Insights into the structural biology of G-protein coupled receptors impacts drug design for central nervous system neurodegenerative processes

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Research Highlights
(1) This review describes new insights into the structural biology of G-protein coupled receptors, with a focus on both allosteric and orthosteric binding, implying G-protein dependent and independent signaling pathways.
(2) The implications are explored for the design of new drugs to treat central nervous system disorders, such as Parkinson’s and Alzheimer’s disease.

Abstract
In the last few years, there have been important new insights into the structural biology of G-protein coupled receptors. It is now known that allosteric binding sites are involved in the affinity and selectivity of ligands for G-protein coupled receptors, and that signaling by these receptors involves both G-protein dependent and independent pathways. The present review outlines the physiological and pharmacological implications of this perspective for the design of new drugs to treat disorders of the central nervous system. Specifically, new possibilities are explored in relation to allosteric and orthosteric binding sites on dopamine receptors for the treatment of Parkinson’s disease, and on muscarinic receptors for Alzheimer’s disease. Future research can seek to identify ligands that can bind to more than one site on the same receptor, or simultaneously bind to two receptors and form a dimer. For example, the design of bivalent drugs that can reach homo/hetero-dimers of D2 dopamine receptor holds promise as a relevant therapeutic strategy for Parkinson’s disease. Regarding the treatment of Alzheimer’s disease, the design of dualistic ligands for mono-oligomeric muscarinic receptors could increase therapeutic effectiveness by generating potent compounds that could activate more than one signaling pathway.

Key Words
neural regeneration; G-Protein coupled receptors; structural biology; drug design; tive disorders; oligomerization; biased signaling; Parkinson’s disease; Alzheimer’s disease; mine receptors; muscarinic receptors; grants-supported paper; neuroregeneration

Conflict of interest: No declared.

doi:10.3969/j.issn.1673-5374.2013.24.009 [http://www.nrronline.org; http://www.sjzyj.org]

Farfán-García Eunice D, Trujillo-Ferrara José G, Castillo-Hernández María C, Guerra-Araiza Christian H, Soriano-Ursúa Marvin A.

Insights into the structural biology of G-protein coupled receptors impacts drug design for central nervous system neurodegenerative processes. Neural Regen Res. 2013;8(24):2290-2302.

Funding: This project was supported by SIP-IPN, CONACYT (CB-168116) and FIS/IMSS (FIS/IMSS/PROT/ G11-2/1013).
INTRODUCTION

The ligands of G-protein coupled receptors represent the largest group of drugs marketed today, based on studies performed on these receptors and the functional consequences of their activation. The discovery of the signal transduction mechanism associated with the activation of these receptors has led to the development of novel therapeutic strategies, including the use of non-peptide ligands as receptor agonists or antagonists. In recent years, the structural biology of G-protein coupled receptors has been extensively studied through high-resolution X-ray crystallography, leading to the identification of several important binding sites other than the orthosteric site on G-protein coupled receptors (GPCRs). These recent advances have important implications for the function of the central nervous system and for the development of new therapeutic agents.

Applications of data from G-protein coupled receptor crystals to the understanding of the central nervous system

In recent years, the structural biology of G-protein coupled receptors (GPCRs) has been extensively studied through high-resolution X-ray crystallography, leading to the identification of several important binding sites other than the orthosteric site on G-protein coupled receptors (GPCRs). These recent advances have important implications for the function of the central nervous system and for the development of new therapeutic agents.
After studies with the β1 adrenergic receptor and β2 adrenergic receptor provided insights into diffusible ligands,[34-42], the high homology of the three dimensional ligand pockets was demonstrated for receptors of the same family. This implies that selectivity involves specific regions in the extracellular loops of each member of a family of receptors,[34], which could represent a key factor in the efforts to treat several maladies that require specific knowledge of a particular subtype of receptors. For example, β2 adrenergic receptor selective agents could offer an opportunity to treat diseases involving certain central nervous system processes related to stress and memory.[55-58].

Another structural insight involves the configuration and conformations of G-protein coupled receptors. Components of bilayer lipidic membranes, particularly cholesterol, modify the folding of receptors on this cellular surface.[59]. The resulting differences in the constitution and/or conformation of intracellular loops are closely related to variations in the transduction of signals.[2]. Thus, the modification of the configuration and conformations of G-protein coupled receptors must certainly be involved in the activation of these receptors, both inside and outside the central nervous system. The cholesterol content of cells is distinct in these two locations.[59].

New information about the structure of A2a adenosine receptors created the opportunity to study a ligand pocket in greater detail than was previously possible. This approach has led to a deeper understanding of why many drugs employed today for the treatment of central nervous system diseases,[43], which are bulkier than catecholamines, exert greater effects than endogenous ligands on A2a adenosine receptors. It turns out that the binding site on adenosine receptors involves a greater number of residue contacts than that on catecholamine receptors. However, the binding sites of both these types of receptors share the same regions, which have been poorly studied.[43].

Two insights have been particularly relevant for understanding G-protein coupled receptors and their relation to central nervous system function. Firstly, recent reports have elucidated the interaction between purine/xanthine derivatives (e.g., caffeine and theophylline, used as therapeutic agents since ancient times) and G-protein coupled receptors.[60]. Secondly, molecular modeling with crystallized G-protein coupled receptors as a template has deepened the understanding of the heterodimeric forms of these receptors (e.g., in relation to D2 dopamine receptors).[60-61]. This has allowed for the study of heterodimers of adenosine A1 adrenergic receptor/A2a adenosine receptor, D2 dopamine receptor/A2a adenosine receptor and D3 dopamine receptor/A2a adenosine receptor, of glutamate metabotropic glutamate receptor 4/A2a adeno-
sine receptor, of cannabinoid cannabinoid receptor 1/A2a adenosine receptor, and of cannabinoid receptor 1/A2a adenosine receptor/D2 dopamine receptor, all involved in several central nervous system processes and disorders\textsuperscript{[61-62]}, including Parkinson’s disease\textsuperscript{[62]}. Crystal structural data for D3 dopamine receptor have allowed for greater understanding of how dopamine modulates movement, cognition and emotion\textsuperscript{[44, 63-64]}, leading to new opportunities for the design of drugs to treat schizophrenia and drug abuse\textsuperscript{[64-65]}. These structural data have provided information about different conformational states of intracellular loops, which could be related to different cellular signaling responses and consequently to different cognitive processes involved in some neural and central nervous system pathologies\textsuperscript{[44]}. Moreover, the findings from this structural data have contributed to knowledge of the binding pocket in G-protein coupled receptors. For instance, it is now known that this pocket includes an extracellular extension which may be related to receptor selectivity. The targeting of this pocket could be useful in the development of drugs that are selective for dopamine receptors, and this selectivity is vital in the treatment of some central nervous system diseases\textsuperscript{[44]}. On the other hand, crystal structural data from CX chemokine receptor 4 have yielded insights into G-protein coupled receptors that are related to inflammation as well as cell migration and development, including neural development and remodeling\textsuperscript{[45]}. Studies have reported the anchoring of a peptide to form a G protein coupled receptors-ligand complex, revealing that the binding of small peptides requires interactions in the extracellular loops and extracellular region of the transmembrane regions of G-protein coupled receptors\textsuperscript{[46]}. The crystallization of the doxepin-H1 histamine complex has led to new opportunities for the design of psychoactive agents, including antidepressants and anxiolytic drugs. H1 histamine is an important pharmacological mediator involved in the pathophysiological processes of allergies and inflammation. New data about binding added to the understanding of a region with a ‘switch/lock’ seem to be important in G-protein coupled receptors activation\textsuperscript{[46]}. Additionally, a region was clearly identified that is not in any other aminegenic receptor, illustrating how minor differences among G-protein coupled receptors can lead to selectivity in the binding of small structurally-related molecules\textsuperscript{[46]}. The crystal structure of sphingosine 1-phosphate recep- tor 1 was obtained in complex with T4-lysozyme and an antagonist (a sphingolipid mimic). The signaling of this complex modulates lymphocyte trafficking, endothelial development and integrity, and maturation\textsuperscript{[47]}, processes that can be related to pathological inflammation in the central nervous system\textsuperscript{[27, 47]}. In this receptor, the amino terminus and extracellular loops occluded the binding pocket, requiring ligands to enter this pocket laterally between helices 1 and 7. This information provides a new way to reach the common orthosteric site and nearby region in other G-protein coupled receptors\textsuperscript{[47]}. The three-dimensional crystal structural data of two muscarinic receptors—m2 acetylcholine receptors and m3 acetylcholine receptors—has revealed the three-dimensional distribution of their orthosteric binding pocket, as well as insights into the amino acids that constitute this site. These receptors mediate the response to acetylcholine released from parasympathetic nerves. Their role in the unconscious regulation of organ and central nervous system function makes them potential therapeutic targets for a broad spectrum of diseases\textsuperscript{[48-49]}. It turns out that the amino acids in the orthosteric binding pocket are identical in all five muscarinic receptor subtypes, supporting the idea that selectivity among a receptor family is related to the distribution of amino acid residues in the extracellular region\textsuperscript{[49]}. Moreover, it was observed that a group of aromatic residues covers the binding site and restricts dissociation of the bound ligand. An allosteric site has also been mapped in a shallower region of the same binding pocket, allowing for greater understanding of the well-known propensity of these receptors to allosteric regulation\textsuperscript{[48]}. Specifically, the crystal of m3 acetylcholine receptor provided new knowledge about a G (q/11)-coupled receptor, which has helped to elucidate the role of different types of heterotrimeric G-proteins in other receptors\textsuperscript{[49]}. Different opioid receptors have also been crystalized with some ligands. The binding of opium and its derivatives to opioid receptors (another type of G-protein coupled receptors) in the central nervous system can produce analgesic effects as well as sedation, disruption of the respiratory drive, dependence and mood disturbances\textsuperscript{[50, 66]}. For instance, the morphinan ligand binds in a relatively large and deep solvent-exposed pocket. The μ-opioid receptor was crystallized as a two-fold symmetrical dimer through a four-helix bundle motif formed by transmembrane segments 5 and 6\textsuperscript{[53]}. Additionally, the activated κ-opioid receptor has been related to dysphoria psychotomimesis and disorders ma-
nifesting these symptoms. The crystal structure of human κ-opioid receptor was studied in complex with the selective antagonist JD'Tic, arranged in parallel dimers at 0.29 nm resolution[51]. The structure revealed important features of the ligand-binding pocket that help to explain the high affinity and subtype selectivity among opioid receptors. Modeling of various ligand-κ-opioid receptor complexes has revealed both common and distinctive features of ligands with selectivity for these receptors, which may facilitate the design of new drugs with greater selectivity[51].

The crystal structure of the mouse δ-opioid receptor, bound to the subtype-selective antagonist naltrindole, complemented what is known about the structural features associated with ligand-subtype selectivity. It turns out that the binding pocket of opioid receptors is comprised of a lower region that is highly conserved among such receptors, and an upper region that contains divergent residues conferring subtype selectivity[58]. Analysis of three-dimensional crystal structural data in relation to the selectivity and efficacy of distinct ligands has been compared to the structure of other G-protein coupled receptors, revealing that this structural organization may be a common feature of other G-protein coupled receptors families[51, 53].

The nociceptin/orphanin FQ peptide receptor (nociceptin/orphanin receptor, also known as ORL-1) has high sequence similarity with classical opioid receptor subtypes (≥ 60%). Nociceptin/orphanin receptor has a markedly distinct pharmacology, featuring activation by an endogenous peptide and unique selectivity for exogenous ligands[52]. This receptor was crystallized with a ligand that mimics the first four amino-terminal residues of a nociceptin/orphanin receptor-selective peptide antagonist, leading to important clues about the binding of these peptides. Interestingly, substantial conformational differences were found in the pocket regions of classic opioid receptors in complex with nociceptin/orphanin receptor[53]. These insights could be invaluable in the development of new drugs that selectively target opioid receptors, as is commonly required in clinical practice.

Finally, X-ray crystal structural data on protease activated receptor 1[54] could be useful for studying the mechanism of ligand binding to G-protein coupled receptors, due to its high structural homology with other receptors of this family. Protease activated receptor 1 mediates cellular responses to thrombin and related proteases[54]. Thrombin irreversibly activates the protease activated receptor 1 by cleaving the amino-terminal ex-

odomain. This exposes a tethered peptide ligand, which in turn binds to the helical bundle of the receptor to affect G-protein activation. Although the binding pocket is superficial, it has little surface area that is exposed to the aqueous solvent[54]. Hence, this ligand has a distinct mechanism for triggering G-protein activation.

LIGAND RECOGNITION OUTSIDE THE ORTHOSTERIC SITE DRUG DESIGN FOR REGENERATION OF THE CENTRAL NERVOUS SYSTEM

Insights into ligand recognition of G-protein coupled receptors point to the involvement of regions other than the classic orthosteric site. Thus, there is apparently more than one signaling pathway for these receptors[5, 67].

Some research work employing crystal structures of G-protein coupled receptors in complex with diffusable ligands has found phenomena that are difficult to explain when considering only the orthosteric binding site[5, 67]. Indeed, the results seem to indicate the existence of one or more allosteric and/or regulator sites on each G-protein coupled receptor, as well as a G-protein independent pathway (the kinase pathway) that can influence and/or activate receptor signaling[32, 68]. Apparently, allosteric/regulator sites influence the conformational states generated and stabilized during the ligand recognition process. It is now known that there are a wide range of conformations that go far beyond what was previously known as the active and inactive states[5], implying a great diversity of effects on biological activity[1, 2, 5, 69]. This wider perspective on G protein coupled receptors signaling has in turn created a deeper understanding of functional selectivity or biased signaling of ligands[70-72]. As a result, there is a new focus of study in relation to the impact of the homo/hetero dimerization or oligomerization of G-protein coupled receptors on the regulation of biological activity (Figure 1)[72-75].

To illustrate the impact of these new concepts, it is useful to track the evolution of the design and use of beta blockers. Currently, it is known that at least two subgroups exist within this group of drugs (inverse agonists and neutral antagonists). These two subgroups include compounds with a wide range of effects on the G-protein independent signaling pathway. Identification of the particular profile of each beta blockers allows for a better use of the compound to reach a specific target. For example, carvedilol is no longer considered just a blocker (antagonist) of β-adrenergic
receptors through the Gs protein pathway. It is now known that this compound is a biased agonist for β-adrenergic receptors. That is, it behaves as an inverse agonist of the G-protein dependent pathway (resulting in activity less than that of the basal state of the receptor) as well as an agonist on the G-protein independent pathway. This could have implications for neuropsychiatric diseases.

Hence, new terminology to describe the phenomena of recognition and activation of G-protein coupled receptors includes allosteric agonists (ligands that have an effect on receptor activity by binding to the allosteric site), dual- or bitopic ligands (ligands that reach the orthosteric and allosteric site at the same time) and superagonists (ligands that have a greater effect than the most potent of endogenous ligands). The latter type of ligand has been related with allosteric sites as well as G-protein independent pathways in G-protein coupled receptors. The increase in nomenclature reflects the expanding knowledge in drug design, a field previously limited to the concepts of orthosteric agonists and antagonists. As a consequence, new drugs aimed at G-protein coupled receptors now have more specific targets. Today new compounds are designed not only to activate or inactivate a G-protein coupled receptors, but also to selectively regulate the action on a particular conformational state and pathway, or a combination of conformational states and pathways (Figure 1).

Since G-protein coupled receptors modulate multiple functions of the central nervous system, this expanded approach opens new opportunities for the rational design of new selective drugs to treat disorders of the central nervous system, including schizophrenia and Parkinson’s disease. Moreover, it now seems possible to develop new histamine-related compounds that may be useful as antidepressant, antipsychotic and anticonvulsive drugs. Future studies on mammalian gonadotropin releasing hormone-receptors could better define the role of multiple gonadotropin releasing hormone receptor conformations in the activation receptors, as well as identify the variety of upstream effectors (e.g., heterotrimeric and monomeric G-proteins).

Figure 1  Evolution of the perspective on G-protein coupled receptors function and neuronal response.
On the left side, the old view of phenomena associated with ligand recognition and activation of G protein coupled receptors. On the right side, the new view based on X-ray structural data of ligand-G protein coupled receptors complexes, and the use of this data in silico with functional assays on these receptors. Today, many factors are taken into account for receptor activation, not just the binding of a ligand to the orthosteric site. For example, consideration is now given to the influence allosteric sites may have on ligand binding to the orthosteric site and thus to G-protein signaling, as well as to the kinase signaling that may be activated by ligand binding to the allosteric site. Moreover, ligands can bind to contiguous G protein coupled receptors, thus forming dimers.
This knowledge could then be employed to explore gonadotropin releasing hormone-receptors-mediated effects on cell migration, cell development and cell death, as well as on gonadotropin releasing hormone receptor trafficking[61]. For instance, new drugs could possibly be designed for the cannabinoid cannabinoid receptor 1 to treat drug addiction, pain, and appetite[82]. The advances made to date have already been applied to create new techniques for diagnosis and treatment of these maladies (Table 1).

**INSIGHTS INTO DOPAMINE RECEPTORS: APPLICATIONS FOR TREATING PARKINSON’S DISEASE**

Regarding Parkinson’s disease, our knowledge is still limited to the mechanism of damage to the dopaminergic system in the central nervous system. Therefore, the drug design strategy currently valid for treating this disease is the activation of dopamine receptors to compensate for the lacked dopaminergic neurons[83]. It is expected that the market for drugs treating Parkinson’s disease will continue to increase in the near future[84].

Suitable methods have been proposed for employing data from structural biology in order to identify new drugs in the treatment of diseases of the central nervous system[85]. For example, D3 dopamine receptor is one G-protein coupled receptors that has been crystalized, yielding information about the differences in the intracellular loops of dopamine receptors that probably is related to distinct cellular signaling responses. D3 dopamine receptor has also provided the coordinates for building models of related dopamine receptors such as D2 dopamine receptor, often targeted for treating Parkinson’s disease[86-87]. It is still unclear whether the new models of D2 dopamine receptor will be able to provide the necessary accuracy for predicting the ligand binding mode[87-88].

In other cases the advantages of recent advances in molecular modeling based on the new crystal structural data of G-protein coupled receptors is unquestionable, having allowed for an understanding of structural features that are important for the design of new compounds with greater potency, efficacy and selectivity on dopamine receptors (Figure 2)[89-92].

For instance, in silico studies have suggested that selectivity for amineergic receptors seems confined to areas near to but shallower than the orthosteric binding site[87, 92], which has been supported by recent evidence involving a great variety of G-protein coupled receptors[69, 93]. On the other hand, studies on the binding of diaryl or piperazine compounds to dopamine receptors have enriched knowledge about G protein coupled receptors function in relation to allosteric modulation and the binding and action of dualsteric/bitopic ligands[94-95].

An interesting topic in relation to G-protein coupled receptors, and particularly to D2 dopamine receptor, is the role of the homo/hetero-dimeric forms of these receptors and the modulation of their biological activity, such as modified pharmacology, trafficking and signaling[61]. Only a few years ago G-protein coupled receptors were considered to be expressed only as monomers on the cell membrane. Nowadays, there is crystallographic data and other evidence showing that these receptors can form homodimers, heterodimers and higher-order oligomers[96, 96]. It is now accepted that cooperativity and/or modulation resulting from intramolecular cross-talk in the homo/hetero-dimer is probably involved in central nervous system function[61]. Thus, the binding of one neurotransmitter to a neural receptor often affects the binding of a second neurotransmitter to the partner receptor. Coactivation of the two receptors in a homo/hetero-dimer can change the signaling pathway triggered by the neurotransmitter as well as the trafficking of the receptors[61].

For Parkinson’s disease treatment, particular interest is now being given to the homodimer of D2 dopamine receptor, recently demonstrated as a functional entity[97], as well as to the heterodimers of different dopamine receptors including D2 dopamine receptor/A2a adenosine receptor, D2 dopamine receptor/metabotropic glutamate receptor 4 and D2 dopamine receptor/5HT2adrenergic receptor[73, 75, 98]. Data from crystalized dimers/oligomers used in molecular modeling allow for the building of models that can be employed in the study of molecular interactions[2, 74]. Moreover, some specific structural features involved in the interactions between the D2 dopamine receptor/A2a adenosine receptor heterodimers have been detailed[99-100]. Due to advances in the structural biology of G-protein coupled receptors, we now know that multiple drugs can be used to target a variety of such receptors, including not only D2 dopamine receptor but also A2a adenosine receptor, metabotropic glutamate receptor 4, 5HT2adrenergic receptor or muscarinic acetylcholine receptors as a simple target[101-102] or as a cluster of targets[103]. Moreover, drugs specific to homo- and hetero-dimers, known as bivalent drugs, are able to activate these two dimeric receptors simultaneously, and thus could prove to be very promising for treatment of central nervous system disorders[96, 104-108].
Finally, D3 dopamine receptor also has been targeted to treat Parkinson’s disease, and in silico/in vitro studies have been carried out to understand the details of agonist binding and improve the design of selective ligands\(^\text{[109-110]}\). However, the limiting factor for the application of drugs targeting this receptor is that they have a great impact on behavior, such as in a great variety of obsessive-compulsive disorders\[^{[111]}\].

**DRUGS TARGETING MUSCARINIC RECEPTORS: APPLICATIONS FOR TREATING ALZHEIMER’S DISEASE**

Effects on the organism mediated by muscarinic acetylcholine receptors are related to multiple processes in the central nervous system, including some related to cognitive, memory and motor functions\[^{[112-113]}\]. These receptors have been studied in relation to disorders associated with aging and neurodegenerative phenomena, especially Parkinson’s disease and Alzheimer’s disease. In the latter two neurodegenerative disorders there is a diminished expression of muscarinic acetylcholine receptors as well as a disruption in their capability to bind to endogenous ligands and/or activate coupled G-protein signaling\[^{[114-119]}\].

Several studies on the three-dimensional crystal structures of muscarinic acetylcholine receptors have reported the loss of muscarinic-1 cholinergic receptor, m2 acetylcholine receptor or m4R receptors in Alzheimer’s disease\[^{[120]}\]. A key role of m1 receptors has been clearly supported by the physiology of cognitive and memory processes, and the fact that the dysfunction of these receptors is related to neurodegenerative processes present in Alzheimer’s disease\[^{[121]}\]. Strategies targeting muscarinic-1 cholinergic receptor have been employed with promising results, including a delay in the onset of manifestations, as well as in related molecular pathophysiological processes—beta-amyloid plaque accumulation and Tau hyperphosphorylation—that prompt an advance in cognitive deficit\[^{[122-123]}\].

The first three-dimensional crystal structure of m2 acetylcholine receptor was reported in a complex with the Gi protein, while the first such report on m3 acetylcholine
conclusions and muscarinic-1 cholinergic receptor was in complex with the Gq/11 protein. The closely related nature of the structures of these two proteins has provided interesting details about the intracellular regions involved in coupling with heterotrimeric G proteins. Much attention has been focused on the distribution of residues in the extracellular region and their relation to the selectivity of ligands on muscarinic acetylcholine receptors through allosteric modulation. The new information on residues has great importance in the design of new cholinergic molecules[68, 124-126], already having been employed to develop compounds that appear to be better that the currently prescribed non-selective muscarinic acetylcholine agonists[127].

Positive allosteric modulation of these receptors could be key to increasing their activity when reached by endogenous ligands[128]. This field of research opens the possibility of finding new superagonists (previously mentioned in relation to peptides on G-protein coupled receptors)[78,126]. Moreover, the study of these extracellular regions could yield insights into the mechanism for regulating the activity of G-protein coupled receptors in a biased manner, aimed at either the G-protein dependent or independent pathway[70]. Since G-protein independent signaling has recently been associated with cognitive processes, interest has increased in developing ligands which activate biased signaling[129-130]. These ligands may positively modulate the allosteric binding site of the acetylcholine m1 receptor, which would be able to retard the disassociation of the concerted bonding of ligands to the orthosteric binding site. Thus, acetylcholine ligands would possibly be able to bind to their receptor with greater affinity. This allosteric positive modulation of m1 muscarinic receptors by new drugs, together with acetylcholinesterase inhibition, could then give rise to a new way of treating Alzheimer’s disease.

CONCLUDING REMARKS

New three-dimensional crystal structural data on G-protein coupled receptors have recently been used in molecular modeling studies to explore new possibilities for drug design. As a result, a new perspective has come to the fore — This view includes allosteric modulation of G-protein coupled receptors—. The new approach of simultaneously targeting the orthosteric and one more allosteric binding sites opens new possibilities for increasing the affinity and selectivity of the endogenous ligands for G-protein coupled receptors, and for activating receptor signaling through G-protein dependent and independent pathways. Moreover, during the submission of this manuscript, relevant works have been published supporting these important observations[131-132]. Hence, future research can seek to identify ligands that can bind to more than one site on the same receptor, or simultaneously bind to two receptors and form a dimer. These new insights have several implications for the treatment of central nervous system disorders. For example, the design of bivalent drugs that can reach homo/hetero-dimers of D2 dopamine receptor holds promise as a relevant therapeutic strategy for Parkinson’s disease. Regarding the treatment of Alzheimer’s disease, the design of dualsteric ligands for mono-oligomeric muscarinic receptors could increase therapeutic effectiveness by generating potent compounds that could activate more than one signaling pathway. In general, the new strategy resulting from recent findings is to identify regions outside of the orthosteric site of G-protein coupled receptors that can influence the G-protein signaling pathway and/or activate the kinase signaling pathway. These non-orthosteric sites could exist either on one receptor or two contiguous receptors in a dimer. As can be seen, with this new perspective there are a multitude of new possibilities of drug activity on a cellular system where G-protein coupled receptors are expressed. Hence, there are new opportunities to discover new compounds that are safer, more effective and more selective for the targeted receptor in the central nervous system of patients with neurodegenerative disorders.

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