SYNTHETIC RECEPTORS: ADVANCEMENTS TOWARD ARTIFICIAL SIGNAL TRANSDUCTION

Reported by Edzna S. Garcia May 2, 2017

INTRODUCTION

Cell-surface receptors are ubiquitous in biology. Many of these receptors participate in signal transduction, which is the process by which cells communicate with their environment. Signal transduction is largely mediated by three major types of receptors: ligand-gated ion channels, tyrosine kinase receptors, and G-protein coupled receptors (GPCRs). These receptors are responsible for communicating chemical signals across the cell membrane to induce an intracellular response. GPCRs make up the largest family of cell surface receptors and it has been estimated that ~40% of drugs target GPCRs.[1] However, the mechanism by which GPCRs communicate extracellular signals across the membrane to induce a response is still not well understood. In the interest to mimic biology or incorporate new signaling pathways, efforts to mimic the mode of action of receptors such a ligand-gated ion channels are known. However, efforts to replicate the mode of action of GPCRs are less well known. Synthetic mimics of GPCRs are of interest for their potential as communication systems for artificial tissues and they may ultimately open new ways to treat medical conditions associated with faulty signal transduction pathways. Synthetic analogues of GPCRs may also help provide insight into the mechanism of the native proteins through an "understanding by building approach" that is necessary for novel drug discovery.

NEW DEVELOPMENTS IN MIMICS OF GPCRs

In the past four years a group at the University of Bristol led by Jonathan Clayden have placed efforts in making synthetic analogues of GPCRs. Their approach involves the use of oligomers that can communicate a change in chiral environment at one end of the oligomer to the other end resulting in a conformational change. Oligomers of achiral amino acid α-aminoisobutyric acid (Aib) are used, which are known to adopt a helical structure called a foldamer. These foldamers rapidly interconvert between left and right-handed helices and adopt a preferred helix sense when a chiral monomer is inserted at the N-terminus of the helix.[2]

The Clayden group has reported that the photoswitch azobenzene can be used to change the conformational population of a foldamer **1** that is known to adopt a left-handed helix preference.[3] They have also reported that reversible binding of a chiral molecule to a binding site at the N-terminus of an

achiral foldamer **2** and **3** leads to adoption of a helical preference both in solution[4,5] and in a membrane environment.[5] However, these studies are done with the assumption that the synthetic receptors are embedded in the membrane and that the helical structure is maintained within this membrane environment. There is still no clear evidence that these receptors are embedded in the membrane and what their orientation in the membrane may be. Also, a clear understanding of what factors play a role in causing different chiral ligands to induce a distinct preferred helix is needed.

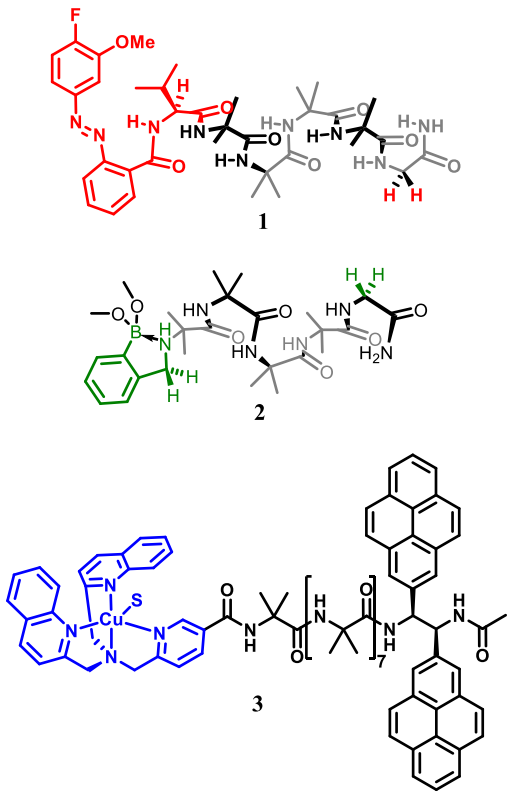

Figure 1. Structures of synthetic receptors.

SUMMARY

The Clayden group has reported synthetic receptors consisting of oligomers of Aib that are able to communicate ligand binding information by adopting a preferred conformation, which is analogous to the behavior of GPCRs. This type of communication still has not been coupled to a response but this might be achieved in the near future. Thus, mimicking the complexity of signal transduction using synthetic receptors has not yet been accomplished. These synthetic mimics of GPCRs are not only fundamentally interesting but they may open opportunities to understand at a more fundamental level the complexities of long-range communication that is common in biology.

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