment of depression.[30,31]

CONCLUSION

Allosteric modulators have a few advantages over orthosteric compounds: lesser side effects, preservation of the orthosteric site and easier drug development. But they also have a few limitations like lower efficacy and less predictable activity because of species differences in allosteric sites.[9] Even though allosteric modulators are a major breakthrough in the field of new drug development, further research is needed to understand the concepts of allostery much better. Going by the current trend of drugs in the pipeline, the future looks bright for allostery and compounds acting allosterically.

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