World Journal of Pharmacology & Toxicology

Short Communication Open Access

Development of novel therapeutic molecules for targeting multiple G protein coupled receptors (GPCRs) as anti-Parkinson's agents

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Abstract

Parkinsons Disease (PD) is a long-term degenerative disorder of the central nervous system that mainly affects the motor system. It is caused by the destruction of dopamine cells in the striatum region of the brain. The main approach in treatment of the disease is to increase the dopaminergic effect. However, it has been shown that simultaneous binding of Adenosine 2A receptor (A2AR) agonist and antagonist to the tetramer, which is the dominant oligomer formed by A2AR and D2R in the striatum, can increase D2R signalling more than that exerted by antagonist alone. These findings suggest that heterobivalent ligands might be used for this purpose. They can provide opportunity of using lower dose of L-dopa than being currently used for the therapy of the disease. Therefore, the risk of onset of motor complications such as motor fluctuations and dyskinesia might be alleviated1. This study has been aimed to synthesize novel heterobivalent ligands consisting of the A2AR antagonist/ A2AR agonist that are targeting the heterotetramer (A2AR - A2AR homodimer) structure as shown in Figure1. Synthesized therapeutic molecules are expected to reduce the side effects expected by administration of L-dopa alone via preventing antagonistic effect of A2AR on D2R, thus treating Parkinson's disease. G protein-coupled receptors (GPCRs) are the most intensively studied drug targets, largely due to their substantial involvement in human pathophysiology and their pharmacological tractability. Here, we report the first analysis of all GPCR drugs and agents in clinical trials. This reveals the current trends across molecule types, drug targets and therapeutic indications, including showing that 481 drugs (~34% of all drugs approved by the FDA) act at 107 unique GPCR targets. Approximately 320 agents are currently in clinical trials, of which ~36% target 64 potentially novel GPCR targets without an approved drug, and the number of biological drugs, allosteric modulators and biased agonists has grown. The major disease indications for GPCR modulators show a shift towards diabetes, obesity, and Alzheimer's disease, while other central nervous system disorders remain highly represented. The 227 (57%) non-olfactory GPCRs that are yet to be explored in clinical trials have broad untapped therapeutic potential, particularly in genetic and immune system disorders. Finally, we provide an interactive online resource to analyse and infer trends in GPCR drug discovery. G protein coupled receptors (GPCRs) represent the most important targets in modern pharmacology because of the different functions they mediate, especially within brain and peripheral nervous system, and also because of their functional and stereochemical properties. In this paper, we illustrate, via a variety of examples, novel advances about the GPCR-related molecules that have been shown to play diverse roles in GPCR pathways and in pathophysiological phenomena. We have exemplified how those GPCRs' pathways are, or might constitute, potential targets for different drugs either to stimulate, modify, regulate or inhibit the cellular mechanisms that are hypothesized to govern some pathologic, physiologic, biologic and cellular or molecular aspects both in vivo and in vitro. Therefore, influencing such pathways will, undoubtedly, lead to different therapeutical applications based on the related pharmacological implications. Furthermore, such new properties can be applied in different fields. In addition to offering fruitful directions for future researches, we hope the reviewed data, together with the elements found within the cited references, will inspire clinicians and researchers devoted to the studies on GPCR's properties.

Note: This work is partly presented at 18th International Conference on Pharmaceutics & Novel Drug Delivery Systems during on May 27-28, 2019 held at Istanbul, Turkey