

Free fatty acid receptors in GtoPdb v.2023.1

Celia Briscoe¹, Andrew Brown², Nick Holliday³, Stephen Jenkinson⁴, Graeme Milligan⁵, Amy E. Monaghan⁶ and Leigh Stoddart⁵

1. Johnson & Johnson Pharmaceutical Research & Development, USA
2. GlaxoSmithKline, UK
3. University of Nottingham, UK
4. Tanabe Research Laboratories, USA
5. University of Glasgow, UK
6. University of Edinburgh, UK

Abstract

Free fatty acid receptors (FFA, **nomenclature as agreed by the NC-IUPHAR Subcommittee on free fatty acid receptors [116, 27]**) are activated by free fatty acids. Long-chain saturated and unsaturated fatty acids (including C14:0 (**myristic acid**), C16:0 (**palmitic acid**), C18:1 (**oleic acid**), C18:2 (**linoleic acid**), C18:3, (**α -linolenic acid**), C20:4 (**arachidonic acid**), C20:5,n-3 (**EPA**) and C22:6,n-3 (**docosahexaenoic acid**)) activate FFA1 [9, 54, 64] and FFA4 receptors [45, 52, 94], while short chain fatty acids (C2 (**acetic acid**), C3 (**propanoic acid**), C4 (**butyric acid**) and C5 (**pentanoic acid**)) activate FFA2 [10, 66, 90] and FFA3 [10, 66] receptors. The crystal structure for agonist bound FFA1 has been described [113].

Contents

This is a citation summary for Free fatty acid receptors in the [Guide to Pharmacology](#) database (GtoPdb). It exists purely as an adjunct to the database to facilitate the recognition of citations to and from the database by citation analyzers. Readers will almost certainly want to visit the relevant sections of the database which are given here under database links.

[GtoPdb](#) is an expert-driven guide to pharmacological targets and the substances that act on them. GtoPdb is a reference work which is most usefully represented as an on-line database. As in any publication this work should be appropriately cited, and the papers it cites should also be recognized. This document provides a citation for the relevant parts of the database, and also provides a reference list for the research cited by those parts. For further details see [12].

Please note that the database version for the citations given in GtoPdb are to the most recent preceding version in which the family or its subfamilies and targets were substantially changed. The links below are to the current version. If you need to consult the cited version, rather than the most recent version, please contact the GtoPdb curators.

Database links

[Free fatty acid receptors](#)

<https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=24>

[Introduction to Free fatty acid receptors](#)

<https://www.guidetopharmacology.org/GRAC/FamilyIntroductionForward?familyId=24>

Receptors

[FFA1 receptor](https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=225)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=225>

[FFA2 receptor](https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=226)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=226>

[FFA3 receptor](https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=227)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=227>

[FFA4 receptor](https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=127)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=127>

[GPR42](https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=228)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=228>

References

1. Adachi T, Yanaka H, Kanai H, Nozaki M, Takahara Y, Tsuda M, Jonouchi T, Tsuda K, Hirasawa A and Tsujimoto G. (2008) Administration of perilla oil coated with Calshell increases glucagon-like peptide secretion. *Biol Pharm Bull* **31**: 1021-3 [PMID:18451539]
2. Azevedo CM, Watterson KR, Wargent ET, Hansen SV, Hudson BD, Kępczyńska MA, Dunlop J, Shimpukade B, Christiansen E and Milligan G *et al.*. (2016) Non-Acidic Free Fatty Acid Receptor 4 Agonists with Antidiabetic Activity. *J Med Chem* **59**: 8868-8878 [PMID:27570890]
3. Bellahcene M, O'Dowd JF, Wargent ET, Zaibi MS, Hislop DC, Ngala RA, Smith DM, Cawthorne MA, Stocker CJ and Arch JR. (2013) Male mice that lack the G-protein-coupled receptor GPR41 have low energy expenditure and increased body fat content. *Br J Nutr* **109**: 1755-64 [PMID:23110765]
4. Berggren AM, Nyman EM, Lundquist I and Björck IM. (1996) Influence of orally and rectally administered propionate on cholesterol and glucose metabolism in obese rats. *Br J Nutr* **76**: 287-94 [PMID:8813902]
5. Bjursell M, Admyre T, Göransson M, Marley AE, Smith DM, Oscarsson J and Bohlooly-Y M. (2011) Improved glucose control and reduced body fat mass in free fatty acid receptor 2-deficient mice fed a high-fat diet. *Am J Physiol Endocrinol Metab* **300**: E211-20 [PMID:20959533]
6. Bolognini D, Moss CE, Nilsson K, Petersson AU, Donnelly I, Sergeev E, König GM, Kostenis E, Kurowska-Stolarska M and Miller A *et al.*. (2016) A Novel Allosteric Activator of Free Fatty Acid 2 Receptor Displays Unique Gi-functional Bias. *J Biol Chem* **291**: 18915-31 [PMID:27385588]
7. Bonini JA, Anderson SM and Steiner DF. (1997) Molecular cloning and tissue expression of a novel orphan G protein-coupled receptor from rat lung. *Biochem Biophys Res Commun* **234**: 190-3 [PMID:9168987]
8. Briscoe CP, Peat AJ, McKeown SC, Corbett DF, Goetz AS, Littleton TR, McCoy DC, Kenakin TP, Andrews JL and Ammala C *et al.*. (2006) Pharmacological regulation of insulin secretion in MIN6 cells through the fatty acid receptor GPR40: identification of agonist and antagonist small molecules. *Br J Pharmacol* **148**: 619-28 [PMID:16702987]
9. Briscoe CP, Tadayyon M, Andrews JL, Benson WG, Chambers JK, Eilert MM, Ellis C, Elshourbagy NA, Goetz AS and Minnick DT *et al.*. (2003) The orphan G protein-coupled receptor GPR40 is activated by medium and long chain fatty acids. *J Biol Chem* **278**: 11303-11 [PMID:12496284]
10. Brown AJ, Goldsworthy SM, Barnes AA, Eilert MM, Tcheang L, Daniels D, Muir AI, Wigglesworth MJ, Kinghorn I and Fraser NJ *et al.*. (2003) The Orphan G protein-coupled receptors GPR41 and GPR43 are activated by propionate and other short chain carboxylic acids. *J Biol Chem* **278**: 11312-9 [PMID:12496283]
11. Brown AJ, Jupe S and Briscoe CP. (2005) A family of fatty acid binding receptors. *DNA Cell Biol* **24**: 54-61 [PMID:15684720]
12. Buneman P, Christie G, Davies JA, Dimitrellou R, Harding SD, Pawson AJ, Sharman JL and Wu Y. (2020) Why data citation isn't working, and what to do about it *Database* **2020** [PMID:32367113]
13. Burns RN and Moniri NH. (2010) Agonism with the omega-3 fatty acids alpha-linolenic acid and docosahexaenoic acid mediates phosphorylation of both the short and long isoforms of the human GPR120 receptor. *Biochem Biophys Res Commun* **396**: 1030-5 [PMID:20471368]
14. Cartoni C, Yasumatsu K, Ohkuri T, Shigemura N, Yoshida R, Godinot N, le Coutre J, Ninomiya Y and Damak S. (2010) Taste preference for fatty acids is mediated by GPR40 and GPR120. *J Neurosci* **30**: 8376-82 [PMID:20573884]

15. Chen Y, Ren Q, Zhou Z, Deng L, Hu L, Zhang L and Li Z. (2020) HWL-088, a new potent free fatty acid receptor 1 (FFAR1) agonist, improves glucolipid metabolism and acts additively with metformin in ob/ob diabetic mice. *Br J Pharmacol* **177**: 2286-2302 [PMID:31971610]
16. Cherbut C, Ferrier L, Rozé C, Anini Y, Blottière H, Lecannu G and Galmiche JP. (1998) Short-chain fatty acids modify colonic motility through nerves and polypeptide YY release in the rat. *Am J Physiol* **275**: G1415-22 [PMID:9843779]
17. Christiansen E, Due-Hansen ME, Urban C, Grundmann M, Schröder R, Hudson BD, Milligan G, Cawthorne MA, Kostenis E and Kassack MU *et al.* (2012) Free fatty acid receptor 1 (FFA1/GPR40) agonists: mesylpropoxy appendage lowers lipophilicity and improves ADME properties. *J Med Chem* **55**: 6624-8 [PMID:22724451]
18. Christiansen E, Hansen SV, Urban C, Hudson BD, Wargent ET, Grundmann M, Jenkins L, Zaibi M, Stocker CJ and Ullrich S *et al.* (2013) Discovery of TUG-770: A Highly Potent Free Fatty Acid Receptor 1 (FFA1/GPR40) Agonist for Treatment of Type 2 Diabetes. *ACS Med Chem Lett* **4**: 441-445 [PMID:23687558]
19. Christiansen E, Hudson BD, Hansen AH, Milligan G and Ulven T. (2016) Development and Characterization of a Potent Free Fatty Acid Receptor 1 (FFA1) Fluorescent Tracer. *J Med Chem* **59**: 4849-58 [PMID:27074625]
20. Christiansen E, Urban C, Merten N, Liebscher K, Karlsen KK, Hamacher A, Spinrath A, Bond AD, Drewke C and Ullrich S *et al.* (2008) Discovery of potent and selective agonists for the free fatty acid receptor 1 (FFA1)/GPR40, a potential target for the treatment of type II diabetes. *J Med Chem* **51**: 7061-4 [PMID:18947221]
21. Christiansen E, Watterson KR, Stocker CJ, Sokol E, Jenkins L, Simon K, Grundmann M, Petersen RK, Wargent ET and Hudson BD *et al.* (2015) Activity of dietary fatty acids on FFA1 and FFA4 and characterisation of pinolenic acid as a dual FFA1/FFA4 agonist with potential effect against metabolic diseases. *Br J Nutr* **113**: 1677-88 [PMID:25916176]
22. Cintra DE, Ropelle ER, Moraes JC, Pauli JR, Morari J, Souza CT, Grimaldi R, Stahl M, Carnevali JB and Saad MJ *et al.* (2012) Unsaturated fatty acids revert diet-induced hypothalamic inflammation in obesity. *PLoS ONE* **7**: e30571 [PMID:22279596]
23. Cornall LM, Mathai ML, Hryciw DH and McAinch AJ. (2011) Diet-induced obesity up-regulates the abundance of GPR43 and GPR120 in a tissue specific manner. *Cell Physiol Biochem* **28**: 949-58 [PMID:22178946]
24. Cornish J, MacGibbon A, Lin JM, Watson M, Callon KE, Tong PC, Dunford JE, van der Does Y, Williams GA, Grey AB, Naot D and Reid IR. (2008) Modulation of osteoclastogenesis by fatty acids. *Endocrinology* **149**: 5688-95 [PMID:18617622]
25. Covington DK, Briscoe CA, Brown AJ and Jayawickreme CK. (2006) The G-protein-coupled receptor 40 family (GPR40-GPR43) and its role in nutrient sensing. *Biochem Soc Trans* **34**: 770-3 [PMID:17052194]
26. Dass NB, John AK, Bassil AK, Crumbley CW, Shehee WR, Maurio FP, Moore GB, Taylor CM and Sanger GJ. (2007) The relationship between the effects of short-chain fatty acids on intestinal motility in vitro and GPR43 receptor activation. *Neurogastroenterol Motil* **19**: 66-74 [PMID:17187590]
27. Davenport AP, Alexander SP, Sharman JL, Pawson AJ, Benson HE, Monaghan AE, Liew WC, Mpmahanga CP, Bonner TI and Neubig RR *et al.* (2013) International Union of Basic and Clinical Pharmacology. LXXXVIII. G protein-coupled receptor list: recommendations for new pairings with cognate ligands. *Pharmacol Rev* **65**: 967-86 [PMID:23686350]
28. Duca FA, Swartz TD, Sakar Y and Covasa M. (2013) Decreased intestinal nutrient response in diet-induced obese rats: role of gut peptides and nutrient receptors. *Int J Obes (Lond.)* **37**: 375-81 [PMID:22546775]
29. Engelstoft MS, Egerod KL, Holst B and Schwartz TW. (2008) A gut feeling for obesity: 7TM sensors on enteroendocrine cells. *Cell Metab* **8**: 447-9 [PMID:19041758]
30. Feng DD, Luo Z, Roh SG, Hernandez M, Tawadros N, Keating DJ and Chen C. (2006) Reduction in voltage-gated K⁺ currents in primary cultured rat pancreatic beta-cells by linoleic acids. *Endocrinology* **147**: 674-682 [PMID:16254037]
31. Flodgren E, Olde B, Meidute-Abaraviciene S, Winzell MS, Ahrén B and Salehi A. (2007) GPR40 is expressed in glucagon producing cells and affects glucagon secretion. *Biochem Biophys Res Commun* **354**: 240-5 [PMID:17214971]
32. Fredriksson R, Höglund PJ, Gloriam DE, Lagerström MC and Schiöth HB. (2003) Seven evolutionarily conserved human rhodopsin G protein-coupled receptors lacking close relatives. *FEBS Lett* **554**: 381-8

[PMID:14623098]

33. Fukumoto S, Tatewaki M, Yamada T, Fujimiya M, Mantyh C, Voss M, Eubanks S, Harris M, Pappas TN and Takahashi T. (2003) Short-chain fatty acids stimulate colonic transit via intraluminal 5-HT release in rats. *Am J Physiol Regul Integr Comp Physiol* **284**: R1269-76 [PMID:12676748]
34. Fukunaga S, Setoguchi S, Hirasawa A and Tsujimoto G. (2006) Monitoring ligand-mediated internalization of G protein-coupled receptor as a novel pharmacological approach. *Life Sci* **80**: 17-23 [PMID:16978657]
35. Gagnon L, Leduc M, Thibodeau JF, Zhang MZ, Grouix B, Sarra-Bournet F, Gagnon W, Hince K, Tremblay M and Geerts L *et al.*. (2018) A Newly Discovered Antifibrotic Pathway Regulated by Two Fatty Acid Receptors: GPR40 and GPR84. *Am J Pathol* **188**: 1132-1148 [PMID:29454750]
36. Garrel G, Simon V, Denoyelle C, Cruciani-Guglielmacci C, Migrenne S, Counis R, Magnan C and Cohen-Tannoudji J. (2011) Unsaturated fatty acids stimulate LH secretion via novel PKCepsilon and -theta in gonadotrope cells and inhibit GnRH-induced LH release. *Endocrinology* **152**: 3905-16 [PMID:21862612]
37. Garrido DM, Corbett DF, Dwornik KA, Goetz AS, Littleton TR, McKeown SC, Mills WY, Smalley Jr TL, Briscoe CP and Peat AJ. (2006) Synthesis and activity of small molecule GPR40 agonists. *Bioorg Med Chem Lett* **16**: 1840-5 [PMID:16439116]
38. Gotoh C, Hong YH, Iga T, Hishikawa D, Suzuki Y, Song SH, Choi KC, Adachi T, Hirasawa A, Tsujimoto G, Sasaki S and Roh SG. (2007) The regulation of adipogenesis through GPR120. *Biochem Biophys Res Commun* **354**: 591-7 [PMID:17250804]
39. Hamid YH, Vissing H, Holst B, Urhammer SA, Pyke C, Hansen SK, Glümer C, Borch-Johnsen K, Jørgensen T and Schwartz TW *et al.*. (2005) Studies of relationships between variation of the human G protein-coupled receptor 40 Gene and Type 2 diabetes and insulin release. *Diabet Med* **22**: 74-80 [PMID:15606695]
40. Hansen AH, Sergeev E, Bolognini D, Sprenger RR, Ekberg JH, Ejsing CS, McKenzie CJ, Rexen Ulven E, Milligan G and Ulven T. (2018) Discovery of a Potent Thiazolidine Free Fatty Acid Receptor 2 Agonist with Favorable Pharmacokinetic Properties. *J Med Chem* **61**: 9534-9550 [PMID:30247908]
41. Hara T, Hirasawa A, Ichimura A, Kimura I and Tsujimoto G. (2011) Free fatty acid receptors FFAR1 and GPR120 as novel therapeutic targets for metabolic disorders. *J Pharm Sci* **100**: 3594-601 [PMID:21618241]
42. Hara T, Hirasawa A, Sun Q, Sadakane K, Itsubo C, Iga T, Adachi T, Koshimizu TA, Hashimoto T and Asakawa Y *et al.*. (2009) Novel selective ligands for free fatty acid receptors GPR120 and GPR40. *Naunyn Schmiedebergs Arch Pharmacol* **380**: 247-55 [PMID:19471906]
43. Hardy S, St-Onge GG, Joly E, Langelier Y and Prentki M. (2005) Oleate promotes the proliferation of breast cancer cells via the G protein-coupled receptor GPR40. *J Biol Chem* **280**: 13285-91 [PMID:15695516]
44. Hirasawa A, Hara T, Katsuma S, Adachi T and Tsujimoto G. (2008) Free fatty acid receptors and drug discovery. *Biol Pharm Bull* **31**: 1847-51 [PMID:18827341]
45. Hirasawa A, Tsumaya K, Awaji T, Katsuma S, Adachi T, Yamada M, Sugimoto Y, Miyazaki S and Tsujimoto G. (2005) Free fatty acids regulate gut incretin glucagon-like peptide-1 secretion through GPR120. *Nat Med* **11**: 90-94 [PMID:15619630]
46. Holliday ND, Watson SJ and Brown AJ. (2011) Drug discovery opportunities and challenges at g protein coupled receptors for long chain free Fatty acids. *Front Endocrinol (Lausanne)* **2**: 112 [PMID:22649399]
47. Hong YH, Nishimura Y, Hishikawa D, Tsuzuki H, Miyahara H, Gotoh C, Choi KC, Feng DD, Chen C and Lee HG *et al.*. (2005) Acetate and propionate short chain fatty acids stimulate adipogenesis via GPCR43. *Endocrinology* **146**: 5092-9 [PMID:16123168]
48. Hudson BD, Christiansen E, Murdoch H, Jenkins L, Hansen AH, Madsen O, Ulven T and Milligan G. (2014) Complex pharmacology of novel allosteric free fatty acid 3 receptor ligands. *Mol Pharmacol* **86**: 200-10 [PMID:24870406]
49. Hudson BD, Christiansen E, Tikhonova IG, Grundmann M, Kostenis E, Adams DR, Ulven T and Milligan G. (2012) Chemically engineering ligand selectivity at the free fatty acid receptor 2 based on pharmacological variation between species orthologs. *FASEB J* **26**: 4951-65 [PMID:22919070]
50. Hudson BD, Due-Hansen ME, Christiansen E, Hansen AM, Mackenzie AE, Murdoch H, Pandey SK, Ward RJ, Marquez R and Tikhonova IG *et al.*. (2013) Defining the molecular basis for the first potent and selective orthosteric agonists of the FFA2 free fatty acid receptor. *J Biol Chem* **288**: 17296-312 [PMID:23589301]

51. Hudson BD, Tikhonova IG, Pandey SK, Ulven T and Milligan G. (2012) Extracellular ionic locks determine variation in constitutive activity and ligand potency between species orthologs of the free fatty acid receptors FFA2 and FFA3. *J Biol Chem* **287**: 41195-209 [PMID:23066016]
52. Ichimura A, Hirasawa A, Poulain-Godefroy O, Bonnefond A, Hara T, Yengo L, Kimura I, Leloire A, Liu N and Iida K *et al.*. (2012) Dysfunction of lipid sensor GPR120 leads to obesity in both mouse and human. *Nature* **483**: 350-4 [PMID:22343897]
53. Ito J, Ito M, Nambu H, Fujikawa T, Tanaka K, Iwaasa H and Tokita S. (2009) Anatomical and histological profiling of orphan G-protein-coupled receptor expression in gastrointestinal tract of C57BL/6J mice. *Cell Tissue Res* **338**: 257-69 [PMID:19763624]
54. Itoh Y, Kawamata Y, Harada M, Kobayashi M, Fujii R, Fukusumi S, Ogi K, Hosoya M, Tanaka Y and Uejima H *et al.*. (2003) Free fatty acids regulate insulin secretion from pancreatic beta cells through GPR40. *Nature* **422**: 173-6 [PMID:12629551]
55. Kaku K, Enya K, Nakaya R, Ohira T and Matsuno R. (2015) Efficacy and safety of fasiglifam (TAK-875), a G protein-coupled receptor 40 agonist, in Japanese patients with type 2 diabetes inadequately controlled by diet and exercise: a randomized, double-blind, placebo-controlled, phase III trial. *Diabetes Obes Metab* **17**: 675-81 [PMID:25787200]
56. Karaki S, Mitsui R, Hayashi H, Kato I, Sugiya H, Iwanaga T, Furness JB and Kuwahara A. (2006) Short-chain fatty acid receptor, GPR43, is expressed by enteroendocrine cells and mucosal mast cells in rat intestine. *Cell Tissue Res* **324**: 353-60 [PMID:16453106]
57. Karaki S, Tazoe H, Hayashi H, Kashiwabara H, Tooyama K, Suzuki Y and Kuwahara A. (2008) Expression of the short-chain fatty acid receptor, GPR43, in the human colon. *J Mol Histol* **39**: 135-42 [PMID:17899402]
58. Katayama S, Tomaru Y, Kasukawa T, Waki K, Nakanishi M, Nakamura M, Nishida H, Yap CC, Suzuki M and Kawai J *et al.*. (2005) Antisense transcription in the mammalian transcriptome. *Science* **309**: 1564-6 [PMID:16141073]
59. Katsuma S, Hatae N, Yano T, Ruike Y, Kimura M, Hirasawa A and Tsujimoto G. (2005) Free fatty acids inhibit serum deprivation-induced apoptosis through GPR120 in a murine enteroendocrine cell line STC-1. *J Biol Chem* **280**: 19507-15 [PMID:15774482]
60. Kazemian P, Kazemi-Bajestani SM, Alherbish A, Steed J and Oudit GY. (2012) The use of ω -3 polyunsaturated fatty acids in heart failure: a preferential role in patients with diabetes. *Cardiovasc Drugs Ther* **26**: 311-20 [PMID:22644698]
61. Kebede MA, Alquier T, Latour MG and Poitout V. (2009) Lipid receptors and islet function: therapeutic implications? *Diabetes Obes Metab* **11 Suppl 4**: 10-20 [PMID:19817784]
62. Kimura I, Inoue D, Maeda T, Hara T, Ichimura A, Miyauchi S, Kobayashi M, Hirasawa A and Tsujimoto G. (2011) Short-chain fatty acids and ketones directly regulate sympathetic nervous system via G protein-coupled receptor 41 (GPR41). *Proc Natl Acad Sci USA* **108**: 8030-5 [PMID:21518883]
63. Kimura M, Mizukami Y, Miura T, Fujimoto K, Kobayashi S and Matsuzaki M. (2001) Orphan G protein-coupled receptor, GPR41, induces apoptosis via a p53/Bax pathway during ischemic hypoxia and reoxygenation. *J Biol Chem* **276**: 26453-60 [PMID:11335718]
64. Kotarsky K, Nilsson NE, Flodgren E, Owman C and Olde B. (2003) A human cell surface receptor activated by free fatty acids and thiazolidinedione drugs. *Biochem Biophys Res Commun* **301**: 406-10 [PMID:12565875]
65. Latour MG, Alquier T, Oseid E, Tremblay C, Jetton TL, Luo J, Lin DC and Poitout V. (2007) GPR40 is necessary but not sufficient for fatty acid stimulation of insulin secretion in vivo. *Diabetes* **56**: 1087-94 [PMID:17395749]
66. Le Poul E, Loison C, Struyf S, Springael JY, Lannoy V, Decobecq ME, Brezillon S, Dupriez V, Vassart G and Van Damme J *et al.*. (2003) Functional characterization of human receptors for short chain fatty acids and their role in polymorphonuclear cell activation. *J Biol Chem* **278**: 25481-9 [PMID:12711604]
67. Lee T, Schwandner R, Swaminath G, Weiszmann J, Cardozo M, Greenberg J, Jaeckel P, Ge H, Wang Y and Jiao X *et al.*. (2008) Identification and functional characterization of allosteric agonists for the G protein-coupled receptor FFA2. *Mol Pharmacol* **74**: 1599-609 [PMID:18818303]
68. Leonard JN, Chu ZL, Bruce MA and Boatman PD. (2006) Pat 2006;PCT/US/2005/039551 (WO2006/052566 A2).: -
69. Leonard JN and Hakak Y. (2006) Pat PCT/US2005/033795(WO 2006/036688 A2).: -
70. Liaw CW and Connolly DT. (2009) Sequence polymorphisms provide a common consensus sequence for

- GPR41 and GPR42. *DNA Cell Biol* **28**: 555-60 [PMID:19630535]
71. Lin DC, Guo Q, Luo J, Zhang J, Nguyen K, Chen M, Tran T, Dransfield PJ, Brown SP and Houze J *et al.* (2012) Identification and pharmacological characterization of multiple allosteric binding sites on the free fatty acid 1 receptor. *Mol Pharmacol* **82**: 843-59 [PMID:22859723]
 72. Liou AP, Lu X, Sei Y, Zhao X, Pechhold S, Carrero RJ, Raybould HE and Wank S. (2011) The G-protein-coupled receptor GPR40 directly mediates long-chain fatty acid-induced secretion of cholecystokinin. *Gastroenterology* **140**: 903-12 [PMID:20955703]
 73. Lu X, Zhao X, Feng J, Liou AP, Anthony S, Pechhold S, Sun Y, Lu H and Wank S. (2012) Postprandial inhibition of gastric ghrelin secretion by long-chain fatty acid through GPR120 in isolated gastric ghrelin cells and mice. *Am J Physiol Gastrointest Liver Physiol* **303**: G367-76 [PMID:22678998]
 74. Ma D, Tao B, Warashina S, Kotani S, Lu L, Kaplamadzhiev DB, Mori Y, Tonchev AB and Yamashita T. (2007) Expression of free fatty acid receptor GPR40 in the central nervous system of adult monkeys. *Neurosci Res* **58**: 394-401 [PMID:17583366]
 75. Ma L, Wang T, Shi M, Fu P, Pei H and Ye H. (2016) Synthesis, Activity, and Docking Study of Novel Phenylthiazole-Carboxamido Acid Derivatives as FFA2 Agonists. *Chem Biol Drug Des* **88**: 26-37 [PMID:26808470]
 76. Martin C, Passilly-Degrace P, Gaillard D, Merlin JF, Chevrot M and Besnard P. (2011) The lipid-sensor candidates CD36 and GPR120 are differentially regulated by dietary lipids in mouse taste buds: impact on spontaneous fat preference. *PLoS ONE* **6**: e24014 [PMID:21901153]
 77. Maslowski KM, Vieira AT, Ng A, Kranich J, Sierro F, Yu D, Schilter HC, Rolph MS, Mackay F and Artis D *et al.* (2009) Regulation of inflammatory responses by gut microbiota and chemoattractant receptor GPR43. *Nature* **461**: 1282-6 [PMID:19865172]
 78. Matsumura S, Eguchi A, Mizushige T, Kitabayashi N, Tsuzuki S, Inoue K and Fushiki T. (2009) Colocalization of GPR120 with phospholipase-Cbeta2 and alpha-gustducin in the taste bud cells in mice. *Neurosci Lett* **450**: 186-90 [PMID:19071193]
 79. Matsumura S, Mizushige T, Yoneda T, Iwanaga T, Tsuzuki S, Inoue K and Fushiki T. (2007) GPR expression in the rat taste bud relating to fatty acid sensing. *Biomed Res* **28**: 49-55 [PMID:17379957]
 80. McKeown SC, Corbett DF, Goetz AS, Littleton TR, Bigham E, Briscoe CP, Peat AJ, Watson SP and Hickey DM. (2007) Solid phase synthesis and SAR of small molecule agonists for the GPR40 receptor. *Bioorg Med Chem Lett* **17**: 1584-9 [PMID:17240142]
 81. McLarnon A. (2012) Obesity: GPR120 dysfunction can cause obesity in mice and humans. *Nat Rev Gastroenterol Hepatol* **9**: 187 [PMID:22410428]
 82. Milligan G, Stoddart LA and Brown AJ. (2006) G protein-coupled receptors for free fatty acids. *Cell Signal* **18**: 1360-5 [PMID:16716567]
 83. Miyauchi S, Hirasawa A, Iga T, Liu N, Itsubo C, Sadakane K, Hara T and Tsujimoto G. (2009) Distribution and regulation of protein expression of the free fatty acid receptor GPR120. *Naunyn Schmiedeberg's Arch Pharmacol* **379**: 427-34 [PMID:19145429]
 84. Moore K, Zhang Q, Murgolo N, Hosted T and Duffy R. (2009) Cloning, expression, and pharmacological characterization of the GPR120 free fatty acid receptor from cynomolgus monkey: comparison with human GPR120 splice variants. *Comp Biochem Physiol B, Biochem Mol Biol* **154**: 419-26 [PMID:19723586]
 85. Morgan NG and Dhayal S. (2009) G-protein coupled receptors mediating long chain fatty acid signalling in the pancreatic beta-cell. *Biochem Pharmacol* **78**: 1419-27 [PMID:19660440]
 86. Nakajima T, Iikura M, Okayama Y, Matsumoto K, Uchiyama C, Shirakawa T, Yang X, Adra CN, Hirai K and Saito H. (2004) Identification of granulocyte subtype-selective receptors and ion channels by using a high-density oligonucleotide probe array. *J Allergy Clin Immunol* **113**: 528-35 [PMID:15007357]
 87. Namour F, Galien R, Van Kaem T, Van der Aa A, Vanhoutte F, Beetens J and Van't Klooster G. (2016) Safety, pharmacokinetics and pharmacodynamics of GLPG0974, a potent and selective FFA2 antagonist, in healthy male subjects. *Br J Clin Pharmacol* **82**: 139-48 [PMID:26852904]
 88. Navarro-Tito N, Robledo T and Salazar EP. (2008) Arachidonic acid promotes FAK activation and migration in MDA-MB-231 breast cancer cells. *Exp Cell Res* **314**: 3340-55 [PMID:18804105]
 89. Negoro N, Sasaki S, Mikami S, Ito M, Suzuki M, Tsujihata Y, Ito R, Harada A, Takeuchi K and Suzuki N *et al.* (2010) Discovery of TAK-875: A Potent, Selective, and Orally Bioavailable GPR40 Agonist. *ACS Med Chem Lett* **1**: 290-4 [PMID:24900210]
 90. Nilsson NE, Kotarsky K, Owman C and Olde B. (2003) Identification of a free fatty acid receptor, FFA2R, expressed on leukocytes and activated by short-chain fatty acids. *Biochem Biophys Res Commun* **303**:

1047-52 [PMID:12684041]

91. Ogawa T, Hirose H, Miyashita K, Saito I and Saruta T. (2005) GPR40 gene Arg211His polymorphism may contribute to the variation of insulin secretory capacity in Japanese men. *Metab Clin Exp* **54**: 296-9 [PMID:15736105]
92. Oh da Y, Walenta E, Akiyama TE, Lagakos WS, Lackey D, Pessentheiner AR, Sasik R, Hah N, Chi TJ and Cox JM *et al.*. (2014) A Gpr120-selective agonist improves insulin resistance and chronic inflammation in obese mice. *Nat Med* **20**: 942-7 [PMID:24997608]
93. Oh DY and Olefsky JM. (2012) Omega 3 fatty acids and GPR120. *Cell Metab* **15**: 564-5 [PMID:22560206]
94. Oh DY, Talukdar S, Bae EJ, Imamura T, Morinaga H, Fan W, Li P, Lu WJ, Watkins SM and Olefsky JM. (2010) GPR120 is an omega-3 fatty acid receptor mediating potent anti-inflammatory and insulin-sensitizing effects. *Cell* **142**: 687-98 [PMID:20813258]
95. Parker HE, Habib AM, Rogers GJ, Gribble FM and Reimann F. (2009) Nutrient-dependent secretion of glucose-dependent insulinotropic polypeptide from primary murine K cells. *Diabetologia* **52**: 289-98 [PMID:19082577]
96. Pizzonero M, Dupont S, Babel M, Beaumont S, Bienvenu N, Blanqué R, Cherel L, Christophe T, Crescenzi B and De Lemos E *et al.*. (2014) Discovery and optimization of an azetidone chemical series as a free fatty acid receptor 2 (FFA2) antagonist: from hit to clinic. *J Med Chem* **57**: 10044-57 [PMID:25380412]
97. Prihandoko R, Kaur D, Wiegman CH, Alvarez-Curto E, Donovan C, Chachi L, Ulven T, Tyas MR, Euston E and Dong Z *et al.*. (2020) Pathophysiological regulation of lung function by the free fatty acid receptor FFA4 *Science Translational Medicine* **12**: eaaw9009
98. Rasoamanana R, Darcel N, Fromentin G and Tomé D. (2012) Nutrient sensing and signalling by the gut. *Proc Nutr Soc* **71**: 446-55 [PMID:22453062]
99. Reber SO, Birkeneder L, Veenema AH, Obermeier F, Falk W, Straub RH and Neumann ID. (2007) Adrenal insufficiency and colonic inflammation after a novel chronic psycho-social stress paradigm in mice: implications and mechanisms. *Endocrinology* **148**: 670-82 [PMID:17110427]
100. Saltiel AR. (2010) Fishing out a sensor for anti-inflammatory oils. *Cell* **142**: 672-4 [PMID:20813253]
101. Samuel BS, Shaito A, Motoike T, Rey FE, Backhed F, Manchester JK, Hammer RE, Williams SC, Crowley J and Yanagisawa M *et al.*. (2008) Effects of the gut microbiota on host adiposity are modulated by the short-chain fatty-acid binding G protein-coupled receptor, Gpr41. *Proc Natl Acad Sci USA* **105**: 16767-72 [PMID:18931303]
102. Sawzdargo M, George SR, Nguyen T, Xu S, Kolakowski LF and O'Dowd BF. (1997) A cluster of four novel human G protein-coupled receptor genes occurring in close proximity to CD22 gene on chromosome 19q13.1. *Biochem Biophys Res Commun* **239**: 543-7 [PMID:9344866]
103. Schmidt J, Smith NJ, Christiansen E, Tikhonova IG, Grundmann M, Hudson BD, Ward RJ, Drewke C, Milligan G and Kostenis E *et al.*. (2011) Selective orthosteric free fatty acid receptor 2 (FFA2) agonists: identification of the structural and chemical requirements for selective activation of FFA2 versus FFA3. *J Biol Chem* **286**: 10628-40 [PMID:21220428]
104. Schröder R, Janssen N, Schmidt J, Kebig A, Merten N, Hennen S, Müller A, Blättermann S, Mohr-Andrä M and Zahn S *et al.*. (2010) Deconvolution of complex G protein-coupled receptor signaling in live cells using dynamic mass redistribution measurements. *Nat Biotechnol* **28**: 943-9 [PMID:20711173]
105. Seljeset S and Siehler S. (2012) Receptor-specific regulation of ERK1/2 activation by members of the "free fatty acid receptor" family. *J Recept Signal Transduct Res* **32**: 196-201 [PMID:22712802]
106. Senga T, Iwamoto S, Yoshida T, Yokota T, Adachi K, Azuma E, Hamaguchi M and Iwamoto T. (2003) LSSIG is a novel murine leukocyte-specific GPCR that is induced by the activation of STAT3. *Blood* **101**: 1185-7 [PMID:12393494]
107. Shimpukade B, Hudson BD, Hovgaard CK, Milligan G and Ulven T. (2012) Discovery of a potent and selective GPR120 agonist. *J Med Chem* **55**: 4511-5 [PMID:22519963]
108. Sina C, Gavrilova O, Förster M, Till A, Derer S, Hildebrand F, Raabe B, Chalaris A, Scheller J and Rehmann A *et al.*. (2009) G protein-coupled receptor 43 is essential for neutrophil recruitment during intestinal inflammation. *J Immunol* **183**: 7514-22 [PMID:19917676]
109. Smith NJ, Ward RJ, Stoddart LA, Hudson BD, Kostenis E, Ulven T, Morris JC, Tränkle C, Tikhonova IG and Adams DR *et al.*. (2011) Extracellular loop 2 of the free fatty acid receptor 2 mediates allosterism of a phenylacetamide ago-allosteric modulator. *Mol Pharmacol* **80**: 163-73 [PMID:21498659]
110. Song F, Lu S, Gunnet J, Xu JZ, Wines P, Proost J, Liang Y, Baumann C, Lenhard J and Murray WV *et al.*. (2007) Synthesis and biological evaluation of 3-aryl-3-(4-phenoxy)-propionic acid as a novel series of G

- protein-coupled receptor 40 agonists. *J Med Chem* **50**: 2807-17 [PMID:17500511]
111. Soto-Guzman A, Robledo T, Lopez-Perez M and Salazar EP. (2008) Oleic acid induces ERK1/2 activation and AP-1 DNA binding activity through a mechanism involving Src kinase and EGFR transactivation in breast cancer cells. *Mol Cell Endocrinol* **294**: 81-91 [PMID:18775472]
 112. Spector AA and Hoak JC. (1975) Letter: Fatty acids, platelets, and microcirculatory obstruction. *Science* **190**: 490-2 [PMID:1166323]
 113. Srivastava A, Yano J, Hirozane Y, Kefala G, Gruswitz F, Snell G, Lane W, Ivetac A, Aertgeerts K and Nguyen J *et al.* (2014) High-resolution structure of the human GPR40 receptor bound to allosteric agonist TAK-875. *Nature* **513**: 124-7 [PMID:25043059]
 114. Steneberg P, Rubins N, Bartoov-Shifman R, Walker MD and Edlund H. (2005) The FFA receptor GPR40 links hyperinsulinemia, hepatic steatosis, and impaired glucose homeostasis in mouse. *Cell Metab* **1**: 245-58 [PMID:16054069]
 115. Stoddart LA, Brown AJ and Milligan G. (2007) Uncovering the pharmacology of the G protein-coupled receptor GPR40: high apparent constitutive activity in guanosine 5'-O-(3-[35S]thio)triphosphate binding studies reflects binding of an endogenous agonist. *Mol Pharmacol* **71**: 994-1005 [PMID:17200419]
 116. Stoddart LA, Smith NJ and Milligan G. (2008) International Union of Pharmacology. LXXI. Free fatty acid receptors FFA1, -2, and -3: pharmacology and pathophysiological functions. *Pharmacol Rev* **60**: 405-17 [PMID:19047536]
 117. Sum CS, Tikhonova IG, Neumann S, Engel S, Raaka BM, Costanzi S and Gershengorn MC. (2007) Identification of residues important for agonist recognition and activation in GPR40. *J Biol Chem* **282**: 29248-55 [PMID:17699519]
 118. Sun Q, Hirasawa A, Hara T, Kimura I, Adachi T, Awaji T, Ishiguro M, Suzuki T, Miyata N and Tsujimoto G. (2010) Structure-Activity Relationships of GPR120 Agonists Based on a Docking Simulation. *Mol Pharmacol* **78**: 804-10 [PMID:20685848]
 119. Suzuki T, Igari S, Hirasawa A, Hata M, Ishiguro M, Fujieda H, Itoh Y, Hirano T, Nakagawa H and Ogura M *et al.* (2008) Identification of G protein-coupled receptor 120-selective agonists derived from PPARgamma agonists. *J Med Chem* **51**: 7640-4 [PMID:19007110]
 120. Sykaras AG, Demenis C, Case RM, McLaughlin JT and Smith CP. (2012) Duodenal enteroendocrine I-cells contain mRNA transcripts encoding key endocannabinoid and fatty acid receptors. *PLoS ONE* **7**: e42373 [PMID:22876318]
 121. Takeuchi M, Hirasawa A, Hara T, Kimura I, Hirano T, Suzuki T, Miyata N, Awaji T, Ishiguro M and Tsujimoto G. (2013) FFA1-selective agonistic activity based on docking simulation using FFA1 and GPR120 homology models. *Br J Pharmacol* **168**: 1570-83 [PMID:22639973]
 122. Tan CP, Feng Y, Zhou YP, Eiermann GJ, Petrov A, Zhou C, Lin S, Salituro G, Meinke P and Mosley R *et al.* (2008) Selective small-molecule agonists of G protein-coupled receptor 40 promote glucose-dependent insulin secretion and reduce blood glucose in mice. *Diabetes* **57**: 2211-9 [PMID:18477808]
 123. Tanaka T, Katsuma S, Adachi T, Koshimizu TA, Hirasawa A and Tsujimoto G. (2008) Free fatty acids induce cholecystokinin secretion through GPR120. *Naunyn Schmiedebergs Arch Pharmacol* **377**: 523-7 [PMID:17972064]
 124. Tanaka T, Yano T, Adachi T, Koshimizu TA, Hirasawa A and Tsujimoto G. (2008) Cloning and characterization of the rat free fatty acid receptor GPR120: in vivo effect of the natural ligand on GLP-1 secretion and proliferation of pancreatic beta cells. *Naunyn Schmiedebergs Arch Pharmacol* **377**: 515-22 [PMID:18320172]
 125. Tang C and Offermanns S. (2017) FFA2 and FFA3 in Metabolic Regulation. *Handb Exp Pharmacol* **236**: 205-220 [PMID:27757760]
 126. Tang Y, Chen Y, Jiang H, Robbins GT and Nie D. (2011) G-protein-coupled receptor for short-chain fatty acids suppresses colon cancer. *Int J Cancer* **128**: 847-56 [PMID:20979106]
 127. Tazoe H, Otomo Y, Karaki S, Kato I, Fukami Y, Terasaki M and Kuwahara A. (2009) Expression of short-chain fatty acid receptor GPR41 in the human colon. *Biomed Res* **30**: 149-56 [PMID:19574715]
 128. Tikhonova IG, Sum CS, Neumann S, Thomas CJ, Raaka BM, Costanzi S and Gershengorn MC. (2007) Bidirectional, iterative approach to the structural delineation of the functional "chemoprint" in GPR40 for agonist recognition. *J Med Chem* **50**: 2981-9 [PMID:17552505]
 129. Tolhurst G, Heffron H, Lam YS, Parker HE, Habib AM, Diakogiannaki E, Cameron J, Grosse J, Reimann F and Gribble FM. (2012) Short-chain fatty acids stimulate glucagon-like peptide-1 secretion via the G-protein-coupled receptor FFAR2. *Diabetes* **61**: 364-71 [PMID:22190648]

130. Tomita T, Masuzaki H, Iwakura H, Fujikura J, Noguchi M, Tanaka T, Ebihara K, Kawamura J, Komoto I and Kawaguchi Y *et al.*. (2006) Expression of the gene for a membrane-bound fatty acid receptor in the pancreas and islet cell tumours in humans: evidence for GPR40 expression in pancreatic beta cells and implications for insulin secretion. *Diabetologia* **49**: 962-8 [PMID:16525841]
131. Tsujihata Y, Ito R, Suzuki M, Harada A, Negoro N, Yasuma T, Momose Y and Takeuchi K. (2011) TAK-875, an orally available G protein-coupled receptor 40/free fatty acid receptor 1 agonist, enhances glucose-dependent insulin secretion and improves both postprandial and fasting hyperglycemia in type 2 diabetic rats. *J Pharmacol Exp Ther* **339**: 228-37 [PMID:21752941]
132. Ulven T. (2012) Short-chain free fatty acid receptors FFA2/GPR43 and FFA3/GPR41 as new potential therapeutic targets. *Front Endocrinol (Lausanne)* **3**: 111 [PMID:23060857]
133. Vassilatis DK, Hohmann JG, Zeng H, Li F, Ranchalis JE, Mortrud MT, Brown A, Rodriguez SS, Weller JR and Wright AC *et al.*. (2003) The G protein-coupled receptor repertoires of human and mouse. *Proc Natl Acad Sci USA* **100**: 4903-8 [PMID:12679517]
134. Vinolo MA, Ferguson GJ, Kulkarni S, Damoulakis G, Anderson K, Bohlooly-Y M, Stephens L, Hawkins PT and Curi R. (2011) SCFAs induce mouse neutrophil chemotaxis through the GPR43 receptor. *PLoS ONE* **6**: e21205 [PMID:21698257]
135. Wang A, Akers RM and Jiang H. (2012) Short communication: Presence of G protein-coupled receptor 43 in rumen epithelium but not in the islets of Langerhans in cattle. *J Dairy Sci* **95**: 1371-5 [PMID:22365220]
136. Wang J, Wu X, Simonavicius N, Tian H and Ling L. (2006) Medium-chain fatty acids as ligands for orphan G protein-coupled receptor GPR84. *J Biol Chem* **281**: 34457-64 [PMID:16966319]
137. Wang Y, Jiao X, Kayser F, Liu J, Wang Z, Wanska M, Greenberg J, Weiszmann J, Ge H and Tian H *et al.*. (2010) The first synthetic agonists of FFA2: Discovery and SAR of phenylacetamides as allosteric modulators. *Bioorg Med Chem Lett* **20**: 493-8 [PMID:20005104]
138. Watson SJ, Brown AJ and Holliday ND. (2012) Differential signaling by splice variants of the human free fatty acid receptor GPR120. *Mol Pharmacol* **81**: 631-42 [PMID:22282525]
139. Wellendorph P, Johansen LD and Bräuner-Osborne H. (2009) Molecular pharmacology of promiscuous seven transmembrane receptors sensing organic nutrients. *Mol Pharmacol* **76**: 453-65 [PMID:19487246]
140. Widmayer P, Küper M, Kramer M, Königsrainer A and Breer H. (2012) Altered expression of gustatory-signaling elements in gastric tissue of morbidly obese patients. *Int J Obes (Lond.)* **36**: 1353-9 [PMID:22083550]
141. Ximenes HM, Hirata AE, Rocha MS, Curi R and Carpinelli AR. (2007) Propionate inhibits glucose-induced insulin secretion in isolated rat pancreatic islets. *Cell Biochem Funct* **25**: 173-8 [PMID:16444779]
142. Xiong Y, Miyamoto N, Shibata K, Valasek MA, Motoike T, Kedzierski RM and Yanagisawa M. (2004) Short-chain fatty acids stimulate leptin production in adipocytes through the G protein-coupled receptor GPR41. *Proc Natl Acad Sci USA* **101**: 1045-50 [PMID:14722361]
143. Xiong Y, Swaminath G, Cao Q, Yang L, Guo Q, Salomonis H, Lu J, Houze JB, Dransfield PJ and Wang Y *et al.*. (2013) Activation of FFA1 mediates GLP-1 secretion in mice. Evidence for allosterism at FFA1. *Mol Cell Endocrinol* **369**: 119-29 [PMID:23403053]
144. Yang W, Xiao Y, Huang X, Chen F, Sun M, Bilotta AJ, Xu L, Lu Y, Yao S and Zhao Q *et al.*. (2019) Microbiota Metabolite Short-Chain Fatty Acids Facilitate Mucosal Adjuvant Activity of Cholera Toxin through GPR43. *J Immunol* **203**: 282-292 [PMID:31076530]
145. Yonezawa T, Kobayashi Y and Obara Y. (2007) Short-chain fatty acids induce acute phosphorylation of the p38 mitogen-activated protein kinase/heat shock protein 27 pathway via GPR43 in the MCF-7 human breast cancer cell line. *Cell Signal* **19**: 185-93 [PMID:16887331]
146. Zaibi MS, Stocker CJ, O'Dowd J, Davies A, Bellahcene M, Cawthorne MA, Brown AJ, Smith DM and Arch JR. (2010) Roles of GPR41 and GPR43 in leptin secretory responses of murine adipocytes to short chain fatty acids. *FEBS Lett* **584**: 2381-6 [PMID:20399779]
147. Zhang Y, Xu M, Zhang S, Yan L, Yang C, Lu W, Li Y and Cheng H. (2007) The role of G protein-coupled receptor 40 in lipoapoptosis in mouse beta-cell line NIT-1. *J Mol Endocrinol* **38**: 651-61 [PMID:17556534]