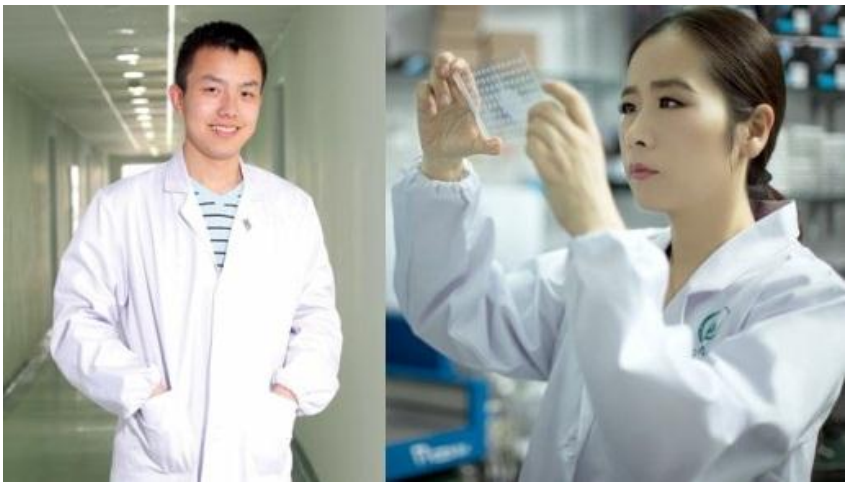
中国科学家成功解析胰高血糖素受体结构

Chinese Scientists Revealed the Structure of the Glucagon Receptor in Complex with a Glucagon Analogue



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1 月 3 日,《Nature》期刊发表了一篇题为“Structure of the glucagon receptor in complex with a glucagon analogue”的文章，揭示了来自于中国科学院上海药物研究所吴蓓丽研究员和赵强研究员团队的最新成果。

他们首次测定了胰高血糖素受体（Glucagon receptor, GCGR）全长蛋白与多肽配体复合物的三维结构，揭示了胰高血糖素受体对细胞信号分子的特异性识别及其活化调控机制。

胰高血糖素受体蛋白是治疗 2 型糖尿病药物的一个重要靶点，在人体内参与调解血糖平衡，在人体处于饥饿状态下，这个受体蛋白可以提高人体血液内的血糖浓度。然而，其结构信息的缺失严重制约了对该受体信号识别和转导机制的认识,这也直接导致了目前尚无靶向胰高血糖素受体的药物上市。

在最新的研究中，团队分析了胰高血糖素受体与多肽配体 NNC1702 结合的复合物结构，并与以往解析的全长胰高血糖素受体结构进行比较。

基于 GCGR-NNC1702 复合物结构，研究人员还运用竞争配体结合、计算机模拟和双电子共振等多种技术手段开展了一系列功能性研究,阐明了胰高血糖素受体在不同功能状态下构象的动态变化，并对受体活化的调控机制进行了深入的探究。

这一蛋白结构的解析有助于开发靶向 GCGR 的药物，从为开发有效治疗 2 型糖尿病的新型药物或疗法提供新思路。

Structure of the glucagon receptor in complex with a glucagon analogue

胰高血糖素受体全长蛋白与多肽配体复合物的三维结构

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Class B G-protein-coupled receptors (GPCRs), which consist of an extracellular domain (ECD) and a transmembrane domain (TMD), respond to secretin peptides to play a key part in hormonal homeostasis, and are important therapeutic targets for a variety of diseases1,2,3,4,5,6,7,8. Previous work9,10,11 has suggested that peptide ligands bind to class B GPCRs according to a two-domain binding model, in which the C-terminal region of the peptide targets the ECD and the N-terminal region of the peptide binds to the TMD binding pocket. Recently, three structures of class B GPCRs in complex with peptide ligands have been solved12,13,14. These structures provide essential insights into peptide ligand recognition by class B GPCRs. However, owing to resolution limitations, the specific molecular interactions for peptide binding to class B GPCRs remain ambiguous. Moreover, these previously solved structures have different ECD conformations relative to the TMD, which introduces questions regarding inter-domain conformational flexibility and the changes required for receptor activation. Here we report the 3.0 Å-resolution crystal structure of the full-length human glucagon receptor (GCGR) in complex with a glucagon analogue and partial agonist, NNC1702. This structure provides molecular details of the interactions between GCGR and the peptide ligand. It reveals a marked change in the relative orientation between the ECD and TMD of GCGR compared to the previously solved structure of the inactive GCGR–NNC0640–mAb1 complex. Notably, the stalk region and the first extracellular loop undergo major conformational changes in secondary structure during peptide binding, forming key interactions with the peptide. We further propose a dual-binding-site trigger model for GCGR activation—which requires conformational changes of the stalk, first extracellular loop and TMD—that extends our understanding of the previously established two-domain peptide-binding model of class B GPCRs.