Title
Insights into GLP-1 Receptor Activation with a Nonpeptide Agonist

Journal
Biochemistry, 59(16)

ISSN
0006-2960

Authors
Martinez, Thomas F
Vaughan, Joan
Saghatelian, Alan

Publication Date
2020-04-28

DOI
10.1021/acs.biochem.0c00180

Peer reviewed

Biochemistry

pubs.acs.org/biochemistry Viewpoint

Insights into GLP-1 Receptor Activation with a Nonpeptide Agonist

Thomas F. Martinez, Joan Vaughan, and Alan Saghatelian*

Cite This: *Biochemistry* 2020, 59, 1549−1550 Read Online

ACCESS | Metrics & More | Article Recommendations

G-protein-coupled receptors (GPCRs) are proteins that mediate extracellular-to-intracellular communication through ligand binding to regulate a variety of physiological processes. Members of the class B GPCR subgroup, which includes the glucagon and glucagon-like peptide 1 receptors (GLP1Rs), have large peptide hormones as cognate ligands. GLP-1 is an intestinal hormone that is released postprandially and enhances glucose-dependent secretion of insulin from the pancreas via GLP1R activation. Peptide analogues of GLP-1, such as the diabetes drugs semaglutide and dulaglutide, are effective GLP1R agonists and lower blood glucose levels by increasing insulin concentrations. However, there are some liabilities with the peptidic GLP1R agonists that lead to nausea and gastrointestinal issues in some patients, and their large size precludes efficient absorption upon oral administration.

A recent work by Zhao et al. reports the first structure of a nonpeptidic small-molecule agonist, TT-OAD2, bound to GLP1R.[1] Insights from this structure could transform the way this receptor is targeted in the future by opening the door to small-molecule nonpeptidic GLP1R agonists.

Atomic studies of GPCRs reveal a conserved seven-transmembrane (7-TM) helical structure[2] that serves as a binding pocket for many kinds of ligands, and comparison of bound and unbound GPCR structures[3,4] affords insight into the mechanism of signal transduction by these receptors. Through biochemical and structural studies of TT-OAD2 (Figure 1), Zhao et al. provide a structure for rational drug design of nonpeptidic agonists and gain insight into the fundamental requirements for GLP1R activation by comparison of TT-OAD2 to GLP-1.

TT-OAD2 has several aromatic and non-aromatic rings connected through flexible linkers. Administration of TT-OAD2 stimulates insulin secretion to an extent similar to that of GLP-1 in mice. Activation of the GLP-1 receptor can stimulate several distinct cellular processes, including cAMP production, calcium release, β-arrestin recruitment, and changes in signal transduction. GLP-1 activates these pathways, while TT-OAD2 enhances cAMP signaling with little to no activity on other pathways. This selectivity is termed biased agonism. Mechanistic studies revealed that GLP-1 and TT-OAD2 activate the intracellular cAMP-generating G stimulatory (Gs) protein with very different kinetics. GLP-1 causes a rapid change in the conformation of Gs, while TT-OAD2 results in a much slower change in the conformation of Gs. These biochemical studies suggested that the GLP-1−GLP1R and TT-OAD2−GLP1R structures are likely to be different.

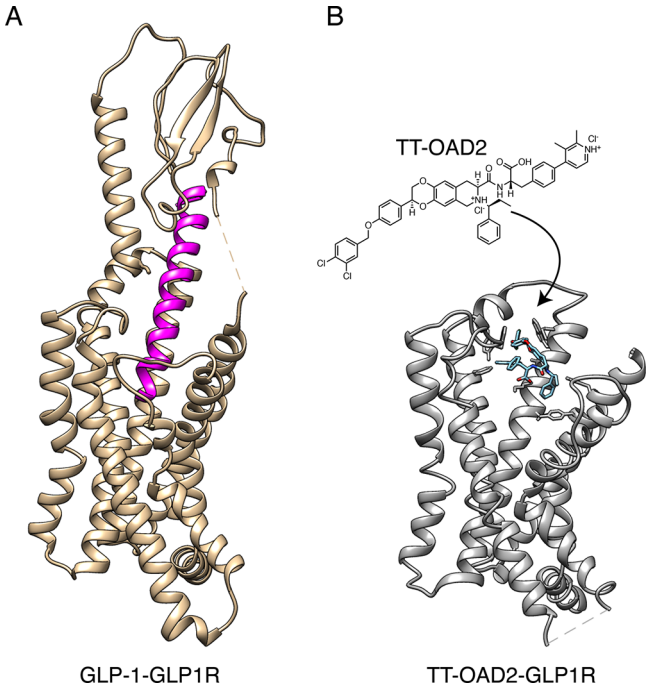

Figure 1. GLP1R bound with (A) GLP-1 or (B) TT-OAD2. (A) GLP-1 (magenta) forms a helix and places its N-terminus within the 7-TM region, and the conformation changes. (B) The structure of TT-OAD2 contains several ring regions that are connected through flexible hinges. When bound to GLP1R, TT-OAD2 reveals a novel nonpeptidic small-molecule agonist binding site.

To test this idea, Zhao et al. obtained a cryo-electron microscopy structure of TT-OAD2 bound to GLP1R at 3 Å resolution and compared the TT-OAD2−GLP1R structure to the available GLP-1−GLP1R structure.[5] TT-OAD2 binds to the 7-TM helices at a much higher position (i.e., closer to the extracellular juncture) than GLP-1, which buries its N-terminus well within the 7-TM cavity. The structure revealed that the flexibility of TT-OAD2 is a prerequisite as this small molecule adopts a unique "boomerang-like" structure that

Received: March 3, 2020
Published: April 16, 2020

https://dx.doi.org/10.1021/acs.biochem.0c00180
Biochemistry 2020, 59, 1549−1550

results in a footprint that is more compact than expected (Figure 1). In addition, one of the TT-OAD2 aromatic rings reaches outside of the 7-TM cavity where it is proposed to interact with the lipid bilayer in cells or tissues. All of these insights are valuable to medicinal chemists, who could now better model this binding site to search for new GLP1R pharmacophores that are conformationally restricted for better binding to GLP1R and modified for improved interactions with the bilayer.

A comparison of GLP-1 and TT-OAD2 binding reveals that there are only a few amino acids that interact with both compounds, although the overall GLP-1−GLP1R and TT-OAD2−GLP1R structures show a similar conformation of the 7-TM region (Figure 1). The molecular mechanism of how the two compounds achieve this structure, however, is markedly different. In particular, GLP-1 uses its N-terminus to bind to the key residues deep within the 7-TM core to reorganize the core and achieve the needed structural change. By contrast, TT-OAD2 modulates the central polar network via allosteric interactions to produce a similar structure but with no direct binding of the residues within this region. Zhao et al. hypothesize that kinetic differences observed between the two compounds are related to the differences in the rate of GLP1R reorganization afforded by the two compounds.

Overall, the work of Zhao et al. makes several significant contributions.[1] A structure of GLP1R with a nonpeptidic small-molecule agonist will prove useful in drug discovery for structure−activity studies, rational design, and computational screening. The findings also suggest that other peptide GPCRs might be amenable to the development of nonpeptidic agonists. One question that remains to be addressed is whether the differences in structures between GLP-1 and TT-OAD2 would result in fewer side effects or diminish the beneficial effects of peptidic GLP1R agonists. Of course, this point can only be addressed through the active pursuit of nonpeptidic small-molecule agonists for GLP1R.

AUTHOR INFORMATION

Corresponding Author

Alan Saghatelian − *Clayton Foundation Laboratories for Peptide Biology, Salk Institute for Biological Studies, La Jolla, California 92037-1002, United States;* orcid.org/0000-0002-0427-563X; Email: asaghatelian@salk.edu

Authors

Thomas F. Martinez − *Clayton Foundation Laboratories for Peptide Biology, Salk Institute for Biological Studies, La Jolla, California 92037-1002, United States*

Joan Vaughan − *Clayton Foundation Laboratories for Peptide Biology, Salk Institute for Biological Studies, La Jolla, California 92037-1002, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.biochem.0c00180

Funding

This work was supported by National Institute of General Medical Sciences (NIGMS) Grant R01 GM102491 (A.S.), Dr. Frederick Paulsen Chair/Ferring Pharmaceuticals (A.S.), and NIGMS Postdoctoral Fellowship F32 GM123685 (T.F.M.).

Notes

The authors declare no competing financial interest.

REFERENCES

(1) Zhao, P., Liang, Y. L., Belousoff, M. J., Deganutti, G., Fletcher, M. M., Willard, F. S., Bell, M. G., Christe, M. E., Sloop, K. W., Inoue, A., Truong, T. T., Clydesdale, L., Furness, S. G. B., Christopoulos, A., Wang, M. W., Miller, L. J., Reynolds, C. A., Danev, R., Sexton, P. M., and Wootten, D. (2020) Activation of the GLP-1 receptor by a non-peptidic agonist. *Nature 577*, 432−436.

(2) Lagerstrom, M. C., and Schioth, H. B. (2008) Structural diversity of G protein-coupled receptors and significance for drug discovery. *Nat. Rev. Drug Discovery 7*, 339−357.

(3) Cherezov, V., Rosenbaum, D. M., Hanson, M. A., Rasmussen, S. G., Thian, F. S., Kobilka, T. S., Choi, H. J., Kuhn, P., Weis, W. I., Kobilka, B. K., and Stevens, R. C. (2007) High-resolution crystal structure of an engineered human beta2-adrenergic G protein-coupled receptor. *Science 318*, 1258−1265.

(4) Rosenbaum, D. M., Zhang, C., Lyons, J. A., Holl, R., Aragao, D., Arlow, D. H., Rasmussen, S. G., Choi, H. J., Devree, B. T., Sunahara, R. K., Chae, P. S., Gellman, S. H., Dror, R. O., Shaw, D. E., Weis, W. I., Caffrey, M., Gmeiner, P., and Kobilka, B. K. (2011) Structure and function of an irreversible agonist-beta(2) adrenoceptor complex. *Nature 469*, 236−240.

(5) Zhang, Y., Sun, B., Feng, D., Hu, H., Chu, M., Qu, Q., Tarrasch, J. T., Li, S., Sun Kobilka, T., Kobilka, B. K., and Skiniotis, G. (2017) Cryo-EM structure of the activated GLP-1 receptor in complex with a G protein. *Nature 546*, 248−253.