CellPress

Opinion

One for the Price of Two. . .Are Bivalent Ligands Targeting Cannabinoid Receptor Dimers Capable of Simultaneously Binding to both Receptors?

Michelle Glass,[1,*] Karan Govindpani,[1] Daniel P. Furkert,[2] Dow P. Hurst,[3] Patricia H. Reggio,[3] and Jack U. Flanagan[1,4]

Bivalent ligands bridging two G-protein-coupled receptors (GPCRs) provide valuable pharmacological tools to target oligomers. The success of therapeutically targeting the cannabinoid CB_1 receptor has been limited, in part due to its widespread neuronal distribution. Therefore, CB_1 ligands targeting oligomers that exhibit restricted distribution or altered pharmacology are highly desirable, and several bivalent ligands containing a CB_1 pharmacophore have been reported. Bivalent ligand action presumes that the ligand simultaneously binds to both receptors within the dimeric complex. However, based on the current understanding of CB_1 ligand binding, existing bivalent ligands are too short to bind both receptors simultaneously. However, ligands with longer linkers may not be the solution, because evidence suggests that ligands enter CB_1 through the lipid bilayer and, thus, linkers are unlikely to exit the receptor through its external face. Thus, the entire premise of designing bivalent ligands targeting CB_1 must be revisited.

Targeting GPCR Dimers

Recent years have seen an explosion in the number of reports of functional oligomerisation of **GPCRs** (see Glossary). In many cases, these are attractive potential therapeutic targets because they provide a higher level of specificity for co-expressed receptors, or altered signalling response compared with targeting either constituent receptor on its own. The most common approach to pharmacologically targeting dimers is the use of **bivalent ligands**, which are compounds that comprise two chemical groups (**pharmacophores**) linked to each other by a spacer sequence of a specific length and composition, and potentially capable of binding to both receptors in a dimer simultaneously [1]. Targeting **oligomers** of **cannabinoid CB_1 receptors** is particularly appealing because the widespread nature of these receptors in the brain makes selectively targeting specific pathways challenging. Targeting receptor pairs could overcome this and open up the therapeutic potential of the cannabinoid receptor [2,3]. Several putative bivalent ligands for CB_1 have been published; however, here we consider the particular challenges that CB_1 receptors, and other structurally similar lipid receptors, present

Trends

GPCRs represent the largest family of membrane proteins involved in cellular signal transduction.

GPCRs are involved in diverse physiological processes and provide valuable drug targets for numerous diseases.

GPCRs are now generally accepted to form dimers or larger oligomeric complexes, but the functional role of receptor association is unclear in most cases.

Targeting of specific heteromers holds promise for enabling activation of subsets of receptors, resulting in greater specificity of therapeutic effect.

One approach utilised to target receptor dimers is the development of bivalent ligands, which comprise two pharmacophores linked by a spacer, with the goal of simultaneous activation of both receptors with higher affinity than they target either constituent receptor on its own.

[1]Department of Pharmacology, School of Medical Sciences, University of Auckland, Private Bag 92019, Auckland, New Zealand
[2]School of Chemical Sciences, University of Auckland, Private Bag 92019, Auckland, New Zealand

© 2016 Elsevier Ltd. All rights reserved.

and why we believe that existing ligands do not in fact target receptor homomers or heteromers.

Design and Detection of Bivalent Ligands for GPCR Dimers

Bivalent ligands comprise two pharmacophores linked by a spacer and are intended to bind to both receptors in the dimer simultaneously. By contrast, **'dual-acting' ligands** similarly comprise two pharmacophores linked together, often with a shorter spacer, and are designed with the intention simply of delivering both ligands simultaneously, without the expectation of simultaneous binding [4] (Figure 1).

Theoretically, by selecting potent and subtype-specific pharmacophores, bivalent ligands that simultaneously target homo- or heterodimers could be rationally designed. However, establishing that both ligands are binding simultaneously to the receptors in practice is far from trivial. Simultaneous binding to both components of the dimer should be detectable as positive cooperativity or higher **affinity** in a conventional competitive binding assay. That is, the binding of the first pharmacophore would increase the local concentration of the second tethered pharmacophore and, therefore, increase its binding to the dimer partner, resulting in either substantially steeper binding curves than for monovalent ligands or higher affinity; examples of such behaviour are observed in the bivalent ligand literature (e.g., [5]). However, Vagner *et al*. [6] noted that higher affinity, or cooperative binding behaviour of short homobivalent ligands for the hMC4R receptor, were likely the effect of 'statistical binding', wherein the binding of one pharmacophore of a bivalent ligand to its receptor increases the local concentration of the ligand, potentially driving the binding equilibrium of the second receptor towards greater receptor binding (i.e., a dual-acting phenotype, rather than a bivalent one). In principle, these two should be distinguishable from each other: when a single pharmacophore of a bivalent ligand is bound, binding of the second pharmacophore should be favoured over binding of a second ligand, because of the small containment volume of the tethered, unbound pharmacophore that is in the region of the unoccupied neighbouring receptor [7]. However, such subtle differences in binding affinity are unlikely to be distinguishable in most, if not all, **radioligand binding assays**. Furthermore, this relies on each receptor monomer behaving similarly with respect to ligand binding; however, negative **allosteric** interactions between receptor dimers have also been

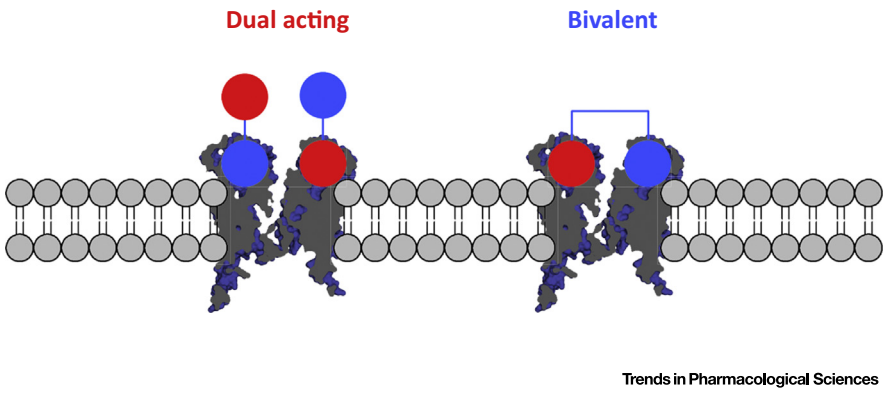

Figure 1. Schematic Diagram Illustrating the Difference between Dual-Acting and Bivalent Ligands. An illustration of the difference between bivalent and dual-acting ligands. Both comprise two pharmacophores linked together by a spacer; however, their theoretical mechanism of action is different. Bivalent ligands are designed such that a single ligand would simultaneously bind to both receptors; by contrast, dual-acting ligands deliver both ligands, but only one or other pharmacophore can be bound at any one time. Both would have the potential to result in simultaneous activation of both receptors, but dual-acting ligands would lack the (at this stage) theoretical ability of bivalent ligands to only target those receptors within the specific dimer pair.

[3]Center for Drug Design, University of North Carolina Greensboro, Greensboro, NC 27402, USA
[4]Auckland Cancer Society Research Centre and Maurice Wilkens Centre for Molecular Biodiscovery, University of Auckland, Private Bag 92019, Auckland, New Zealand

*Correspondence: m.glass@auckland.ac.nz (M. Glass).

Download English Version:

https://daneshyari.com/en/article/2572516

Download Persian Version:

https://daneshyari.com/article/2572516

Daneshyari.com