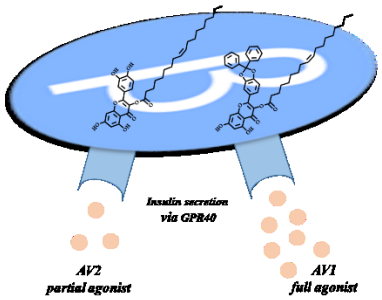
GPR40 as a template for the development of new insulin secretagogues with wound healing properties

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Abstract

Free Fatty Acid Receptors, belonging to GPCRs family, are emerging as new targets to treat diabetes or related disorders, representing a versatile family of receptors, activated by fatty acids contained in vegetable oils. In this context, extra-virgin olive oil is a "natural antidiabetic agent", favoring GLP-1 secretion from pancreas. Its principal component, olive oil is the endogenous ligand of FFAR1/GPR40. This receptor is highly expressed in pancreatic β-cells, where its activation promotes insulin secretion. Starting from oleic acid, which is able to promote glucose-stimulated insulin secretion (GSIS) at lipo-toxic doses, new hybrid derivatives of oleic acid with quercetin were designed and synthesized. 2-(2,2-diphenylbenzo[d][1,3]dioxol-5-yl)-5,7-dihydroxy-4-oxo-4H-chromen-3-yl oleate (AV1) was synthesized in order to prevent C3-OH auto-oxidation of quercetin and obtained in good yield. Docking simulations demonstated that AV1 could be accommodated within the long transmembrane crevice of the receptor. These data suggested for the first time that this binding site could recognize exogenous ligands. AV1 was able to evocate insulin release (EC_{50}=5μM) by both pancreatic islets and in vitro β-cells system (INS-1 832-13). Furthermore, Quercetin-3-oleate (AV2) was synthesized through a green synthesis and was able to favor GSIS at higher concentrations than AV1 (EC_{50}=21μM). Functional assays, conducted by using DC260126 as known antagonist, demonstrated that AV1 is a full GPR40 agonist, whilst AV2 is a partial agonist. AV2 was also assayed for its wound healing properties in HaCaT cell line (stably expressing GPR40). AV2 was able to promote wound healing at very low concentration (10 nM), enhancing the production of TGF-β. Moreover, in THP-1 monocytes, AV2 was able to promote IL-6 prodcution, not affecting IL-1β or TNF-α. These data confirmed that AV2 could be used as a suitable tool in the management of Type 2 Diabetes Mellitus, limiting lipotoxicity due to excessive GPR40 activation and especially in diabetic foot ulcer.

Image



Recent Publications

1. Milligan G, Shimpukade B, Ulven T, Hudson BD (2017) Complex Pharmacology of Free Fatty Acid Receptors. Chemical Reviews 117:67-110.
2. Badolato M, Carullo G, Perri M, Cione E, Manetti F, Di Gioia ML, Brizzi A, Caroleo MC, Aiello F (2017) Quercetin/oleic acid-based G-protein-coupled receptor 40 ligands as new insulin secretion modulators. Future Medicinal Chemistry 9(11):1873-1885.
3. Carullo G, Aiello F (2018) Quercetin-3-oleate. Molbank M1006.
4. Sloop KW, Briere DA, Emmerson PJ, Willard FS (2018) Beyond Glucagon-like Peptide-1: Is G-Protein Coupled Receptor Polypharmacology the Path Forward to Treating Metabolic Diseases? ACS Pharmacology Translational Science 1(1), 3-11.
5. Ho JD, Chau B, Rodgers L, Lu F, Wilbur KL, Otto KA, Chen Y, Song M, Riley JP, Yang H, Reynolds NA, kahl SD, Patel Lewis A, Groshong C, Madsen RE, Conners K, Lineswala JP, Gheyi T, Decipulo Saflor M, Lee MR, Benach J, Baker KA, Montrose-Rafizadeh C, Genin ML, Miller AR, Hadmouchi C (2018) Structural basis for GPR40 allosteric agonism and incretin stimulation. Nature Communications 9, 1645.



Biography

Gabriele Carullo has his expertise in green chemistry and development of hybrid compounds for the development of interesting pharmacological tools. In particulat, he is developing new polyphenols-fatty acids hybrids as new GPR40/GPR120 ligands in order to treat type 2 diabetes and its comorbidities. In addition, he works on the development of new antihypertensive agents starting from flavonoids as a surge of KCa1.1 and Cav1.2 channel modulators. His pharmacological research is also devoted to the production of new functional foods, for the treatment of hypertension and diabetes, starting from food wastes.

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Notes/Comment