

Succinate receptor in GtoPdb v.2023.1

Anthony P. Davenport¹, Julien Hanson² and Wen Chiy Liew³

1. University of Cambridge, UK
2. University of Liege, Belgium
3. University of Edinburgh, UK

Abstract

Nomenclature as recommended by NC-IUPHAR [8]. The succinate receptor (GPR91, *SUCNR1*) is activated by the tricarboxylic acid (or Krebs) cycle intermediate succinate and other dicarboxylic acids with less clear physiological relevance such as maleate [17]. Since its pairing with its endogenous ligand in 2004, intense research has focused on the receptor-ligand pair role in various (patho)physiological processes such as regulation of renin production [17, 39], ischemia injury [17], fibrosis [25], retinal angiogenesis [34], inflammation [25, 23], immune response [32], obesity [44, 26, 21], diabetes [42, 22, 39], platelet aggregation [38, 36] or cancer [28, 46]. The succinate receptor is coupled to G_{i/o} [11, 17] and G_{q/11} protein families [31, 17, 40]. Although the receptor is, upon ligand addition, rapidly desensitized [19, 31], and in some cells internalized [17], it seems to recruit arrestins weakly [10]. The cellular activation of the succinate receptor triggers various signalling pathways such as decrease of cAMP levels, [Ca²⁺]ⁱ mobilization and activation of kinases (ERK, c-Jun, Akt, Src, p38, PI3Kβ, etc.) [12]. The receptor is broadly expressed but is notably abundant in immune cells (M2 macrophages [40, 21], monocytes [32], immature dendritic cells [32], adipocytes [44], platelets [38, 36], etc.) and in the kidney [17].

Contents

This is a citation summary for Succinate receptor 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 [5].

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

[Succinate receptor](#)

<https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=446>

[Introduction to Succinate receptor](#)

<https://www.guidetopharmacology.org/GRAC/FamilyIntroductionForward?familyId=446>

Receptors

succinate receptor

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=166>

References

1. Abbracchio MP, Burnstock G, Boeynaems JM, Barnard EA, Boyer JL, Kennedy C, Knight GE, Fumagalli M, Gachet C and Jacobson KA *et al.* (2006) International Union of Pharmacology LVIII: update on the P2Y G protein-coupled nucleotide receptors: from molecular mechanisms and pathophysiology to therapy. *Pharmacol Rev* **58**: 281-341 [PMID:16968944]
2. Aguiar CJ, Andrade VL, Gomes ER, Alves MN, Ladeira MS, Pinheiro AC, Gomes DA, Almeida AP, Goes AM and Resende RR *et al.* (2010) Succinate modulates Ca(2+) transient and cardiomyocyte viability through PKA-dependent pathway. *Cell Calcium* **47**: 37-46 [PMID:20018372]
3. Ariza AC, Deen PM and Robben JH. (2012) The succinate receptor as a novel therapeutic target for oxidative and metabolic stress-related conditions. *Front Endocrinol (Lausanne)* **3**: 22 [PMID:22649411]
4. Bhuniya D, Umrani D, Dave B, Salunke D, Kukreja G, Gundu J, Naykodi M, Shaikh NS, Shitole P and Kurhade S *et al.* (2011) Discovery of a potent and selective small molecule hGPR91 antagonist. *Bioorg Med Chem Lett* **21**: 3596-602 [PMID:21571530]
5. 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]
6. Cantagrel V, Lossi AM, Boulanger S, Depetrис D, Mattei MG, Gecz J, Schwartz CE, Van Maldergem L and Villard L. (2004) Disruption of a new X linked gene highly expressed in brain in a family with two mentally retarded males. *J Med Genet* **41**: 736-42 [PMID:15466006]
7. Correa PR, Kruglov EA, Thompson M, Leite MF, Dranoff JA and Nathanson MH. (2007) Succinate is a paracrine signal for liver damage. *J Hepatol* **47**: 262-9 [PMID:17451837]
8. Davenport AP, Alexander SP, Sharman JL, Pawson AJ, Benson HE, Monaghan AE, Liew WC, Mpamhangwa 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]
9. Fredriksson R, Lagerström MC, Lundin LG and Schiöth HB. (2003) The G-protein-coupled receptors in the human genome form five main families. Phylogenetic analysis, paralogue groups, and fingerprints. *Mol Pharmacol* **63**: 1256-72 [PMID:12761335]
10. Geubelle P, Gilissen J, Dilly S, Poma L, Dupuis N, Laschet C, Abboud D, Inoue A, Jouret F and Pirotte B *et al.* (2017) Identification and pharmacological characterization of succinate receptor agonists. *Br J Pharmacol* **174**: 796-808 [PMID:28160606]
11. Gilissen J, Geubelle P, Dupuis N, Laschet C, Pirotte B and Hanson J. (2015) Forskolin-free cAMP assay for Gi-coupled receptors. *Biochem Pharmacol* **98**: 381-91 [PMID:26386312]
12. Gilissen J, Jouret F, Pirotte B and Hanson J. (2016) Insight into SUCNR1 (GPR91) structure and function. *Pharmacol Ther* **159**: 56-65 [PMID:26808164]
13. Gnana-Prakasam JP, Ananth S, Prasad PD, Zhang M, Atherton SS, Martin PM, Smith SB and Ganapathy V. (2011) Expression and iron-dependent regulation of succinate receptor GPR91 in retinal pigment epithelium. *Invest Ophthalmol Vis Sci* **52**: 3751-8 [PMID:21357408]
14. Gonzalez NS, Communi D, Hannedouche S and Boeynaems JM. (2004) The fate of P2Y-related orphan receptors: GPR80/99 and GPR91 are receptors of dicarboxylic acids. *Purinergic Signal* **1**: 17-20 [PMID:18404396]
15. Haffke M, Fehlmann D, Rummel G, Boivineau J, Duckely M, Gommermann N, Cotesta S, Sirockin F, Freuler F and Littlewood-Evans A *et al.* (2019) Structural basis of species-selective antagonist binding to the succinate receptor. *Nature* **574**: 581-585 [PMID:31645725]
16. Hakak Y, Lehmann-Bruinsma K, Phillips S, Le T, Liaw C, Connolly DT and Behan DP. (2009) The role of the GPR91 ligand succinate in hematopoiesis. *J Leukoc Biol* **85**: 837-43 [PMID:19204147]
17. He W, Miao FJ, Lin DC, Schwandner RT, Wang Z, Gao J, Chen JL, Tian H and Ling L. (2004) Citric acid cycle intermediates as ligands for orphan G-protein-coupled receptors. *Nature* **429**: 188-93 [PMID:15141213]
18. Hebert SC. (2004) Physiology: orphan detectors of metabolism. *Nature* **429**: 143-5 [PMID:15141197]

19. Höglberg C, Gidlöf O, Tan C, Svensson S, Nilsson-Öhman J, Erlinge D and Olde B. (2011) Succinate independently stimulates full platelet activation via cAMP and phosphoinositide 3-kinase-β signaling. *J Thromb Haemost* **9**: 361-72 [PMID:21143371]
20. Joost P and Methner A. (2002) Phylogenetic analysis of 277 human G-protein-coupled receptors as a tool for the prediction of orphan receptor ligands. *Genome Biol* **3**: RESEARCH0063 [PMID:12429062]
21. Keiran N, Ceperuelo-Mallafré V, Calvo E, Hernández-Alvarez MI, Ejarque M, Núñez-Roa C, Horrillo D, Maymó-Masip E, Rodríguez MM and Fradera R *et al.*. (2019) SUCNR1 controls an anti-inflammatory program in macrophages to regulate the metabolic response to obesity. *Nat Immunol* **20**: 581-592 [PMID:30962591]
22. Li T, Hu J, Du S, Chen Y, Wang S and Wu Q. (2014) ERK1/2/COX-2/PGE2 signaling pathway mediates GPR91-dependent VEGF release in streptozotocin-induced diabetes. *Mol Vis* **20**: 1109-21 [PMID:25324681]
23. Littlewood-Evans A, Sarret S, Apfel V, Loesle P, Dawson J, Zhang J, Muller A, Tigani B, Kneuer R and Patel S *et al.*. (2016) GPR91 senses extracellular succinate released from inflammatory macrophages and exacerbates rheumatoid arthritis. *J Exp Med* **213**: 1655-62 [PMID:27481132]
24. Macaulay IC, Tijssen MR, Thijssen-Timmer DC, Gusnanto A, Steward M, Burns P, Langford CF, Ellis PD, Dudbridge F, Zwaginga JJ, Watkins NA, van der Schoot CE and Ouwehand WH. (2007) Comparative gene expression profiling of in vitro differentiated megakaryocytes and erythroblasts identifies novel activatory and inhibitory platelet membrane proteins. *Blood* **109**: 3260-9 [PMID:17192395]
25. Macias-Ceja DC, Ortiz-Masiá D, Salvador P, Gisbert-Ferrández L, Hernández C, Hausmann M, Rogler G, Esplugues JV, Hinojosa J and Alós R *et al.*. (2019) Succinate receptor mediates intestinal inflammation and fibrosis. *Mucosal Immunol* **12**: 178-187 [PMID:30279517]
26. McCreath KJ, Espada S, Gálvez BG, Benito M, de Molina A, Sepúlveda P and Cervera AM. (2015) Targeted disruption of the SUCNR1 metabolic receptor leads to dichotomous effects on obesity. *Diabetes* **64**: 1154-67 [PMID:25352636]
27. Molnár T, Héra L, Emri Z, Simon A, Nyitrai G, Pál I and Kardos J. (2011) Activation of astroglial calcium signaling by endogenous metabolites succinate and gamma-hydroxybutyrate in the nucleus accumbens. *Front Neuroenergetics* **3**: 7 [PMID:22180742]
28. Rabe P, Liebing AD, Krumbholz P, Kraft R and Stäubert C. (2022) Succinate receptor 1 inhibits mitochondrial respiration in cancer cells addicted to glutamine. *Cancer Lett* **526**: 91-102 [PMID:34813893]
29. Regard JB, Sato IT and Coughlin SR. (2008) Anatomical profiling of G protein-coupled receptor expression. *Cell* **135**: 561-71 [PMID:18984166]
30. Rexen Ulven E, Trauelsen M, Brvar M, Lückmann M, Bielefeldt LØ, Jensen LKI, Schwartz TW and Frimurer TM. (2018) Structure-Activity Investigations and Optimisations of Non-metabolite Agonists for the Succinate Receptor 1. *Sci Rep* **8**: 10010 [PMID:29968758]
31. Robben JH, Fenton RA, Vargas SL, Schweer H, Peti-Peterdi J, Deen PM and Milligan G. (2009) Localization of the succinate receptor in the distal nephron and its signaling in polarized MDCK cells. *Kidney Int* **76**: 1258-67 [PMID:19776718]
32. Rubic T, Lametschwandtner G, Jost S, Hinteregger S, Kund J, Carballido-Perrig N, Schwärzler C, Junt T, Voshol H and Meingassner JG *et al.*. (2008) Triggering the succinate receptor GPR91 on dendritic cells enhances immunity. *Nat Immunol* **9**: 1261-9 [PMID:18820681]
33. Rubić-Schneider T, Carballido-Perrig N, Regairaz C, Raad L, Jost S, Rauld C, Christen B, Wieczorek G, Kreutzer R and Dawson J *et al.*. (2017) GPR91 deficiency exacerbates allergic contact dermatitis while reducing arthritic disease in mice. *Allergy* **72**: 444-452 [PMID:27527650]
34. Sapieha P, Sirinyan M, Hamel D, Zaniolo K, Joyal JS, Cho JH, Honoré JC, Kermorvant-Duchemin E, Varma DR and Tremblay S *et al.*. (2008) The succinate receptor GPR91 in neurons has a major role in retinal angiogenesis. *Nat Med* **14**: 1067-76 [PMID:18836459]
35. Southern C, Cook JM, Neetoo-Isseljee Z, Taylor DL, Kettleborough CA, Merritt A, Bassoni DL, Raab WJ, Quinn E and Wehrman TS *et al.*. (2013) Screening β-Arrestin Recruitment for the Identification of Natural Ligands for Orphan G-Protein-Coupled Receptors. *J Biomol Screen* **18**: 599-609 [PMID:23396314]
36. Spath B, Hansen A, Bokemeyer C and Langer F. (2012) Succinate reverses in-vitro platelet inhibition by acetylsalicylic acid and P2Y receptor antagonists. *Platelets* **23**: 60-8 [PMID:21736422]
37. Sundström L, Greasley PJ, Engberg S, Wallander M and Ryberg E. (2013) Succinate receptor GPR91, a Gα(i) coupled receptor that increases intracellular calcium concentrations through PLCβ. *FEBS Lett* **587**:

- 2399-404 [PMID:23770096]
38. Tang X, Fuchs D, Tan S, Trauelson M, Schwartz TW, Wheelock CE, Li N and Haeggström JZ. (2020) Activation of metabolite receptor GPR91 promotes platelet aggregation and transcellular biosynthesis of leukotriene C₄. *J Thromb Haemost* **18**: 976-984 [PMID:31930602]
 39. Toma I, Kang JJ, Sipos A, Vargas S, Bansal E, Hanner F, Meer E and Peti-Peterdi J. (2008) Succinate receptor GPR91 provides a direct link between high glucose levels and renin release in murine and rabbit kidney. *J Clin Invest* **118**: 2526-34 [PMID:18535668]
 40. Trauelson M, Hiron TK, Lin D, Petersen JE, Breton B, Husted AS, Hjorth SA, Inoue A, Frimurer TM and Bouvier M *et al.* (2021) Extracellular succinate hyperpolarizes M2 macrophages through SUCNR1/GPR91-mediated Gq signaling. *Cell Rep* **35**: 109246 [PMID:34133934]
 41. Trauelson M, Rexen Ulven E, Hjorth SA, Brvar M, Monaco C, Frimurer TM and Schwartz TW. (2017) Receptor structure-based discovery of non-metabolite agonists for the succinate receptor GPR91. *Mol Metab* **6**: 1585-1596 [PMID:29157600]
 42. van Diepen JA, Robben JH, Hooiveld GJ, Carmone C, Alsady M, Boutens L, Bekkenkamp-Grovenstein M, Hijmans A, Engelke UFH and Wevers RA *et al.* (2017) SUCNR1-mediated chemotaxis of macrophages aggravates obesity-induced inflammation and diabetes. *Diabetologia* **60**: 1304-1313 [PMID:28382382]
 43. Vargas SL, Toma I, Kang JJ, Meer EJ and Peti-Peterdi J. (2009) Activation of the succinate receptor GPR91 in macula densa cells causes renin release. *J Am Soc Nephrol* **20**: 1002-11 [PMID:19389848]
 44. Villanueva-Carmona T, Cedó L, Madeira A, Ceperuelo-Mallafré V, Rodríguez-Peña MM, Núñez-Roa C, Maymó-Masip E, Repollés-de-Dalmau M, Badia J and Keiran N *et al.* (2023) SUCNR1 signaling in adipocytes controls energy metabolism by modulating circadian clock and leptin expression. *Cell Metab* **35**: 601-619.e10 [PMID:36977414]
 45. Wittenberger T, Schaller HC and Hellebrand S. (2001) An expressed sequence tag (EST) data mining strategy succeeding in the discovery of new G-protein coupled receptors. *J Mol Biol* **307**: 799-813 [PMID:11273702]
 46. Wu JY, Huang TW, Hsieh YT, Wang YF, Yen CC, Lee GL, Yeh CC, Peng YJ, Kuo YY and Wen HT *et al.* (2020) Cancer-Derived Succinate Promotes Macrophage Polarization and Cancer Metastasis via Succinate Receptor. *Mol Cell* **77**: 213-227.e5 [PMID:31735641]
 47. Zhang D, Gao ZG, Zhang K, Kiselev E, Crane S, Wang J, Paoletta S, Yi C, Ma L and Zhang W *et al.* (2015) Two disparate ligand-binding sites in the human P2Y1 receptor. *Nature* **520**: 317-21 [PMID:25822790]
 48. Zhang J, Zhang K, Gao ZG, Paoletta S, Zhang D, Han GW, Li T, Ma L, Zhang W and Müller CE *et al.* (2014) Agonist-bound structure of the human P2Y12 receptor. *Nature* **509**: 119-22 [PMID:24784220]
 49. Zhang K, Zhang J, Gao ZG, Zhang D, Zhu L, Han GW, Moss SM, Paoletta S, Kiselev E and Lu W *et al.* (2014) Structure of the human P2Y12 receptor in complex with an antithrombotic drug. *Nature* **509**: 115-8 [PMID:24670650]